Studies on circadian rhythm disturbances and melatonin in delirium

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Chapter 6

Underrepresentation of patients with pre-existing cognitive impairment in pharmaceutical trials on prophylactic or therapeutic treatments for delirium:

A systematic review

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Submitted for publication
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Abstract

**Objective:** Representation of hospitalized patients with pre-existing cognitive impairment in pharmaceutical delirium trials is important because these patients are at high risk for developing delirium. The aim of this systematic review is to investigate whether patients with cognitive impairment were included in studies on pharmacological prophylaxis or treatment of delirium and to explore the motivations for their exclusion (if they were excluded).

**Study design:** This study was a systematic review. A MEDLINE search was performed for publications dated from 1 January 1985 to 15 November 2012. Randomized and non-randomized controlled trials that investigated medication to prevent or treat delirium were included. The number of patients with cognitive impairment was counted, and if they were excluded, motivations were noted.

**Results:** The search yielded 4293 hits, ultimately resulting in 31 studies that met the inclusion criteria. Of these, five studies explicitly mentioned the percentage of patients with cognitive impairment that were included. These patients comprised a total of 8% (n=279 patients) of the 3476 patients included in all 31 studies. Ten studies might have included cognitively impaired patients but did not mention the exact percentage, and sixteen studies excluded all patients with cognitive impairment. The motivations for exclusion varied, but most were related to the influence of dementia on delirium.

**Conclusion:** The exclusion of patients with pre-existing cognitive impairment hampers the generalizability of the results of these trials and leaves clinicians with limited evidence about the pharmacological treatment of this group of vulnerable patients who have an increased risk of side effects.
Patients with cognitive impairment in delirium trials

Introduction
Cognitive impairment and dementia are recognized as major risk factors for delirium, especially in hospitalized patients (1, 2). Studies have shown that the number of patients with Alzheimer’s disease who experience delirium varies from 22% to 89% in community-based and hospitalized populations (3). After experiencing delirium, patients with pre-existing cognitive impairment can experience a significant decline in both functional and cognitive abilities (4, 5) that affects self-maintenance and independent living. Therefore, (non-) pharmacological interventions that aim to prevent or decrease the severity of delirium symptoms are important for preventing the sequelae of delirium. Although patients with pre-existing cognitive impairment represent a large portion of the patients with delirium, it is unknown if they are indeed included in pharmaceutical delirium research. For practical and statistical reasons, these trials often only include patients who are relatively healthy. However, the patients who will actually use the medications in daily life may differ in important ways (6). Frequently, studies do not include a clear statement explaining why older patients with multimorbidity were not included (7). In patients with cognitive impairment, underlying pathophysiological mechanisms, such as imbalances in various neurotransmitter systems or the effects of inflammation on the brain via cytokines, may differ between patients with and without neurodegeneration. These differences may also cause variations in the effects and side effects of medications (8, 9). Therefore, the aim of this systematic review is to investigate whether patients with pre-existing cognitive impairment were included in studies on the pharmacological prophylaxis or treatment of delirium and the motivations for their exclusion if they were excluded.

Methods

Search strategy
We conducted a systematic search of the literature published from 1 January 1985 to 15 November 2012 in MEDLINE. We used a search strategy developed by the Cochrane Dementia and Cognitive Improvement Group and combined this strategy with the search strategy used for the 2010 National Institute for Health and Clinical Excellence (NICE) guideline (10). Furthermore, we checked the references of the NICE guideline and the review by Devlin et al. (11). See Appendix 1 for a complete description of the search strategy.

Selection procedure
We included original studies in the English or Dutch language that included participants older than 18. Both randomized and non-randomized controlled trials that investigated medication for the prevention and/or treatment of delirium in adults were included. The studies had to use the term delirium and/or diagnose delirium by using the criteria in the Diagnostic and Statistical Manual of Mental Disorders (DSM). The outcome measures of
interest were the incidence/prevalence, severity or duration of delirium. We excluded studies that did not report one of these outcomes as a primary outcome or reported them only in a post hoc analysis, as well as studies on children and delirium tremens.

**Data extraction**

All data were independently extracted by two investigators (EG and AJ). In addition to the study and participant characteristics, we registered whether cognitive impairment or dementia was an exclusion criterion and whether cognitively impaired patients were enrolled. If cognitively impaired patients were excluded, the authors were approached to determine their motivation for exclusion. Disagreements that arose during the data abstraction were resolved through discussion with a third investigator (BM).

