*Systematic Review*

# Sleep and Stroke-Related Delirium: A Systematic Review

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**Abstract: Study objectives**: Sleep and circadian rhythms disorders are frequent in the acute stroke. Sleep modifications are likely to contribute to the development of stroke-related delirium, a common neuropsychiatric complication of acute stroke. This systematic review aimed to clarify the association between sleep modifications and the occurrence of delirium in patients with acute stroke. **Methods**: The current systematic review was performed according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines. The search was performed on PubMed and Scopus databases. Only studies that provided data concerning sleep, or pre-existing sleep disorders, in acute stroke and performed a formal evaluation of delirium were included. **Results**: The literature search enabled the identification of 15 studies, which exhibited high heterogeneity in terms of study design, settings, sleep assessments, delirium measures, and types of sleep intervention. In the study quality assessment, the majority of the studies were rated as weak or moderate. In most of the cases, sleep was subjectively assessed by the patients or rated by clinicians. None of the studies performed polysomnography for the evaluation of sleep. Only four of the studies assessed the impact of a sleep intervention on delirium, suggesting the potentially protective role of sleep promotion in reducing the prevalence and severity of stroke-related delirium. **Conclusions**: The evidence arising from the present systematic review supports that sleep disruption is a potential promoting factor for stroke-related delirium. We suggest that a formal sleep assessment and sleep promotion should be included in routine stroke care.

**Keywords:** delirium; intensive care unit; melatonin; night-time care; sleep; sleep apnea; sleep intervention; sleep–wake cycle; stroke; stroke unit

## 1. Introduction

Delirium is a neuropsychiatric syndrome characterized by a disturbance of attention, awareness, and cognition, with an acute onset and a fluctuating course [1]. Delirium frequently occurs as a complication of the acute phase of stroke, affecting approximately one in four patients [2]. Delirium has a negative impact on prognosis, leading to increased mortality [3], disability [4], and prolonged hospitalization [5]. The pathogenesis of delirium is believed to be multifactorial, with its onset dependent on the interaction between predisposing risk factors and precipitating factors occurring during hospitalization [6]. A

bidirectional relationship between sleep and delirium is commonly hypothesized. In fact, sleep deprivation and delirium share several common risk factors and clinical manifestations. In particular, sleep and circadian rhythms disruption has been closely associated with delirium in the Intensive Care Unit (ICU) [7]. Several mechanisms affecting sleep in critically ill patients have been described, such as noise, altered light–dark cycle, sedation, mechanical ventilation, pain, and stress response. All these factors may have potential bidirectional effects on sleep disruption and delirium occurrence [7–9].

Sleep is disrupted in the acute phase of stroke as well [10]. Sleep architecture and quality are particularly compromised after a stroke, with thalamic and cortical strokes exhibiting the most severe alterations [11,12]. Additionally, circadian rhythm is disrupted in the acute phase of stroke: melatonin is significantly reduced after an ischemic stroke when compared to controls [12]. Furthermore, a high prevalence of sleep disorders has been reported in acute stroke patients. Sleep-disordered breathing (SDB) affects around 60% of patients, with nearly one-third of them experiencing severe SDB [13]. Other highly prevalent sleep disorders in acute stroke include insomnia, periodic limb movements, and restless leg syndrome, affecting, respectively, 40%, 30%, and 10% of patients [14]. Also, hypersomnia and excessive daytime sleepiness are frequent in the first month after a stroke [15].

The existing evidence arising from the literature points towards the role of pre-existing sleep disorders and sleep modifications occurring in the acute phase of stroke as contributing factors to the development of stroke-related delirium [16]. As sleep disturbances are potentially modifiable factors, a growing interest has been directed to sleep interventions aimed at preventing delirium in acute stroke patients [17].

The purpose of the current study is to systematically review the medical literature that has evaluated the role of sleep disturbances associated with delirium in acute stroke patients and to investigate the efficacy of sleep interventions on stroke-related delirium.

## 2. Methods

The current systematic review was performed according to the latest Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement [18] and was registered on PROSPERO International Prospective Register of Systematic Reviews (ID: CRD42022346332).

### 2.1. Eligibility Criteria for Systematic Review

The eligibility criteria were established according to the PICO methodology, detailed as follows:

*Population:* Patients within one month from acute stroke.

*Intervention:* Where available, sleep interventions to prevent or treat delirium in patients with acute stroke.

*Comparison:* Comparisons were made between sleep interventions and no interventions, or between patients with subjective or objective disruption of nocturnal sleep and patients without subjective or objective disruption of nocturnal sleep.

*Outcome:* The considered outcome measures were the incidence, duration, and severity of the stroke-related delirium.

The following search criteria were applied for study eligibility: human studies, English language, and involving adults (≥18 years). Case reports, reviews, comments, editorials, perspectives, erratum, unpublished manuscripts, and conference abstracts were excluded. Only studies that reported data about sleep, and in which delirium was formally evaluated with a validated tool, were included. No time limit was applied to the search.

### 2.2. Information Sources and Search Strategy

The search was performed on PubMed and Scopus databases. In order to reduce the risk of bias due to missing results, we also performed a search for unpublished studies on

clinicaltrials.gov. The last search was conducted on 15 July 2022. The following string was used to perform the search:

"(((stroke) OR (cerebrovascular disease) OR (cerebral bleeding) OR (brain hemorrhage) OR (brain ischemia) OR (brain hematoma)) AND ((delirium) OR (agitation) OR (confusional state) OR (confusion) OR (attention)) AND ((sleep) OR (circadian rhythm) OR (sleep-wake cycle) OR (insomnia) OR (hypersomnia) OR (somnolence) OR (sleepiness) OR (hypnotics) OR (melatonin) OR (nocturnal) OR (nighttime) OR (apnea)))".

In order to find other eligible studies, we screened the reference lists of selected articles and of other reviews and meta-analyses focused on the same topic.

### 2.3. Selection Process

The search strategy identified 2894 reports. All the authors of the current research screened the identified reports for the title and abstract. Subsequently, three of the reviewers (VB, ER, and GDM) read the full text of the retrieved papers to assess their eligibility. At the end of this process, the reference list of eligible articles, and of other reviews and meta-analyses focused on the same topic of the current research, were screened to identify further eligible reports. The choice to include or exclude a report in this systematic review was solved by consensus of the three reviewers (VB, ER, and GDM).

The search strategy and study selection are described in detail in the PRISMA flow diagram (Figure 1).

### 2.4. Data Collection Process

VB, ER, IS, and GDM independently extracted the data from the selected studies. The following data were obtained: first author, year of publication, study design, sample size of the study population and of the control group, age, study setting, outcome measures, sleep measures, type of sleep intervention, type of stroke, incidence and measures of delirium, and main findings.

### 2.5. Outcomes

The main endpoint of the present systematic review was to establish whether sleep modifications were associated with the occurrence and/or severity of delirium in patients with acute stroke. The secondary endpoint was to evaluate whether sleep interventions were effective in reducing the incidence and severity of delirium in patients with acute stroke.

