TOPICAL REVIEW

Exposure to light and darkness and its influence on physiological measures of intensive care unit patients—a systematic literature review

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Exposure to light and darkness and its influence on physiological measures of intensive care unit patients—a systematic literature review

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Abstract

Sleep-wake patterns are often significantly disturbed in critically ill patients. This disturbance is closely linked to secondary brain dysfunctions in these patients. Sedation not only impairs sleep quality in ICU patients but also has detrimental effects on short- and long-term outcome. In other contexts, light therapy has been proven to be effective in maintaining and resynchronizing circadian rhythmicity in humans. The objective of this systematic review was to analyse studies that investigated the effect of exposure to light or darkness on physiological measures and clinical outcomes of adult ICU patients. Studies were systematically identified by searching electronic bibliographic databases (The Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library, 2002) and MEDLINE via PubMed). The search algorithm identified a total of 156 articles, 10 of which were taken into final review. These 10 selected articles included 3 were monocentric RCTs, five prospective cohort studies, one retrospective cohort study, and one manuscript that included a partial systematic review of the literature. Included trials were published between 2007 and 2015. Five of these studies used multiple intervention approaches while four trials used a single intervention approach. Among all studies, 1,278 patients were analysed (489 prospectively). There was a high heterogeneity among the studies in terms of applied intervention.
Topical Review

and outcome measures. The most frequent methodological limitations were a lack of precise definitions regarding the illuminance and the light spectrum utilised. The analyses indicate that further studies including clearly defined interventions with objective outcome measures, as these are currently lacking, would add significant knowledge to this new field of research.

Keywords: light, intensive care unit, critical care, sleep, melatonin

Online supplementary data available from stacks.iop.org/PM/37/R73/mmedia

(Some figures may appear in colour only in the online journal)

1. Introduction

ICU patients frequently suffer from organ dysfunctions. The most common manifestation of acute brain dysfunction in the context of critical illness is delirium.

According to the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5), delirium is defined as an acute disturbance in attention, awareness, and cognition, which typically fluctuates during the course of the day (European Delirium Association and American Delirium Society 2014). Delirium is independently associated with a longer ICU and hospital length of stay (LOS) (Luetz et al 2010), a higher incidence of long-term cognitive impairments (Pandharipande et al 2013), and an increased mortality rate (Ely et al 2004). While delirium symptoms typically fluctuate, delirious patients also suffer from disturbances of the circadian system (Figueroa-Ramos et al 2009), and have a severely impaired day-night rhythm.

The circadian rhythm is regulated by the suprachiasmatic nucleus (SCN), which is located in the anterior hypothalamus, and light is the most important external stimulus influencing the circadian rhythmicity. Through the retina, the SCN receives information regarding ambient light, using it to adjust the secretion of melatonin produced by the pineal gland. The association between sleep and plasma melatonin levels has been confirmed in several studies (Nakagawa et al 1992, McArthur et al 1996, Lockley et al 1997, Uchiyama et al 2000). An increase in melatonin secretion is related to a decrease in wakefulness, thus promoting sleep. Conversely, sleep progressively deteriorates during phases of low melatonin production in the circadian cycle. In this context, ICU patients, who have limited exposure to natural light throughout the day are at an increased risk of developing disturbances in circadian rhythmicity and sleep patterns, possibly contributing to the development of delirium.

Surveys on survivors of critical illness revealed that sleeplessness is among the most stressful perceived events during an ICU stay (Novaes et al 1997, Chahraoui et al 2015). In fact, several studies reported significant abnormalities in the sleep architecture of ICU patients, characterized by a decrease or absence of stage 3 and rapid eye movement (REM) sleep phases (Friese et al 2007, Elliott et al 2013). In addition, critically ill patients show disturbances, or even the complete lack, of a circadian melatonin secretion rhythm (Mundigler et al 2002).