**Quality assessment**

To assess internal validity, all the retrieved articles were scored using the risk of bias tool developed by the Cochrane Collaboration (12). This tool includes the following items:
- Random sequence generation (selection bias)
- Allocation concealment (selection bias)
- Blinding of participants and personnel (performance bias)
- Blinding of outcome assessments (detection bias)
- Completeness of outcome data (attrition bias)
- Selective outcome reporting (reporting bias)

The studies could be assessed as having either a ‘low risk of bias’ or a ‘high risk of bias’ for each of these six domains. A study was considered to be of good methodological quality when it had a ‘low risk of bias’ for four items or more; moderate quality was defined as a ‘low risk of bias’ for three items; and low quality was defined as two or fewer items that received a ‘low risk’ rating.

**Results**

**Search results**

The combination of search terms yielded 4293 hits. Checking the references of the Devlin review did not yield any additional studies; checking the references of the NICE guideline produced two additional studies (Figure 1). We screened the titles and the abstracts of 1269 potentially relevant papers and read the full text of 48 papers (Figure 1). The search ultimately yielded 31 studies that met the inclusion criteria (13-26, 26-42).

**Quality assessment**

Of the 31 included studies, the majority (n=22) had good methodological quality. Three studies (26, 28, 40) had moderate methodological quality, and the remaining six studies had low methodological quality (20, 32, 35, 41, 43, 44) (Figure 2). Seven studies did not describe the randomization process clearly (20, 26, 28, 32, 35, 37, 43, 44), and one study
Patients with cognitive impairment in delirium trials

Figure 1: Flowchart

Articles retrieved using the NICE search strategy
n=392

Excluded n=98
Language (n=27)
Case report/Letter/Editorial/Review (n=52)
Delirium in children (n=11)
Other diseases (n=8)

n=294

Articles retrieved using the Cochrane search strategy
n=3901

Excluded n=2784
Language (n=1095)
Case report/Letter/Editorial/Review (n=165)
Delirium in children (n=135)
Delirium tremens (n=286)
Other diseases (n=576)
Other reason (n=527)

n=1117

Total n=1411

Articles added from the NICE guideline citation list n=2

n=1269

Excluded n=1221
no RCT/CCT or other subject

Screened full text n=48

Excluded n=17
No RCT/CCT n=9
No delirium according to DSM n=7
Post hoc analysis n=1

Inclusion n=31
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was a controlled clinical trial (20) that had a high risk of allocation concealment and random sequence generation bias. Three studies were open-label studies (22, 28, 35), four studies had a single-blind design in which only the outcome assessor was blinded (22, 26, 30, 35) and three studies (15, 20, 43) were not blinded. In these cases, there was a high risk of bias in the blinding of the participants and personnel and outcome assessment. Two studies failed to describe the procedure (41, 45). In total, eight studies did not perform an intention-to-treat analysis, which may have introduced attrition bias (14, 16, 23, 26, 34, 39, 41, 46). In most cases, all outcomes described in the methods section were reported in the results section; therefore, the risk of reporting bias was low in all of the studies except one (23).

Figure 2: Quality assessment of the 31 included studies

![Quality assessment of included studies](image)

The black bars represent the percent meeting quality criteria.

**Characteristics of included studies**

The total number of participants was n=3467, ranging from 15 to 457 per study. The mean age of the participants ranged from 39.2 to 88.0 years. The study settings included outpatient clinics, hospital wards and intensive care units (ICUs) (see Tables 1 and 2).