### 2.6. Quality and Certainty of Evidence Assessment

The eligible reports were independently evaluated for a quality assessment by VB, ER, IS, and JM. In case of disagreement among the reviewers' scoring, further reviewers (GDM and CI) were consulted. Studies were evaluated by means of the "Quality assessment tools for quantitative studies" developed by the Effective Public Healthcare Practice Project (EPHPP) [19]. This tool consists of six components (selection bias, design, confounders, blinding, data collection methods, and withdrawals and drop-outs) which are rated as strong, moderate, or weak according to a standardized guide ("Dictionary for the Effective Public Health Practice Project Quality Assessment Tool for Quantitative Studies"). After assessing each component, we obtained a global rating as follows: strong for studies with no weak and at least four strong ratings, moderate for studies with one weak and/or less than four strong ratings, and weak for studies with two or more weak ratings.
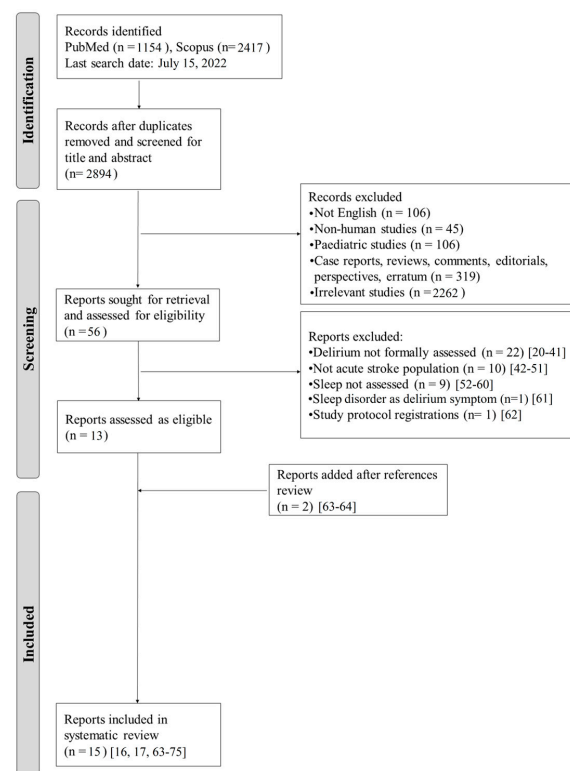
Records identified
PubMed (n = 1154 ), Scopus (n= 2417 )
Last search date: July 15, 2022

Records after duplicates
removed and screened for
title and abstract
(n= 2894 )

Records excluded
• Not English (n = 106)
• Non-human studies (n = 45)
• Paediatric studies (n = 106)
• Case reports, reviews, comments, editorials, perspectives, erratum (n = 319)
• Irrelevant studies (n = 2262 )

Reports sought for retrieval
and assessed for eligibility
(n = 56 )

Reports excluded:
• Delirium not formally assessed (n = 22) [20-41]
• Not acute stroke population (n = 10) [42-51]
• Sleep not assessed (n = 9) [52-60]
• Sleep disorder as delirium symptom (n=1) [61]
• Study protocol registrations (n= 1) [62]

Reports assessed as eligible
(n = 13)

Reports added after references
review
(n = 2) [63-64]

Reports included in
systematic review
(n = 15 ) [16, 17, 63-75]

Identification

Screening

Included

**Figure 1.** Flow chart of studies identification, screening, and inclusion in this systematic review according to the PRISMA guidelines.

## 3. Results

### 3.1. Study Selection

The search strategy identified 2894 reports. The preliminary screening for titles and abstracts excluded 2838 reports; therefore, 56 papers were retrieved and their full text was obtained. After reading the full text of the retrieved papers, 13 were assessed as eligible. The other 43 reports were excluded for the following reasons: 22 did not provide any formal assessment of delirium [20–41], 10 did not include patients with acute stroke [42–51], 9 did not report any sleep evaluation [52–60], in one study sleep disorders were considered as delirium-related symptoms [61], and one was a study protocol registration [62].

Two more reports were added after screening the reference lists of the eligible articles and of other reviews and meta-analyses focused on the same topic of the current research [63,64]. At the end of this process, 15 reports were included in this systematic review [16,17,63–75]. Two reports included in this systematic review evaluated the same study population, although the main outcome measure differed between the studies [16,69].

No relevant unpublished studies were found from the search on clinicaltrials.gov.

### 3.2. Study Characteristics

Among the studies included in this systematic review, two studies were retrospective, interventional studies [67,70], one study was retrospective and observational [66], five were prospective, observational studies [68,69,71,73,75], and seven were prospective, interventional studies [16,17,63–65,72,74]. Table 1 describes the studies' designs, patients' characteristics, outcome measures, and main findings of the included studies. Six of the studies were performed in a stroke unit [16,17,66,69,71,74], whereas the Intensive Care Unit was the setting for five studies [63,64,68,71,75]; in two cases the study was conducted in a geriatric stroke rehabilitation ward [72,73]. Most of the studies included both ischemic and hemorrhagic stroke patients [16,66–70,72,73]; one study included only hemorrhagic patients [71] and two studies included a cohort of ischemic patients [17,65]. In two studies, patients with stroke represented a subgroup of the total cohort [63,64].

**Table 1.** Characteristics and main findings of the studies included in this systematic review.

| First Author (Year) | Study Design | Age (Years) | Pt | Ctl | Setting | Outcome Measures | Sleep Measures | Sleep Interventions | Stroke Type | Delirium Incidence | Delirium Measures | Sleep Factors Associated with Delirium |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Mengel (2021) [17] | Int | Melatonin: 64 ± 13 Controls: 73 ± 15 | 300 (164) † | 273 (164) † | SU | DLR: prevalence, risk factors, characteristics, time to onset, and duration | None | Melatonin 2 mg nightly | Ischemic | Melatonin: 42/164 Controls: 60/164 | RASS, ICDSC | Melatonin prevents DLR (OR 0.597, CI 0.372–0.958) |
| Nakamizo (2021) [16] | Int | Total: 75 (64–83) DLR+: 84 (72–89) DLR−: 74 (64–83) | 83 | 304 | SU | Incidence of DLR within 5 days from admission | History of insomnia and nocturnal lifestyle | Frequent night-time care | Ischemic and hemorrhagic | Frequent night-time care: 20/83 Controls: 22/304 | ICDSC | Frequent night-time care (OR 2.1, CI 1.2–3.7) |
| Nakamizo (2020) [69] | Obs | Total: 75 (64–83) DLR+: 84 (72–89) DLR−: 74 (64–83) | 387 | 0 | SU | Prediction model for DLR | Nocturnal lifestyle, insomnia, and frequent night-time care | Frequent night-time care | Ischemic and hemorrhagic | 42/387 | ICDSC | Insomnia OR 2.5 (CI 1.1–5.4) Nocturnal lifestyle OR 5.5 (CI 1.7–16.4) Frequent night-time care OR 4.1 (CI 2.0–8.3) |
| Reznik (2019) [71] | Obs | Total: 68 ± 18 DLR+: 70 ± 19 DLR−: 65 ± 18 | 60 | 0 | NICU, SU | DLR: incidence and features | Sleep–wake disturbance | Not performed | Hemorrhagic | 34/60 | CAM-ICU, ICDSC, DSM-V | Sleep–wake cycle disturbances are increased in DLR ($p < 0.001$) |
| Hosoya (2018) [66] | Obs | DLR+: 75 ± 1 DLR−: 69 ± 1 | 269 | 0 | SU | DLR incidence | Somnolence and prior sleep medications | Not performed | Ischemic, hemorrhagic, and SAH | 97/269 | ICDSC | Post-stroke somnolence ($p < 0.001$), medications before stroke ($p = 0.032$) |
| Kawada (2018) [67] | Int | Suvorexant: 79 (72–84) GABAR-A: 76 (67–84) | 232 | 0 | Not specified | Sleep improvement, DLR incidence, and length of hospitalization | Subjective sleep, nursing observations, and hospital records | Ramelteon + suvorexant vs. Ramelteon + GABAR-A | Ischemic and hemorrhagic | Suvorexant: 9/128 GABAR-A: 32/104 | CAM-ICU, RASS | Suvorexant prevents DLR (OR 0.19, CI 0.09–0.44) |
| McLaughlin (2018) [68] | Obs | 54 (34–88) | 20 | 0 | NICU | DLR incidence and neurological deterioration | Sleep deprivation | Hourly neurological examination | Ischemic, hemorrhagic, and SAH (16/20) | 15/20 | CAM-ICU | Hourly neurological examinations favors DLR * |
| Wang (2018) [75] | Obs | DLR+: 56 (45–64) DLR−: 57 (46–65) | 128 | 0 | NICU | DLR: incidence and risk factors | Sleep deprivation | Not performed | Not specified | 27/64 | CAM-ICU | Sleep deprivation OR 8.03 (CI 1.04–62.17) |
| Song (2017) [74] | Int | Treated: 75 ± 6 Control: 74 ± 7 | 54 | 54 | SU | DLR incidence and severity, stroke impact, and length of hospitalization | History of sleep disorder | Multicomponent intervention | Not specified | Treated: 4/54 Controls: 13/54 | DOS | Multicomponent intervention prevents DLR ($p = 0.017$) |