Shigeta and colleagues conducted a study on melatonin levels in postoperative patients following major abdominal surgery. They could show that patients with delirium displayed two distinct melatonin patterns: delirious patients who developed no further complications had lower postoperative melatonin levels, whereas levels were markedly increased in delirious patients that suffered additional complications (Shigeta et al 2001). The increased melatonin levels seen in patients with a high severity of illness may explain why a nocturnal
administration of melatonin or melatonin receptor agonists showed inconsistent results in terms of clinical outcome parameters (Ibrahim et al 2006, Bourne et al 2008, Hatta et al 2014).

From other fields, it is known that disruptions in the circadian rhythmicity not only cause sleep disturbances, but can also have profound effects on the function of the immune system (Haimovich et al 2010, Silver et al 2012).

For a long period of time, nocturnal sedation was typically used by clinicians to treat patients with sleeplessness. Recently, several trials showed that nocturnal sedation further impairs sleep architecture (Kondili et al 2012), as well as—depending on the used pharmacological agent—places the patient at an increased risk for delirium (Seymour et al 2012). Studies have shown that there are detrimental effects of sedation on outcome. Early sedation increases the risk of mortality (Shehabi et al 2012) even two years after ICU-admission (Balzer et al 2015). This underlines the need to focus on non-pharmacological measures.

A therapeutically driven, non-pharmacologic approach for maintaining or restoring the endogenous clock could have a positive impact in ICU patients. In this context, ‘steering’ light and darkness seems an interesting intervention, as it likely provides a much better risk-benefit ratio than those used in clinical routine today. These interventions can be implemented in an architectural approach to redesign ICUs (Halpern 2014a, 2014b, 2014c).

However, there is no aggregate evidence on the effectiveness of interventions based on exposure to light and darkness, or their influence on the outcome of ICU patients. Therefore, we conducted a systematic review of the current literature regarding this emerging topic.

2. Methods

2.1. Objective

We conducted a systematic literature review aiming to identify all studies dealing with the effects of light and/or darkness exposure on physical or clinical outcomes measurements in critically ill patients.

2.2. Type of studies, interventions and participants

The search strategy aimed to identify studies involving light exposure as an intervention, either by increasing (e.g. architectural modifications of patient rooms or use of artificial lighting) or decreasing (both, reducing artificial lighting in rooms or providing eye-masks for patients) patient exposure to light, regardless of the time of day, these interventions were undertaken. These could be either single intervention approaches, or a non-pharmacological intervention bundle with a focus on environmental changes. Studies were excluded if the non-pharmacological intervention accompanied a pharmacological intervention. We included studies that were targeted at adult ICU patients in a surgical or medical context, and excluded studies that dealt with infants or neonates. Experimental animal-studies were also excluded.

2.3. Outcome measures

Studies were required to have at least one predefined, patient related outcome. Predefined clinical outcome measures were: mortality (in-hospital-, 30 d-, 60 d-, 90 d-, one-year-, long-term- (>1 year) mortality), morbidity (intensive care unit length of stay, length of mechanical ventilation, lengths of hospitalization, long-term quality of life measurements), ICU sleep evaluations (with either technical or questionnaire based assessments), measurements of activity, measurements of melatonin and cortisol levels, structured interviews, technical light
measurements, incidence and severity of pain, delirium, use of neuroleptics, analgesics, and sedative agents. We primarily targeted the main outcome measure of the study, but accounted for secondary outcome measures if adequately described in the methodology.

2.4. Literature search

Trials were identified by searching electronic bibliographic databases, namely The Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library, 2002) and MEDLINE, via the web-based interface PubMed. No time limit was set. All articles were screened for relevance on the basis of title and abstract.

Our search strategy was designed as follows:

| A. Terms related to light interventions and light-related outcome measures (light, lux, circadian, melatonin, 6-hydroxymelatonin, eye, window, darkness, sleep, illuminance, luminance, cycle) | PLUS |
| B. Terms related to intensive care unit patients (ICU, intensive care unit, critical illness critically ill, intensive care, critical ill) |

The precise search syntax can be found in a supplement to the manuscript stacks.iop.org/PM/37/R73/mmedia.