**Table 1.** *Cont.*

| First Author (Year) | Study Design | Age (Years) | Pt | Ctl | Setting | Outcome Measures | Sleep Measures | Sleep Interventions | Stroke Type | Delirium Incidence | Delirium Measures | Sleep Factors Associated with Delirium |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Hatta (2017) [63] | Int | Suvorexant: 79 ± 7 Placebo: 78 ± 6 | 36 | 36 | ICU, acute wards | DLR incidence and severity and serum biomarkers predictor of DLR | Subjective sleep and staff observations | Suvorexant 15 mg/nightly for 3 days | Stroke prevalence: 7/36 placebo group and 7/36 suvorexant group | Suvorexant: 0/36 Placebo: 6/36 | DSM-V, DRS-R98 | Suvorexant prevents DLR ($p = 0.025$) |
| Duan (2016) [65] | Int | 81 (64–94) | 18 | 0 | Not specified | DLR severity | Sleep–wake cycle disturbance | Naloxone (1.2–4.0 mg) once or twice daily | Ischemic | 18/18 | DRS-R98 | Naloxone improves DLR severity * |
| Hatta (2014) [64] | Int | Ramelteon: 78 ± 7 Placebo: 78 ± 7 | 33 | 34 | ICU, acute wards | DLR incidence and severity | Subjective sleep and staff observations | Ramelteon 8 mg/nightly for 7 days | Stroke prevalence: 9/34 placebo group and 12/33 ramelteon group | Ramelteon: 1/33 Placebo: 11/34 | DSM-IV, DRS-R98 | Ramelteon prevents DLR ($p = 0.003$) |
| Ohta (2013) [70] | Int | Ramelteon: 76 ± 6 Sedatives: 77 ± 6 | 7 | 21 | Not specified | DLR severity | Insomnia | Ramelteon vs. other sedatives | Ischemic, hemorrhagic, and subarachnoid hemorrhage | 28/28 | CAM-ICU, RASS | Ramelteon improves RASS ($p = 0.013$) |
| Sandberg (2001) [72] | Int | CPAP: 78 ± 6 Controls: 77 ± 8 | 31 | 28 | Geriatric Stroke Rehab | Depressive symptoms, ADL, cognitive functions, and DLR incidence | Cardiorespiratory polygraphy | nCPAP for 4 weeks | Ischemic and hemorrhagic | Baseline: nCPAP—22/31 and Control—24/28 Day 28: nCPAP—15% and Control—19% | DSM-IV | nCPAP not effective ($p = 0.881$) |
| Sandberg (2001) [73] | Obs | Total: 77 ± 8 | 133 | 0 | Geriatric Stroke Rehab | Depressive symptoms, ADL, cognitive functions, and DLR incidence | Cardiorespiratory polygraphy | Not performed | Ischemic and hemorrhagic | Sleep apnea: 58/78 Not Sleep apnea: 30/55 | DSM-IV, OBS | Sleep apnea ($p = 0.018$) and apnea-related desaturation (OR 12.1, CI 3.0–48.5) |

Abbreviations: ADL, activity of daily living; CAM-ICU, Cognitive Assessment Method-Intensive Care Unit; CI, confidence interval; Ctl, controls; DLR, delirium; DLR+, patients with delirium; DLR−, patients without delirium; DOS, Delirium Observation Screening; DRS-R98, Delirium Rating Scale-Revised 98; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders IV Edition; DSM-V, Diagnostic and Statistical Manual of Mental Disorders V Edition; GABAR-A, Gamma aminobutyric acid receptor agonist; ICDSC, Intensive Care Delirium Screening Checklist; ICU, Intensive Care Unit; Int, interventional; nCPAP, nasal Continuous Positive Airway Pressure; NICU, Neuro Intensive Care Unit; OBS, Organic Brain Syndrome Scale; Obs, observational; OR, odds ratio; Pt, patients; RASS, Richmond Agitation Sedation Scale; SAH, subarachnoid hemorrhage; SU, stroke unit. * These studies did not provide any statistical data for the outcome measured. † The actual study cohort, included in the matched comparisons, represents a subgroup of the total study cohort.

The number of patients included ranged from 18 [65] to 573 patients [17]. The mean age of the enrolled patients ranged from 54 (34–88) [68] to 81 (64–94) [65]. The following tools for delirium detection were used: the Cognitive Assessment Method-Intensive Care Unit (CAM-ICU) [67,68,70,71,75], the Intensive Care Delirium Screening Checklist (ICDSC) [16,17,66,69,71], the Delirium Rating Scale-Revised 98 (DRS-R98) [63–65], and the Delirium Observation Screening (DOS) [74]. In some of the studies, diagnosis was established according to the Diagnostic and Statistical Manual of Mental Disorders criteria for delirium [63,64,71–73].

Most of the studies evaluated the incidence of delirium as the primary or secondary outcome [16,17,63,64,66–68,71–75], whereas two studies evaluated the severity of delirium as the primary outcome [65,70]. The incidence of delirium ranged from 8.3% [63] to 78% [72].

Concerning sleep assessment, none of the reviewed studies performed an instrumental evaluation of sleep by means of polysomnography. Two studies objectively assessed sleep apnea by means of cardiorespiratory polygraphy [72,73]. The study by Sandberg et al. evaluated the effectiveness of nasal-CPAP by means of nocturnal finger-oximetry, and assessed compliance with treatment, as well as sleep duration, from the pressure-sensitive bed recordings [72]. In most of the studies, sleep evaluation was based on the medical records or nurse observations [63,64,67,70,73], or from a patient-subjective point of view [63,64,67]. In three studies the method for sleep evaluation was not specified [16,69,74]; the study by Mengel et al. did not provide any sleep measure [17].

Sleep interventions were heterogeneous across the studies. A multicomponent intervention, which included sleep-related items, was performed by Song et al. [74]. Nakamizo et al. [16] and McLaughlin et al. [68] evaluated sleep disruption in terms of frequent night-time care. A pharmacological intervention was the most common strategy, with various drugs acting on sleep and circadian rhythms [17,63–65,67,70]. A four-week treatment with nasal CPAP was performed by Sandberg et al. [72]. Four studies did not perform any type of sleep intervention [66,71,73,75].

### 3.3. Study Quality Assessment

The EPHPP scores for each selected study are detailed in Figure 2 (upper panel). Following the EPHPP quality criteria, four studies received a strong rating [17,63,64,72], eight studies a moderate rating [16,66,67,69,71,73–75], and three studies a weak rating [65,68,70]. The main weakness of the studies included in this systematic review was the presence of a selection bias in the collection of the study sample; in fact, none of the studies showed a strong score in this component. A proper study design was observed only in five studies. Other frequently observed weaknesses of the selected studies included the lack of blinding of delirium assessors or patients (13 studies) and the lack of controls for possible confounders (5 studies).

On the other hand, most of the papers showed a satisfactory data collection method and a low number of withdrawals and drop-outs.

The global score for each component of all the studies included in this systematic review is shown in Figure 2 (lower panel).

### 3.4. Outcome Measures

The main endpoint of the current study was to systematically review the existing literature focused on the role of sleep modifications in triggering or improving stroke-related delirium. A total of six studies evaluated sleep modifications as predictive factors of delirium occurrence in acute stroke [66,68,69,71,73,75]. Notably, these studies present a high heterogeneity for what concerns the "measure" of sleep.