After several pilot searches comprising four known landmark studies, the final search was performed on October 14th, 2015. After this date, no further studies were included. We searched for cross-references in PubMed in order to identify potentially missing articles.

2.5. Study selection

Two reviewers (BW, AL) independently screened titles and abstracts of the electronic search results manually, so as to check for inclusion and exclusion criteria. After this preliminary selection based on title and abstracts, the reviewers retrieved full-texts. After the full-texts were analyzed, a final decision on inclusion or exclusion of articles was made on the basis of the predefined inclusion and exclusion criteria. The reference lists of all found articles were screened to identify articles missing in the systematic search.

2.6. Data extraction and quality assessment

Data extraction was performed independently by two researchers (BW, AL), whereas discrepancies or disagreements on extracted data were resolved through discussions. The reviewers did not contact the authors of trials. Data extraction included patient characteristics and case number, study type, intervention type, main-outcome measure, and select secondary outcome measures. The pre-selected articles were evaluated according to the critical appraisal worksheets from the Centre for Evidence-Based Medicine of the University of Oxford (CEBM). The Level of Evidence was indicated in accordance to the CEBM for each study on an individual basis.

2.7. Statistical analysis

Aside from the reported statistical details, no additional statistical analysis, especially no meta-analyses, were performed. The reviewers did not review the statistics performed in the identified studies.
3. Results

A total of 156 articles were identified by our search strategy. One additional article was found by a cross-reference check in PubMed, so that a total of 157 articles were screened. The exclusion criteria screening process revealed that 43 abstracts were not related to the topic, 8 articles were not available in the English language, 4 studies were not performed in humans, 30 studies were not performed in adults, 9 studies were not performed in ICU patients, 22 were non-clinical trials, 19 were non-interventional designs, one with an intervention not aimed at light (regardless of the time of day), and one not targeting patient specific outcome. Full texts of 19 from 20 articles were available. Of those, 2 studies were excluded for failure to analyze light as an intervention, 5 due to a focus on noise control, having neither light as an intervention nor an outcome measure that was directly linked to light, and 2 other studies that were not targeted at critically ill patients, but rather healthy volunteers. Ten studies went into the final review (figure 1).

3.1. Study characteristics

Of the 10 identified trials, 5 were prospective cohort studies (Perras et al 2007, Richardson et al 2007, Zaal et al 2013, Patel et al 2014, Engwall et al 2015), 3 were RCTs (Taguchi et al 2007, Le Guen et al 2014, Hu et al 2015b), one was a retrospective cohort study (Wunsch et al 2011),
and one manuscript including a systematic review of literature that partly included studies on infants and neonates (Engwall et al. 2014). Included trials were published between 2007 and 2015. Five studies reported multiple interventions (Richardson et al. 2007, Zaal et al. 2013, Le Guen et al. 2014, Patel et al. 2014, Hu et al. 2015b), while four studies reported single interventions (Perras et al. 2007, Taguchi et al. 2007, Wunsch et al. 2011, Engwall et al. 2015). Among all studies, 1,278 patients were analyzed, 489 of which prospectively, which indicates that the average study size was rather small. Four studies had less than 45 participants, and only 2 studies (Le Guen et al. 2014, Hu et al. 2015b) reported a statistical sample-size calculation. No high quality systematic review on light or illumination was found.

3.2. Level of evidence evaluation

All identified studies were classified as either low quality randomized controlled trials (Oxford LoE 2b), cohort studies (Oxford LoE 2b), case series, cohort studies with quality issues (Oxford LoE 4), or case-reports and expert opinions with a first proof of principle (Oxford LoE 5) (table 1). No study used a single-blinded approach regarding the intervention. Treatment could not be double-blinded due to the nature of intervention.