Wang et al. reported that sleep deprivation is an independent predictor of delirium in patients with acute cerebrovascular diseases (OR: 8.03) [75]. Reznik et al. reported that sleep–wake disturbance, rather than being a risk factor, is a prominent characteristic of delirious patients with intracerebral hemorrhage [71]. Two reports observed that sleep disruption as result of frequent nocturnal care may result in a higher incidence of delirium [68,69].

On the other hand, Hosoya et al. observed that "somnolence" after a stroke is a predictor of delirium [66]. However, in all these reports a formal assessment of sleep was missing; therefore, the definitions of "sleep deprivation" and "somnolence" remain unclear.
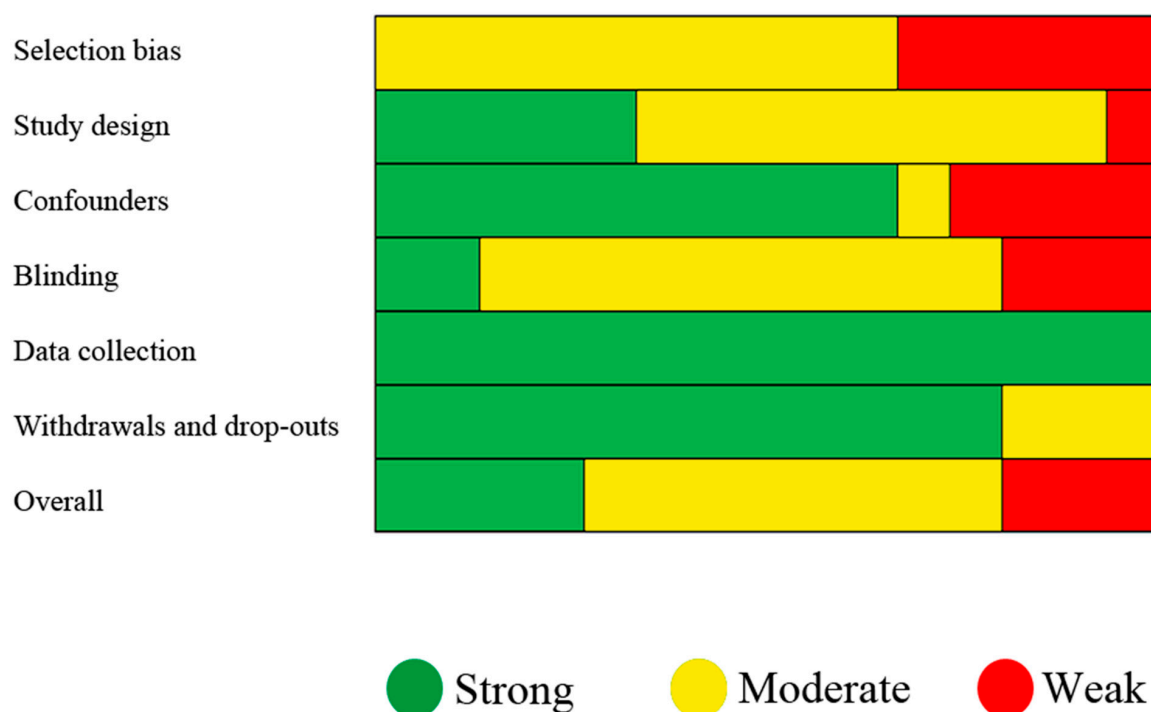


**Figure 2.** Upper panel: EPHPP assessment of risk of bias of the studies included in this systematic review. Lower panel: global ratings of the different components, according to the EPHPP assessment of risk of bias. Green color indicates strong rating, yellow color moderate rating, and red color weak rating.

A specific sleep disorder (e.g., SDB) has been investigated by Sandberg et al. [72,73]. The authors observed that sleep apneas (defined as an Apnea-Hypopnea Index $\geq$ 10 events/h) are a risk factor for delirium. Remarkably, these are the only research studies in which an instrumental evaluation of sleep was performed. However, the sleep study was limited to a cardio-respiratory polygraphy; therefore, in this case as well, any information regarding the sleep–wake cycle or sleep architecture is missing.

Two studies have highlighted that a history of sleep disturbances prior to stroke (e.g., insomnia, irregular nocturnal lifestyle, and the use of sleep medications) is a risk factor for delirium in the acute stroke phase [66,69]. In the study from Song et al., such an association remains controversial [74].

The secondary endpoint of the current review was to evaluate whether sleep interventions could reduce the impact of delirium in acute stroke. A total of eight studies evaluated sleep interventions to prevent or treat delirium in acute stroke [17,63–65,67,70,72,74]. We observed that the proposed interventions differed significantly: in particular, sleep management included the use of exogenous circadian rhythm synchronizers [17,64,67,70], sleep medications [63,67,70], naloxone [65], a multicomponent intervention including sleep hygiene measures [74], and nasal CPAP [72]. Conversely, the studies by Nakamizo et al. [16,69] and McLaughlin et al. [68] evaluated the role of iatrogenic sleep disruption induced by frequent night-time care in delirium precipitation.

Concerning the use of exogenous circadian rhythm synchronizers, melatonin and ramelteon, a selective melatonin receptors agonist, have been tested for stroke-related delirium prevention and treatment. In the DREAMS study, prophylactic treatment with melatonin at 2 mg nightly started upon admission was shown to reduce the incidence of delirium in patients with acute ischemic stroke (OR: 0.60), while no significant effect on its duration was observed [17]. Also, a nightly administration of 8 mg ramelteon was effective, compared to placebo, in delirium prevention (OR: 0.07) in a small cohort of acute patients, regardless of significant modifications to subjective sleep parameters [64]. Moreover, ramelteon showed a higher efficacy as compared to other sedative drugs for reducing the clinical severity of delirium in elderly patients with acute stroke and concomitant insomnia [70].

Suvorexant, a selective orexin receptor antagonist, was tested by Hatta et al. in an elderly population of acute patients at a daily dose of 15 mg on three consecutive evenings, starting upon admission; the percentage of acute stroke patients in this cohort was 31% [63]. No patients developed delirium in the study group (0/36) compared to a prevalence of delirium of 17% (6/36) in the placebo group, thus suggesting a potential role for suvorexant in delirium prevention [63]. In a subsequent retrospective study, suvorexant, in addition to ramelteon, improved subjective sleep quality and reduced the incidence of delirium in comparison to GABAR agonists [67].

Similarly, sleep hygiene measures (i.e., reducing night-time care, avoiding daytime naps, and applying earplugs and eyepatches) alone [16], or in the context of a multicomponent intervention [74], may be protective regarding delirium incidence and severity.

On the other hand, the treatment of sleep apnea with nasal-CPAP is effective for improving the depressive symptoms of patients with acute stroke, but does not reduce the incidence of delirium in this population [72]. Rather, delirium per se reduces compliance to ventilatory support in patients with acute stroke [72].

## 4. Discussion

The purpose of this study was to review the effect of sleep modifications on the occurrence of delirium in acute stroke patients ("stroke-related delirium"). In this systematic review, we identified 15 studies.

The evidence from these studies suggests that sleep disruption is a precipitating factor for the occurrence of delirium. However, this evidence should be considered weak. According to the EPHPP scores, only 4 of the studies included could be evaluated as strong, whereas the remaining 11 were considered to be of moderate or weak quality. The main

flaw was the lack of standardized tools for the evaluation of sleep: only the studies by Sandberg et al. [72,73] performed an instrumental evaluation of sleep, but it consisted of cardio-respiratory monitoring for sleep apnea. Thus, no study provided information based on direct measures of sleep architecture. Finally, only in the studies by Hatta et al. [63] and Sandberg et al. [72] were the evaluators blinded with respect to the study measures and outcome.

The studies were highly inconsistent with regards to the criteria used for the definition of sleep disruption, the availability of objective sleep measures and the tools used to assess sleep, the types of stroke, the time interval from stroke to evaluation of delirium, and the tools used to assess delirium. In particular, most of the studies did not use validated sleep measures, and only two studies used objective measures. A further element of inconsistency are the settings of the studies: only seven were performed in a stroke unit.