3.3. Effects of interventions on outcome

3.3.1. Sleep. Five studies investigated the effects of an intervention on sleep quality: 4 studies used nighttime eye-masks as a component of a multi-intervention bundle (Richardson et al. 2007, Le Guen et al. 2014, Patel et al. 2014, Hu et al. 2015b), and 1 study used a 2 h light therapy intervention following patient extubation (Taguchi et al. 2007). Four studies used a questionnaire based assessment of sleep quality. Only 1 study used accelerometry and a memory heart-recorder to assess heart rate variability (HRV) (Taguchi et al. 2007). Le Guen et al. used actigraphy as an additional assessment of sleep quality (Le Guen et al. 2014).

Results obtained by questionnaires revealed a significantly improved sleep quality for patients in the intervention groups. Accelerometry, actigraphy, as well as assessment of HRV revealed no significant differences between intervention and control groups.

3.3.2. Melatonin and cortisol levels. Two studies (Perras et al. 2007, Hu et al. 2015b) measured melatonin-levels. Perras et al. used no control group, but performed a 1 h bright light intervention (>10 000 lux) preceded by 1 h of darkness (<1 lux) in all patients. Hu et al. used a multi-component intervention consisting of 2 × 60 min of relaxing music, accompanied by earplugs and eye-masks, which were distributed before surgery and could be used on the ICU on a voluntary basis. Perras et al. measured plasma melatonin levels every 30 min at 7 time points. Hu et al. measured a melatonin metabolite (6-hydroxymelatonin) in urine samples collected over a 12 h period, as well as cortisol measurements from the same sample.

In the study performed by Perras et al., melatonin showed distinct patterns: three quarters of the study population had low melatonin levels, while one quarter had high melatonin levels. The darkness and bright-light intervention did not change the melatonin levels, and the authors concluded that light and darkness fail to regulate melatonin levels in critically ill patients. Hu et al. also found no significant differences attributable to their intervention, but rather a significant difference in ANOVA analysis of 6-sulfoxymelatonin (6-SMT) levels on the first and second postoperative nights, which revealed significantly lower levels than those from the night before surgery. Additionally, the urine cortisol levels from the first and second postoperative nights were significantly higher than those from the night before surgery.
<table>
<thead>
<tr>
<th>Reference</th>
<th>Study-type</th>
<th>Oxford LoE</th>
<th>Participants</th>
<th>Light and/or darkness intervention</th>
<th>Multicomponent intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perras et al (2007) (Germany)</td>
<td>Cohort study (experimental, prospective)</td>
<td>4</td>
<td>$n = 20$ mixed ICU median age 'melatonin low': 60 ($n = 15$) median age 'melatonin high': 55 ($n = 5$)</td>
<td>1 h of darkness (&lt;1 lux) followed by 1 h light therapy (&gt;10,000 lux)</td>
<td>None</td>
</tr>
<tr>
<td>Taguchi et al (2007) (Japan)</td>
<td>RCT (Pilot)</td>
<td>5</td>
<td>Randomized: $n = 15$ (analyzed: $n = 11$) surgical ICU (patients with oesophageal cancer) Intervention: $n = 8$ (6, mean age: 56), Control: $n = 7$ (5, mean age: 59)</td>
<td>2 h light therapy (5000 lux) the day after extubation control group: no light therapy</td>
<td>None</td>
</tr>
<tr>
<td>Richardson et al (2007) (United Kingdom)</td>
<td>Cohort study (prospective, two group post-test quasi-experimental design)</td>
<td>4</td>
<td>$n = 64$ surgical (cardiothoracic) ICU Intervention: $n = 34$ (mean age: not indicated) Control: $n = 28$ (mean age: not indicated), two subjects drop-out in intervention/control assignment</td>
<td>Eye mask</td>
<td>Yes: provision of earplugs for noise shielding</td>
</tr>
<tr>
<td>Wunsch et al (2011) (USA)</td>
<td>Cohort study (retrospective, pseudo-randomization)</td>
<td>2b</td>
<td>$n = 789$; neurosurgical ICU (patients with SAH) Window group: $n = 455$ (mean age: 54.5) No window group: $n = 334$ (mean age: 54.5)</td>
<td>Window-room versus window lessroom assignment (balanced baseline characteristics,)</td>
<td>None</td>
</tr>
<tr>
<td>Zaal et al (2013) (Netherlands)</td>
<td>Cohort study (prospective, before-after)</td>
<td>2b</td>
<td>$n = 130$ Mixed ICU New ICU: $n = 75$ (mean age: 58.2) Old ICU: $n = 55$ (mean age: 59.9)</td>
<td>New versus old ICU design—light situation was found to be significantly different between ICUs (old: 0.42 V min$^{-1}$, IQR 0.35–0.55; new: 0.81 V min$^{-1}$, IQR 0.60–1.17, $p &gt; 0.001$)</td>
<td>Yes: patients had view to nature, single patient rooms, noise-absorbent materials, separating patient rooms from the corridors, improved alarm systems</td>
</tr>
</tbody>
</table>
Table 1. (Continued)

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study-type</th>
<th>Oxford LoE</th>
<th>Participants</th>
<th>Light and/or darkness intervention</th>
<th>Multicomponent intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patel et al (2014)</td>
<td>Cohort study (prospective before-after)</td>
<td>4</td>
<td>$n = 59$ mixed ICU before $n = 30$ (mean age: 61.9) after $n = 29$ (mean age: 60.5) (total admittance before $n = 167$; after $n = 171$)</td>
<td>Light intervention bundle: dim main light between 11 pm and 7 am, use bedside lighting for patient care, offer eye masks to patients with RASS $&gt;-4$</td>
<td>$594 (88.2)$ lux (before) versus $301 (53.5)$ lux (after), $p = 0.003$ measured during full duration of study</td>
</tr>
<tr>
<td>Engwall et al (2014)</td>
<td>1. Systematic literature search</td>
<td>2a $^b$</td>
<td>1. NA</td>
<td>- Cycled light versus non cycled light in the intensive care unit including Neuro-, paediatric ICU, and adult intensive care</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>2. Experience report</td>
<td></td>
<td>2. NA</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3. Experimental light measurement</td>
<td></td>
<td>3. NA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hu et al (2015)</td>
<td>RCT</td>
<td>2b</td>
<td>$n = 45$ surgical ICU Intervention group: $n = 20$ (mean age: 56.6) Control group: $n = 25$ (mean age: 56.8)</td>
<td>- Eye masks</td>
<td>Yes: $2 \times 60$ min of relaxing music ($7:30 - 8:30$ am, 8-9 pm) + ear plugs</td>
</tr>
</tbody>
</table>

(A)
<table>
<thead>
<tr>
<th>Reference</th>
<th>Main outcomes measure</th>
<th>Main results</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perras et al (2007) (Germany)</td>
<td>Melatonin plasma levels (every 30 min from 12am to 3am)</td>
<td>No effects of interventions on plasma melatonin levels – Patients were sedated</td>
<td>No control group – Intervention after extubation</td>
</tr>
<tr>
<td>Taguchi et al (2007) (Japan)</td>
<td>Physical activity (accelerometer); HRV; delirium (NEECHAM scale)</td>
<td>Delirium incidence 40% versus 16% (intervention group), not significant; no significant differences between groups in terms of physical activity or HRV  – No control group – Intervention after extubation</td>
<td>Assignment according to preferences of participant</td>
</tr>
<tr>
<td>Richardson et al (2007) (UK)</td>
<td>TST and sleep quality (patients’ perception using rating scales and questionnaires)</td>
<td>Reduced TST (0–2 h / 2–4 h): 56% (intervention group) versus 65% (control group); sleep quality in the positive band: 18% (intervention group) versus 7% (control group) – No control group – Intervention after extubation</td>
<td>Assignment according to preferences of participant</td>
</tr>
<tr>
<td>Wunsch et al (2011) (USA)</td>
<td>Global functional status (using mRS) at hospital discharge, 3 months and 1 year; grouped to 0–3 (no to moderate disability) and 4–6 (severe disability to death)</td>
<td>No significant differences in mRS between groups at the different time points</td>
<td>None</td>
</tr>
<tr>
<td>Zaal et al (2013) (Netherlands)</td>
<td>Days of delirium (CAM-ICU)</td>
<td>0.4 d less of delirium (95% CI 0.1–0.7) in new ICU; no difference in delirium incidence</td>
<td>None</td>
</tr>
<tr>
<td>Le Guen et al (2014) (France)</td>
<td>Sleep quality (MOSS scale, Spiegel scale, actigraphy, external and intermittent measurement of the patient’s sleep by a nurse)</td>
<td>Number of patients with pathological sleep (Spiegel scale) was significantly increased in control group compared to intervention group (p &lt; 0.01); Spiegel score significantly higher in intervention group (20) compared to control group (15) (p = 0.006); no significant differences in parameters from actigraphy or nurses’ assessments</td>
<td>None</td>
</tr>
<tr>
<td>Patel et al (2014) (UK)</td>
<td>Incidence of sleep deprivation (RCSQ); incidence of delirium (CAM-ICU)</td>
<td>No difference between groups before hospital admission, after admission (IQR [range]): 4 (3–5 [2–7]) before versus 7 (7–8 [5–9]) after – significant reduction of daytime sleep and significant improvement of sleep efficiency (according to RCSQ) – Delirium: reduction of delirium incidence – Before after design</td>
<td>Low rate of responders n = 59 (completed primary end-point) n (total) = 338</td>
</tr>
</tbody>
</table>