Importantly, none of the studies properly investigated the complex interaction between delirium and sleep. An unsolved issue is the disentanglement of the interrelation between delirium and sleep. In fact, sleep disturbances cannot only precipitate delirium, but delirium, once present, can itself be associated with disruption of the sleep–wake cycle [6]. Thus, it should be taken into the account that sleep disorders may also be an early sign of delirium, and not the trigger [61]. A bidirectional relationship between sleep and delirium has been proposed. Sleep deprivation affects various areas of the brain, including key brain areas involved in delirium, such as the pre-frontal cortex, thalamus, and posterior parietal cortex [76]. From a molecular point of view, a potential link between sleep disturbances and the pathogenesis of delirium may exist in the Ascending Reticular Activating System (ARAS), a neuronal network located in the brainstem responsible for the arousal response. A hypothesized pathway for delirium involves dysfunction in the ARAS system, resulting in a depletion of acetylcholinergic projections and excessive dopaminergic production, which causes disturbances in alertness and attention [77]. Delirium may be the consequence of the failure of the arousal system to sustain full wakefulness. In this view, delirium can be interpreted as a sleep–wake state dissociation [78].

Aside from acetylcholine depletion and dopamine, another molecular link between delirium and sleep can be found in tryptophan, a precursor of serotonin and melatonin. Serotoninergic pathways from dorsal raphe nuclei play a central role in the maintenance of wakefulness and REM sleep suppression. Recent evidence points towards a protective role of selective serotonin reuptake inhibitors (SSRI) in ICU-related delirium [79]. Melatonin is the major regulator of circadian rhythm and, in the hospital setting, circadian misalignment is a recognized precipitating factor for delirium; moreover, the reduction of plasmatic levels of melatonin was associated with post-operative delirium [80].

The secondary aim of our study was to assess the effect of sleep interventions on the incidence of delirium in acute stroke. Current available data from the literature suggest that sleep interventions may reduce the incidence of delirium in patients with acute stroke. Also, this evidence should be considered weak. Only four such studies were available in the literature [16,17,72,74]; other studies performed sleep interventions and measured the outcome as 'delirium', but either no data were available concerning the number of enrolled patients with stroke [63,64], or an untreated control group was not enrolled [65,67,70]. The results comes from a few studies [16,17,72,74], only two of which were rated as strong according to the EPHPP scores (see Figure 2); nevertheless, the interventions were highly dissimilar: only one used a pharmacological treatment, whereas in the case of Nakamizo, the intervention consisted of reducing night-time care. None of the interventional studies adopted objective or validated sleep measures, and the evaluators were not blinded with respect to the endpoints, study measures, or outcome. It is not possible to establish a direct correlation between the changes in sleep patterns resulting from the sleep-aimed intervention and the occurrence of delirium, due to insufficient sleep measurements both prior to and after the intervention. However, to date, the limited evidence coming from the existing literature suggests that a combined pharmacological (exogenous circadian rhythms synchronizers, sleep promoting medications) and non-pharmacological approach

(avoidance of iatrogenic sleep disruption, adoption of multicomponent sleep promoting interventions) should be considered in stroke units to prevent or treat delirium.

Overall, our findings suggest that sleep disruption is a possible risk factor, or a trigger factor, in the development of delirium in acute stroke patients (stroke-related delirium). Even when the sleep disorder (such as insomnia, use of sleeping pills, or circadian misalignment) was pre-existent to the cerebrovascular event, it appeared to be associated with delirium development in the acute phase of stroke. Indeed, acute medical illness and hospitalization are known to exacerbate or worsen a pre-existing sleep disturbance, thus having a role in delirium predisposition or precipitation.

We believe that this grade of evidence is sufficient to justify the adoption of measures aimed at improving sleep, or at avoiding sleep disruption, in acute stroke. As concerns the specific sleep interventions used in the literature, no definite evidence is available on their efficacy, and no evidence-based recommendations on their use can be made.

Sleep disruption in an ICU setting and its relationship with delirium is a widely explored issue, whereas little evidence is available in stroke units' settings, due to their recent development.

Future studies should consider the weaknesses that have emerged from this systematic review. In particular, randomized, controlled clinical trials are necessary to assess the effectiveness of sleep interventions and to establish evidence-based recommendations for delirium prevention and treatment in stroke units. Moreover, future studies should adopt validated sleep measures (i.e., polysomnography) to clarify whether sleep disruptions and sleep modifications promote delirium, and to identify specific sleep patterns that could be considered as predictors of delirium, in order to identify those patients that would benefit from preventive sleep therapy. Ideally, sleep should be assessed prospectively before and after delirium onset to demonstrate its association with stroke-related delirium and its pathogenic role. Finally, it should be kept in mind that sleep disruption may also be an initial sign of delirium and not the trigger [61]. The challenge of disentangling this interrelation requires thoroughly designed prospective studies with sensitive delirium and sleep primary outcomes.

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## Abbreviations

| | |
|---|---|
| CAM-ICU | Cognitive Assessment Method-Intensive Care Unit |
| DOS | Delirium Observation Screening |
| DRS-R98 | Delirium Rating Scale-Revised 98 |
| DSM-IV | Diagnostic and Statistical Manual of Mental Disorders IV Edition |
| DSM-V | Diagnostic and Statistical Manual of Mental Disorders V Edition |
| EPHPP | Effective Public Healthcare Practice Project |

| GABAR-A | Gamma aminobutyric acid receptor agonist |
| ICDSC | Intensive Care Delirium Screening Checklist |
| ICU | Intensive Care Unit |
| nCPAP | nasal Continuous Positive Airway Pressure |
| NICU | Neuro Intensive Care Unit |
| OBS | Organic Brain Syndrome Scale |
| PICO | Population, Intervention, Comparison, Outcome |
| PRISMA | Preferred Reporting Items for Systematic reviews and Meta-Analyses |
| RASS | Richmond Agitation Sedation Scale |
| SDB | Sleep-disordered breathing |
| SU | Stroke unit |