(Continued)
Table 1. (Continued)

<table>
<thead>
<tr>
<th>Reference</th>
<th>Main outcomes measure</th>
<th>Main results</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Engwall et al (2014) (Sweden)</td>
<td>1. Systematic review</td>
<td>1. 5/8 studies revealed a positive effect of cycled lighting</td>
<td>– no statistical analysis</td>
</tr>
<tr>
<td></td>
<td>2. Semantic bipolar questionnaire</td>
<td>2. Significant perceptive differences in hedonic tone, and brightness</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3. Illuminance and luminance with a Hagner S1 Universal Photometer; irradiance with a spectroradiometer AVASpec-2048-USB2</td>
<td>3. Descriptive results for illuminance, luminance, and irradiance—no statistical analysis</td>
<td></td>
</tr>
<tr>
<td>Hu et al 2015 (China)</td>
<td>– Richards-Campbell sleep questionnaire</td>
<td>Subjective sleep quality was significantly higher in the intervention group</td>
<td></td>
</tr>
<tr>
<td></td>
<td>– Melatonin metabolite 6-SMT level: level 12 h urine sample</td>
<td>– Melatonin: no significant differences between groups</td>
<td></td>
</tr>
<tr>
<td></td>
<td>– Cortisol Level 12 h urine sample</td>
<td>– Cortisol: no significant differences between groups</td>
<td></td>
</tr>
<tr>
<td></td>
<td>– Part 1 written questionnaire, semantic questionnaire</td>
<td>Part 2: all patients were pleased with cycled lighting</td>
<td></td>
</tr>
</tbody>
</table>

*First prove of principle, Pilot design; Systematic review with significant heterogeneity of individual study results (evaluated was only part 1, as 2 + 3 do not fulfil the inclusion criteria of this review).*

*According to criteria: no narrow confidence interval.*

*Statistical sample size calculation reported.*

**Note:** level of evidence (LoE) was assessed regarding the critical appraisal worksheets from the Centre for Evidence-Based Medicine of the University of Oxford (CEBM). The Level of evidence was indicated according to the CEBM for each study on an individual basis. CAM-ICU: Confusion assessment method for the intensive care unit; CI: confidence interval; HRV: heart rate variability; LoE: level of evidence; NEECHAM Scale: Neelon and Champagne confusion scale; n: number (analysed if not further specified); mRS: modified Rankin scale; PACU: post anaesthesia care unit; NA: not applicable; RASS: Richmond Agitation-Sedation Scale; RCSQ: Richards-Campbell sleep questionnaire; RCT: randomized controlled trial; TST: total sleep time.
3.3.3. **Delirium.** There were three studies (Taguchi *et al* 2007, Zaal *et al* 2013, Patel *et al* 2014) that examined the effect of interventions on the occurrence of delirium. Zaal *et al* investigated the effect of an all new ICU environment using a before-after design, taking a multi-component approach aimed at providing the patient with sufficient daylight exposure. Patel *et al* listed 17 different interventions aimed at modifications in patient care, noise reduction, and a reduction of light exposure, including the use of eye-masks. Taguchi *et al* used 2 h of light therapy (5000 lux) following extubation of patients undergoing oesophageal surgery.

All studies used a validated delirium assessment method (Zaal *et al*, Patel *et al*: confusion assessment method for the intensive care unite (CAM-ICU); Taguchi *et al*: Neelon and Champagne Confusion Scale).

Zaal *et al* indicated a reduction of 0.4 d in delirium duration, although there was no change in incidence. In spite of a remarkable reduction of the delirium incidence in the study by Taguchi *et al*, it still failed to reach significance due to the low case number. Patel *et al* showed a significant reduction in the incidence and duration of delirium, as well as a link between a (self reported) positive sleep quality and a lower risk of delirium.

3.3.4. **Other outcome parameters.** The only study that aimed primarily at basic outcome was the retrospective cohort study around Wunsch and co-workers (Wunsch *et al* 2011). This study compared patients with subarachnoid hemorrhage treated in an ICU room in the presence or absence of natural light from a window. Outcome parameters included ICU-, in-hospital-, 3 months-, and 1 year-mortality, as well as the global functional status (assessed with the modified Rankin Scale score, mRS), the ICU-LOS, the hospital LOS, duration of mechanical ventilation (MV), as well as complications.

The study revealed no differences between groups in any of the measured outcome parameters.

4. **Discussion**

In this systematic review, we identified 10 studies that deal with interventions based on exposure to light and darkness, either within single or multiple non-pharmacological approaches. In regards to methodology and results, the heterogeneity of the studies was high, and interventions aimed at light and darkness did not show a consistent effect on the chosen outcome measures. Heterogeneity was reflected in the different qualitative and quantitative measures of interventions, the outcome-measures, and the wide range of quality, with a respectively variability in evidence-levels assigned to the studies.

Perras and colleagues concluded that light and darkness fail to regulate melatonin levels in the critical care setting (Perras *et al* 2007). However, their findings showed that baseline melatonin-levels in patients were highly dependent on severity of illness, which is consistent with previous investigations (Shilo *et al* 1999, Mundigler *et al* 2002). What the authors did not discuss was that the limitations in the intervention itself might account for the lack of results. For a light exposure intervention, open eyes are essential for an adequate stimulation of retinal cells, so as to ensure the stimulation of the visual subsystem that mediates the light-induced suppression of melatonin secretion (Czeisler *et al* 1995, Lockley *et al* 1998). Perras reported that study patients were deeply sedated and had their eyes closed, which reduced the stimulation of this visual subsystem (Perras *et al* 2007). Had the eyes of their study patients been opened, however, the reported light intensity of over 10,000 lux would have been excessive. Therefore, this intervention might have failed to show results even in awake patients, as the high luminance would likely have induced glaring effects—especially if applied in the middle of the night, after total darkness (<1 lux 1 h before the light therapy). While neglected
in this study, a potential solution to this problem would be an even distribution of the light source to a larger surface.

This was also an issue in the Taguchi study (Taguchi et al 2007), which applied a light stimulus of 5,000 lux directly in front of the patients’ eyes that might have exceeded thresholds for absolute glare (>10,000 candela) (Piazena et al 2010). However, in contrast to the study of Perras, the fact that the patients were awake might explain the effectiveness of their intervention. Although the study failed to reach statistical significance (probably due to the low case number), the authors did show a trend for delirium reduction, which has also been described in other studies (Zaal et al 2013, Patel et al 2014). However, since these studies used a multi-component, non-pharmacological bundle, the reduction of delirium was not clearly attributable to the light intervention.