## References

1. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*, 5th ed.; American Psychiatric Association: Washington, DC, USA, 2013.
2. Shaw, R.C.; Walker, G.; Elliott, E.; Quinn, T.J. Occurrence Rate of Delirium in Acute Stroke Settings: Systematic Review and Meta-Analysis. *Stroke* **2019**, *50*, 3028–3036. [CrossRef]
3. Pasińska, P.; Wilk, A.; Kowalska, K.; Szyper-Maciejowska, A.; Klimkowicz-Mrowiec, A. The long-term prognosis of patients with delirium in the acute phase of stroke: PRospective Observational POLIsh Study (PROPOLIS). *J. Neurol.* **2019**, *266*, 2710–2717. [CrossRef]
4. Rollo, E.; Brunetti, V.; Scala, I.; Callea, A.; Marotta, J.; Vollono, C.; Frisullo, G.; Broccolini, A.; Calabresi, P.; Della Marca, G. Impact of delirium on the outcome of stroke: A prospective, observational, cohort study. *J. Neurol.* **2022**, *in press*. [CrossRef]
5. Oldenbeuving, A.W.; de Kort, P.L.M.; Jansen, B.P.W.; Algra, A.; Kappelle, L.J.; Roks, G. Delirium in the acute phase after stroke: Incidence, risk factors, and outcome. *Neurology* **2011**, *76*, 993–999. [CrossRef]
6. Inouye, S.K.; Westendorp, R.G.; Saczynski, J.S. Delirium in elderly people. *Lancet* **2014**, *383*, 911–922. [CrossRef]
7. Telias, I.; Wilcox, M.E. Sleep and Circadian Rhythm in Critical Illness. *Crit. Care.* **2019**, *23*, 82. [CrossRef]
8. Lu, Y.; Li, Y.W.; Wang, L.; Lydic, R.; Baghdoyan, H.A.; Shi, X.Y.; Zhang, H. Promoting sleep and circadian health may prevent postoperative delirium: A systematic review and meta-analysis of randomized clinical trials. *Sleep Med. Rev.* **2019**, *48*, 101207. [CrossRef]
9. Weinhouse, G.L.; Schwab, R.J.; Watson, P.L.; Patil, N.; Vaccaro, B.; Pandharipande, P.; Ely, E.W. Bench-to-bedside review: Delirium in ICU patients—Importance of sleep deprivation. *Crit. Care* **2009**, *13*, 234. [CrossRef]
10. Brunetti, V.; Rollo, E.; Broccolini, A.; Frisullo, G.; Scala, I.; Della Marca, G. Sleep and Stroke: Opening Our Eyes to Current Knowledge of a Key Relationship. *Curr. Neurol. Neurosci. Rep.* **2022**, *22*, 767–779. [CrossRef]
11. Jaramillo, V.; Jendoubi, J.; Maric, A.; Mensen, A.; Heyse, N.C.; Eberhard-Moscicka, A.K.; Wiest, R.; Bassetti, C.L.A.; Huber, R. Thalamic Influence on Slow Wave Slope Renormalization during Sleep. *Ann. Neurol.* **2021**, *90*, 821–833. [CrossRef]
12. Gottlieb, E.; Landau, E.; Baxter, H.; Werden, E.; Howard, M.E.; Brodtmann, A. The bidirectional impact of sleep and circadian rhythm dysfunction in human ischaemic stroke: A systematic review. *Sleep Med. Rev.* **2019**, *45*, 54–69. [CrossRef]
13. Johnson, K.G.; Johnson, D.C. Frequency of Sleep Apnea in Stroke and TIA Patients: A Meta-analysis. *J. Clin. Sleep Med.* **2010**, *6*, 131–137. [CrossRef]
14. Hasan, F.; Gordon, C.; Wu, D.; Huang, H.C.; Yuliana, L.T.; Susatia, B.; Marta, O.F.D.; Chiu, H.Y. Dynamic Prevalence of Sleep Disorders Following Stroke or Transient Ischemic Attack: Systematic Review and Meta-Analysis. *Stroke* **2021**, *52*, 655–663. [CrossRef]
15. Bassetti, C.L.; Hermann, D.M. Sleep and stroke. *Handb. Clin. Neurol.* **2011**, *99*, 1051–1072.
16. Nakamizo, T.; Kanda, T.; Kudo, Y.; Sugawara, E.; Hashimoto, E.; Okazaki, A.; Usuda, M.; Nagai, T.; Hara, H.; Johkura, K. Effects of uncomfortable care and histamine H2-antagonists on delirium in acute stroke: A propensity score analysis. *J. Neurol. Sci.* **2020**, *420*, 117251. [CrossRef]
17. Mengel, A.; Zurloh, J.; Boßelmann, C.; Brendel, B.; Stadler, V.; Sartor-Pfeiffer, J.; Meisel, A.; Fleischmann, R.; Ziemann, U.; Poli, S.; et al. Delirium REduction after administration of melatonin in acute ischemic stroke (DREAMS): A propensity score–matched analysis. *Eur. J. Neurol.* **2021**, *28*, 1958–1966. [CrossRef]
18. Page, M.J.; Moher, D.; Bossuyt, P.M.; Boutron, I.; Hoffmann, T.C.; Mulrow, C.D.; Shamseer, L.; Tetzlaff, J.M.; Akl, E.A.; Brennan, S.E.; et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *BMJ* **2021**, *372*, n71. [CrossRef]
19. Thomas, B.H.; Ciliska, D.; Dobbins, M.; Micucci, S. A process for systematically reviewing the literature: Providing the research evidence for public health nursing interventions. *Worldviews Evid Based Nurs.* **2004**, *1*, 176–184. [CrossRef]
20. Aaronson, J.A.; van Bennekom, C.A.; Hofman, W.F.; van Bezeij, T.; Aardweg, J.G.v.D.; Groet, E.; Kylstra, W.A.; Schmand, B. Obstructive Sleep Apnea is Related to Impaired Cognitive and Functional Status after Stroke. *Sleep* **2015**, *38*, 1431–1437. [CrossRef] [PubMed]
21. Alverzo, J.P. Predictors of disorientation among brain injury and stroke patients during rehabilitation. *Rehabil. Nurs.* **2005**, *30*, 230–238. [CrossRef]

22. Bakken, L.N.; Kim, H.S.; Finset, A.; Lerdal, A. Stroke patients' functions in personal activities of daily living in relation to sleep and socio-demographic and clinical variables in the acute phase after first-time stroke and at six months of follow-up. *J. Clin. Nurs.* **2012**, *21*, 1886–1895. [CrossRef]

23. Sangiorgi, G.B.; Barbagallo, M.; Giordano, M.; Meli, M.; Panzarasa, R. alpha-Glycerophosphocholine in the mental recovery of cerebral ischemic attacks. An Italian multicenter clinical trial. *Ann. N. Y. Acad. Sci.* **1994**, *717*, 253–269. [CrossRef]

24. Buijck, B.I.; Zuidema, S.U.; Spruit-van Eijk, M.; Geurts, A.C.; Koopmans, R.T. Neuropsychiatric symptoms in geriatric patients admitted to skilled nursing facilities in nursing homes for rehabilitation after stroke: A longitudinal multicenter study. *Int. J. Geriatr. Psychiatry* **2012**, *27*, 734–741. [CrossRef] [PubMed]

25. Castellanos-Pinedo, F.; Hernández-Pérez, J.M.; Zurdo, M.; Rodríguez-Fúnez, B.; Hernández-Bayo, J.M.; García-Fernández, C.; Cueli-Rincón, B.; Castro-Posada, J.A. Influence of premorbid psychopathology and lesion location on affective and behavioral disorders after ischemic stroke. *J. Neuropsychiatry Clin. Neurosci.* **2011**, *23*, 340–347. [CrossRef] [PubMed]

26. Gong, W.; Zhang, S.; Li, X.; Shi, L. Dexmedetomidine is superior to midazolam for sedation and cerebral protection in postoperative hypertensive intracerebral hemorrhage patients: A retrospective study. *J. Int. Med. Res.* **2020**, *48*, 300060520957554. [CrossRef] [PubMed]

27. Harris, A.L.; Elder, J.; Schiff, N.D.; Victor, J.D.; Goldfine, A.M. Post-Stroke Apathy and Hypersomnia Lead to Worse Outcomes from Acute Rehabilitation. *Transl. Stroke Res.* **2014**, *5*, 292–300. [CrossRef] [PubMed]

28. Hermann, D.M.; Siccoli, M.; Brugger, P.; Wachter, K.; Mathis, J.; Achermann, P.; Bassetti, C.L. Evolution of Neurological, Neuropsychological and Sleep-Wake Disturbances after Paramedian Thalamic Stroke. *Stroke* **2008**, *39*, 62–68. [CrossRef]

29. Jacquin, A.; Binquet, C.; Rouaud, O.; Graule-Petot, A.; Daubail, B.; Osseby, G.-V.; Bonithon-Kopp, C.; Giroud, M.; Béjot, Y. Post-Stroke Cognitive Impairment: High Prevalence and Determining Factors in a Cohort of Mild Stroke. *J. Alzheimers Dis.* **2014**, *40*, 1029–1038. [CrossRef]

30. Johnson, M.L.; Roberts, M.D.; Ross, A.R.; Witten, C.M. Methylphenidate in stroke patients with depression. *Am. J. Phys. Med. Rehabil.* **1992**, *71*, 239–241. [CrossRef]

31. Li, J.; You, S.-J.; Xu, Y.-N.; Yuan, W.; Shen, Y.; Huang, J.-Y.; Xiong, K.-P.; Liu, C.-F. Cognitive impairment and sleep disturbances after minor ischemic stroke. *Sleep Breath.* **2018**, *23*, 455–462. [CrossRef]