The investigation from Wunsch and colleagues provided the largest homogeneous cohort of patients, and delivered a methodologically sound retrospective analysis (Wunsch et al 2011). The authors compared patients exposed to natural light from the window from those who had no windows. There was no quantification of the intervention. The effect of natural light is highly dependent on the orientation of the bed and the distance from the window, neither of which have been reported by Wunsch and co-workers. Experimental measurements revealed that daytime illuminance on an intensive care unit averaged <200 lux at the bedside, which is not enough to provide melatonin suppression (Bullough et al 1996). Another limitation mentioned by the authors was that the study cohort consisted of patients with subarachnoidal hemorrhage, a patient collective that typically suffers from photophobia (Suarez et al 2006), so that it was likely that the luminance-tolerability was reduced a priori.

In contrast to light-interventions, studies aimed at exposure to darkness showed more consistent results, namely an improved subjective sleep quality in terms of patient-based sleep evaluation. The only two studies that used objective sleep assessment methods (accelerometer, actigraphy and HRV) revealed ambiguous results (Taguchi et al 2007, Le Guen et al 2014). However, it is unknown whether or not these measures are valid and reliable in the critical care setting. Although there are studies investigating the use of accelerometers and HRV in patients suffering from sleep disorders (Kawada et al 2012, Kondo et al 2014), there are factors in critical illness that might interfere with these measurements, such as heart-failure and certain medication (Drouot and Quentin 2016).

Hu et al compared melatonin metabolites and cortisol levels between patients provided with eye-masks versus a control group, but also failed to find significant differences (Hu et al 2015b). In this case, the failure might not be attributable to the intervention, but rather the chosen outcome-measure. The 12h timespan between samples may have lacked enough sensitivity to detect relevant fluctuations. Although the use of eye-masks was perceived as a stress-reducing measure, patients were still able to choose whether or not to wear them. Hu and colleagues also reported patients who refused to wear the masks. The use of eye-masks in patients who are delirious or anxious may lead to deprivation and stress, ultimately deteriorating outcome instead of improving it. These factors may constitute a relevant bias in further studies.

The discussed high heterogeneity among non-pharmacological research is a common phenomenon. This was emphasized by a recently published review focusing on the effects of non-pharmacological interventions on sleep (Hu et al 2015a), where the authors found a high inconsistency in the value of non-pharmacological measures, which was attributed to differing populations and outcome measures. Additionally, our review revealed that the type of intervention might also be a cause for heterogeneity.

Our systematic review has methodological limitations that should be considered when interpreting the results. We only included studies from select electronic bibliographic
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databases (MEDLINE via Pubmed, The Cochrane Library), which increased the risk of omit-
ting important literature. Additionally, the trials were too heterogeneous for a meta-analysis,
as either the interventions were not comparable, or there were discrepancies on the outcome
measures. We also lacked access to all identified articles, and we did not contact the authors
to ensure that additional, non-published data could be included. Finally, we decided to use the
Oxford System to determine the Level of Evidence on a study base, as the authors were more
experienced with this system. Certainly, outcome-based assessments would also be interesting
(e.g. GRADE (Jaeschke et al 2008)), and could possibly add some knowledge to the topic.
However, despite their renowned advantages, these systems have severe constraints if the
identified body of evidence is heterogeneous, which makes a comparison across outcomes
increasingly unreliable.

In conclusion, while experimental data show that illuminance and the spectral horizontal
irradiance of a light source are critical for melatonin suppression in healthy subjects (Brainard
et al 2001), there is no study evaluating which type of light intervention is effective in ICU
patients. Incidentally, further studies are required to investigate specific thresholds of lumi-
nance levels for this patient group, so as to ensure tolerability of light interventions. Most
importantly, light interventions may only be effective if patients are awake, making it neces-
sary to carefully consider the study collective. The outcome measures should be tested against
validity and reliability, so as to ensure that study endpoints are meaningful. We conclude that
adequate single-interventions, which are tested in awake patients with reliable and valid out-
come measures, as well as accounting for the above mentioned arguments, might be the most
promising trial designs to increase knowledge in this topic.

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