32. Ma, G.; Sun, L.; Qie, Z.; He, J.; Cui, F. Factors Associated with Benzodiazepines Prolonged-Term Use in Post-Stroke Subjective Sleep Disturbance: A Single-Centre Retrospective Study from China. *Drug Des. Dev. Ther.* **2021**, *15*, 2469–2481. [CrossRef] [PubMed]

33. Malik, P.R.A.; Muir, R.T.; Black, S.E.; Gao, F.; Swartz, R.H.; Murray, B.J.; Boulos, M.I. Subcortical Brain Involvement Is Associated with Impaired Performance on the Psychomotor Vigilance Task after Minor Stroke. *Neurorehabilit. Neural Repair* **2018**, *32*, 999–1007. [CrossRef] [PubMed]

34. Nakase, T.; Tobisawa, M.; Sasaki, M.; Suzuki, A. Outstanding Symptoms of Poststroke Depression during the Acute Phase of Stroke. *PLoS ONE* **2016**, *11*, e0163038. [CrossRef] [PubMed]

35. Pearce, S.C.; Stolwyk, R.J.; New, P.W.; Anderson, C. Sleep disturbance and deficits of sustained attention following stroke. *J. Clin. Exp. Neuropsychol.* **2016**, *38*, 1–11. [CrossRef] [PubMed]

36. Ryan, C.M.; Bayley, M.; Green, R.; Murray, B.J.; Bradley, T.D. Influence of Continuous Positive Airway Pressure on Outcomes of Rehabilitation in Stroke Patients with Obstructive Sleep Apnea. *Stroke* **2011**, *42*, 1062–1067. [CrossRef]

37. Siccoli, M.M.; Rölli-Baumeler, N.; Achermann, P.; Bassetti, C.L. Correlation between sleep and cognitive functions after hemispheric ischaemic stroke. *Eur. J. Neurol.* **2008**, *15*, 565–572. [CrossRef]

38. Trewin, V.F.; Lawrence, C.J.; Veitch, G.B.A. An investigation of the association of benzodiazepines and other hypnotics with the incidence of falls in the elderly. *J. Clin. Pharm. Ther.* **1992**, *17*, 129–133. [CrossRef]

39. van Almenkerk, S.; Depla, M.F.; Smalbrugge, M.; Eefsting, J.A.; Hertogh, C.M. Institutionalized Stroke Patients: Status of Functioning of an Under Researched Population. *J. Am. Med. Dir. Assoc.* **2012**, *13*, 634–639. [CrossRef]

40. Matsuzono, K.; Mashiko, T.; Ozawa, T.; Miura, K.; Suzuki, M.; Furuya, K.; Ozawa, M.; Anan, Y.; Shimazaki, H.; Koide, R.; et al. Management Effort for Delirium and Insomnia in Patients with Acute Ischemic Stroke (MEDIAS) Study. *Psychiatry Clin. Neurosci.* **2020**, *74*, 279–280. [CrossRef]

41. Küçükdeveci, A.A.; Tennant, A.; Hardo, P.; Chamberlain, M.A. Sleep problems in stroke patients: Relationship with shoulder pain. *Clin. Rehabil.* **1996**, *10*, 166–172. [CrossRef]

42. Bohlken, J.; Kostev, K. Prevalence and risk factors for delirium diagnosis in patients followed in general practices in Germany. *Int. Psychogeriatry* **2018**, *30*, 511–518. [CrossRef] [PubMed]

43. Burns, A.; Allen, H.; Tomenson, B.; Duignan, D.; Byrne, J. Bright light therapy for agitation in dementia: A randomized controlled trial. *Int. Psychogeriatry* **2009**, *21*, 711–721. [CrossRef] [PubMed]

44. Colombo, R.; Corona, A.; Praga, F.; Minari, C.; Giannotti, C.; Castelli, A.; Raimondi, F. A reorientation strategy for reducing delirium in the critically ill. Results of an interventional study. *Minerva Anestesiol.* **2012**, *78*, 1026–1033.

45. Conn, D.K.; Goldman, Z. Pattern of Use of Antidepressants in Long-Term Care Facilities for the Elderly. *J. Geriatr. Psychiatry Neurol.* **1992**, *5*, 228–232. [CrossRef] [PubMed]

46. Cui, Z.; Cui, L.; Xu, Y.; Pradeep, P.; Li, G. The risk factors of the permanent pacemaker implantation in patients with postoperative delirium. *Int. J. Cardiol.* **2015**, *179*, 214–216. [CrossRef]

47. Dai, H.; Liu, X.; Feng, D.; Li, R.; Shen, H. Evidence-based nursing combined with cognitive function training can reduce the incidence of delirium in ICU patients and improve their cognitive function. *Am. J. Transl. Res.* **2021**, *13*, 3262–3269.

48. Douven, E.; Köhler, S.; Schievink, S.H.; van Oostenbrugge, R.J.; Staals, J.; Verhey, F.R.; Aalten, P. Temporal Associations between Fatigue, Depression, and Apathy after Stroke: Results of the Cognition and Affect after Stroke, a Prospective Evaluation of Risks Study. *Cerebrovasc. Dis.* **2017**, *44*, 330–337. [CrossRef]

49. Foroughan, M.; Delbari, A.; Said, S.E.; AkbariKamrani, A.A.; Rashedi, V.; Zandi, T. Risk factors and clinical aspects of delirium in elderly hospitalized patients in Iran. *Aging Clin. Exp. Res.* **2016**, *28*, 313–319. [CrossRef]

50. Harris, Y.; Gorelick, P.B.; Cohen, D.; Dollear, W.; Forman, H.; Freels, S. Psychiatric symptoms in dementia associated with stroke: A case-control analysis among predominantly African-American patients. *J. Natl. Med. Assoc.* **1994**, *86*, 697–702.

51. Kim, H.; Chung, S.; Joo, Y.H.; Lee, J.S. The major risk factors for delirium in a clinical setting. *Neuropsychiatr. Dis. Treat.* **2016**, *12*, 1787–1793.

52. Limpawattana, P.; Panitchote, A.; Tangvoraphonkchai, K.; Suebsoh, N.; Eamma, W.; Chanthonglarng, B.; Tiamkao, S. Delirium in critical care: A study of incidence, prevalence, and associated factors in the tertiary care hospital of older Thai adults. *Aging Ment. Health* **2016**, *20*, 74–80. [CrossRef]

53. Mirski, M.A.; Lewin, J.J., 3rd; LeDroux, S.; Thompson, C.; Murakami, P.; Zink, E.K.; Griswold, M. Cognitive improvement during continuous sedation in critically ill, awake and responsive patients: The Acute Neurological ICU Sedation Trial (ANIST). *Intensive Care Med.* **2010**, *36*, 1505–1513. [CrossRef] [PubMed]

54. Needham, D.M.; Korupolu, R. Rehabilitation Quality Improvement in an Intensive Care Unit Setting: Implementation of a Quality Improvement Model. *Top. Stroke Rehabil.* **2010**, *17*, 271–281. [CrossRef] [PubMed]

55. Owusu, K.A.; Kurczewski, L.; Armahizer, M.J.; Zichichi, A.; Maciel, C.B.; Heavner, M.S. DEXmedetomidine compared to PROpofol in NEurocritical Care [DEXPRONE]: A multicenter retrospective evaluation of clinical utility and safety. *J. Crit. Care* **2020**, *60*, 79–83. [CrossRef]

56. Rollo, E.; Callea, A.; Brunetti, V.; Vollono, C.; Marotta, J.; Della Marca, G. Physical restraint precipitates delirium in stroke patients. *J. Neurol. Sci.* **2021**, *421*, 117290. [CrossRef]

57. Su, C.-C.; Yang, Y.-H.K.; Lai, E.C.-C.; Hsieh, C.-Y.; Cheng, C.-L.; Chen, C.-H.; Lin, H.-J.; Sung, S.-F.; Chen, Y.-W. Comparative safety of antipsychotic medications in elderly stroke survivors: A nationwide claim data and stroke registry linkage cohort study. *J. Psychiatr. Res.* **2021**, *139*, 159–166. [CrossRef] [PubMed]

58. Tachibana, M.; Inada, T.; Ichida, M.; Ozaki, N. Risk factors for inducing violence in patients with delirium. *Brain Behav.* **2021**, *11*, e2276. [CrossRef]

59. Tutuarima, J.; van der Meulen, J.; de Haan, R.; van Straten, A.; Limburg, M. Risk Factors for Falls of Hospitalized Stroke Patients. *Stroke* **1997**, *28*, 297–301. [CrossRef]

60. Weiss, B.; Paul, N.; Spies, C.D.; Ullrich, D.; Ansorge, I.; Salih, F.; Wolf, S.; Luetz, A. Influence of Patient-Specific Covariates on Test Validity of Two Delirium Screening Instruments in Neurocritical Care Patients (DEMON-ICU). *Neurocrit. Care* **2021**, *36*, 452–462. [CrossRef]

61. Nydahl, P.; Baumgarte, F.; Berg, D.; Bergjan, M.; Borzikowsky, C.; Franke, C.; Green, D.; Hannig, A.; Hansen, H.C.; Hauss, A.; et al. Delirium on stroke units: A prospective, multicentric quality-improvement project. *J. Neurol.* **2022**, *269*, 3735–3744. [CrossRef]

62. Azimaraghi, O.; Hammer, M.; Santer, P.; Platzbecker, K.; Althoff, F.C.; Patrocinio, M.; Grabitz, S.D.; Wongtangman, K.; Rumyantsev, S.; Xu, X.; et al. Study protocol for a randomised controlled trial evaluating the effects of the orexin receptor antagonist suvorexant on sleep architecture and delirium in the intensive care unit. *BMJ Open* **2020**, *10*, e038474. [CrossRef] [PubMed]

63. Hatta, K.; Kishi, Y.; Wada, K.; Takeuchi, T.; Ito, S.; Kurata, A.; Murakami, K.; Sugita, M.; Usui, C.; Nakamura, H. Preventive Effects of Suvorexant on Delirium: A Randomized Placebo-Controlled Trial. *J. Clin. Psychiatry* **2017**, *78*, e970–e979. [CrossRef] [PubMed]

64. Hatta, K.; Kishi, Y.; Wada, K.; Takeuchi, T.; Ito, S.; Kurata, A.; Murakami, K.; Sugita, M.; Usui, C.; Nakamura, H. Preventive effects of ramelteon on delirium: A randomized placebo-controlled trial. *JAMA Psychiatry* **2014**, *71*, 397–403. [CrossRef] [PubMed]

65. Duan, X.; Li, C.-Y.; Qiu, B.; Ma, G.-Y. Naloxone Treatment for Poststroke Agitated Delirium in Hospitalized Older Adults: A Pilot Study. *J. Am. Geriatr. Soc.* **2016**, *64*, 663–665. [CrossRef] [PubMed]

66. Hosoya, R.; Sato, Y.; Ishida, E.; Shibamoto, H.; Hino, S.; Yokote, H.; Kamata, T. Association between Delirium and Prehospitalization Medication in Poststroke Patients. *J. Stroke Cerebrovasc. Dis.* **2018**, *27*, 1914–1920. [CrossRef]

67. Kawada, K.; Ohta, T.; Tanaka, K.; Miyamura, M.; Tanaka, S. Addition of Suvorexant to Ramelteon Therapy for Improved Sleep Quality with Reduced Delirium Risk in Acute Stroke Patients. *J. Stroke Cerebrovasc. Dis.* **2019**, *28*, 142–148. [CrossRef]

68. McLaughlin, D.C.; Hartjes, T.M.; Freeman, W.D. Sleep Deprivation in Neurointensive Care Unit Patients from Serial Neurological Checks: How Much Is Too Much? *J. Neurosci. Nurs.* **2018**, *50*, 205–210. [CrossRef]

69. Nakamizo, T.; Kanda, T.; Kudo, Y.; Sugawara, E.; Hashimoto, E.; Okazaki, A.; Usuda, M.; Nagai, T.; Hara, H.; Johkura, K. Development of a clinical score, PANDA, to predict delirium in stroke care unit. *J. Neurol. Sci.* **2020**, *415*, 116956. [CrossRef]

70. Ohta, T.; Murao, K.; Miyake, K.; Takemoto, K. Melatonin Receptor Agonists for Treating Delirium in Elderly Patients with Acute Stroke. *J. Stroke Cerebrovasc. Dis.* **2013**, *22*, 1107–1110. [CrossRef]

71. Reznik, M.E.; Drake, J.; Margolis, S.A.; Moody, S.; Murray, K.; Costa, S.; Mahta, A.; Wendell, L.C.; Thompson, B.B.; Rao, S.S.; et al. Deconstructing Poststroke Delirium in a Prospective Cohort of Patients with Intracerebral Hemorrhage*. *Crit. Care Med.* **2020**, *48*, 111–118. [CrossRef]

72. Sandberg, O.; Franklin, K.; Bucht, G.; Eriksson, S.; Gustafson, Y. Nasal continuous positive airway pressure in stroke patients with sleep apnoea: A randomized treatment study. *Eur. Respir. J.* **2001**, *18*, 630–634. [CrossRef] [PubMed]

73. Sandberg, O.; Franklin, K.A.; Bucht, G.; Gustafson, Y. Sleep Apnea, Delirium, Depressed Mood, Cognition, and ADL Ability after Stroke. *J. Am. Geriatr. Soc.* **2001**, *49*, 391–397. [CrossRef] [PubMed]

74. Song, J.; Lee, M.; Jung, D. The Effects of Delirium Prevention Guidelines on Elderly Stroke Patients. *Clin. Nurs. Res.* **2018**, *27*, 967–983. [CrossRef] [PubMed]

75. Wang, J.; Ji, Y.; Wang, N.; Chen, W.; Bao, Y.; Qin, Q.; Xiao, Q.; Li, S. Risk factors for the incidence of delirium in cerebrovascular patients in a Neurosurgery Intensive Care Unit: A prospective study. *J. Clin. Nurs.* **2018**, *27*, 407–415. [CrossRef]

76. Thomas, M.; Sing, H.; Belenky, G.; Holcomb, H.; Mayberg, H.; Dannals, R.; Wagner, H., Jr.; Thorne, D.; Popp, K.; Rowland, L.; et al. Neural basis of alertness cognitive performance impairments during sleepiness, I. Effects of 24 h of sleep deprivation on waking human regional brain activity. *J. Sleep Res.* **2000**, *9*, 335–352. [CrossRef]

77. Daou, M.; Telias, I.; Younes, M.; Brochard, L.; Wilcox, M.E. Abnormal Sleep, Circadian Rhythm Disruption, and Delirium in the ICU: Are They Related? *Front. Neurol.* **2020**, *11*, 549908. [CrossRef]

78. Terzaghi, M.; Sartori, I.; Rustioni, V.; Manni, R. Sleep disorders and acute nocturnal delirium in the elderly: A comorbidity not to be overlooked. *Eur. J. Intern. Med.* **2014**, *25*, 350–355. [CrossRef]

79. Austin, C.A.M.; Yi, J.B.; Lin, F.-C.; Pandharipande, P.M.; Ely, E.W.; Busby-Whitehead, J.; Carson, S.S. The Association of Selective Serotonin Reuptake Inhibitors with Delirium in Critically Ill Adults: A Secondary Analysis of the Bringing to Light the Risk Factors and Incidence of Neuropsychologic Dysfunction in ICU Survivors ICU Study. *Crit. Care Explor.* **2022**, *4*, e0740. [CrossRef]

80. Watson, P.L.; Ceriana, P.; Fanfulla, F. Delirium: Is sleep important? *Best Pract. Res. Clin. Anaesthesiol.* **2012**, *26*, 355–366. [CrossRef]