**Representation of patients with pre-existing cognitive impairment**

Five studies with a total of 486 patients reported the percentages of patients with cognitive impairment who were included. The percentages varied between 7.5 and 100%, for a total of 274 patients with cognitive impairment (see Table 1). Ten studies might have included patients with cognitive impairment; they did not specify cognitive impairment as an exclusion criterion. Sixteen studies clearly excluded patients with cognitive impairment. There was no difference in methodological quality between the studies that did and did not include patients with dementia.
Table 1: RCTs included in this review that did not exclude patients with cognitive impairment

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Type of study</th>
<th>Study population</th>
<th>Sample Size</th>
<th>Intervention</th>
<th>% of patients with cognitive impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Al-Aama T (2011)</td>
<td>Prophylactic</td>
<td>Acute medical care patients</td>
<td>145</td>
<td>Melatonin 0.5 mg vs. placebo</td>
<td>20%</td>
</tr>
<tr>
<td>Breitbart W (1996)</td>
<td>Treatment</td>
<td>Adult patients with AIDS and delirium</td>
<td>30</td>
<td>Haloperidol vs. chlorpromazine vs. lorazepam at flexible dosages</td>
<td>Not reported</td>
</tr>
<tr>
<td>Gamberini M (2009)</td>
<td>Prophylactic</td>
<td>Elective cardiac surgery patients</td>
<td>120</td>
<td>Rivastigmine 1.5 mg 3dd vs. placebo</td>
<td>Not reported</td>
</tr>
<tr>
<td>Girard TD (2010)</td>
<td>Prophylactic</td>
<td>Mechanically ventilated patients</td>
<td>101</td>
<td>Haloperidol 5 mg vs. ziprasidone 40 mg vs. placebo</td>
<td>Not reported</td>
</tr>
<tr>
<td>Kaneko T (1999)</td>
<td>Prophylactic</td>
<td>Elective gastrointestinal surgery patients</td>
<td>80</td>
<td>Haloperidol 5 mg iv vs. saline 0.9%</td>
<td>7.5%</td>
</tr>
<tr>
<td>Kim KY (1996)</td>
<td>Prophylactic</td>
<td>Cardiac surgery ICU patients</td>
<td>127</td>
<td>Flexible dosages, usually cimetidine 900 mg iv/24 h or ranitidine 150 mg iv/24h</td>
<td>Not reported</td>
</tr>
<tr>
<td>Marcantonio ER (2011)</td>
<td>Prophylactic</td>
<td>Patients undergoing hip fracture repair</td>
<td>16</td>
<td>Donepezil 5 mg vs. placebo</td>
<td>43%</td>
</tr>
<tr>
<td>Moretti R (2004) *</td>
<td>Prophylactic</td>
<td>Subcortical vascular or multi-infarct dementia patients</td>
<td>230</td>
<td>Rivastigmine 3-6 mg/day vs. cardio aspirin 100 mg/day</td>
<td>100%</td>
</tr>
<tr>
<td>Overshott R (2010)</td>
<td>Treatment</td>
<td>Patients with incident and prevalent delirium</td>
<td>15</td>
<td>Rivastigmine 1.5 mg once a day increasing to twice a day after 7 days vs. placebo</td>
<td>47%</td>
</tr>
<tr>
<td>Pandharipande PP (2007)</td>
<td>Prophylactic</td>
<td>Mechanically ventilated medical and surgical ICU patients</td>
<td>106</td>
<td>Sedation with dexmedetomidine vs. lorazepam</td>
<td>Not reported</td>
</tr>
<tr>
<td>Reade MC (2009)</td>
<td>Treatment</td>
<td>Agitated delirious mechanically ventilated patients</td>
<td>20</td>
<td>0.2-0.7 mcg/kg/hour dexmedetomidine (loading dose optional) vs. haldol 0.5 to 2 mg/hour idem</td>
<td>Not reported</td>
</tr>
<tr>
<td>Tahir TA (2010)</td>
<td>Treatment</td>
<td>Medical and surgical patients with delirium</td>
<td>42</td>
<td>Quetiapine flexible dosage 25-175 mg/day vs. placebo</td>
<td>Not reported</td>
</tr>
<tr>
<td>Van Eijk MM (2010)</td>
<td>Treatment</td>
<td>ICU patients</td>
<td>104</td>
<td>Rivastigmine according to scheme vs. placebo.</td>
<td>Not reported</td>
</tr>
<tr>
<td>Wang W (2012)</td>
<td>Prophylactic</td>
<td>Noncardiac surgery ICU patients</td>
<td>457</td>
<td>Haloperidol 0.5 mg bolus followed by 0.1 mg/hr iv vs. placebo</td>
<td>Not reported</td>
</tr>
</tbody>
</table>

* Controlled Clinical Trial
### Table 2: RCTs included in this review that excluded patients with cognitive impairment

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Type of study</th>
<th>Study population</th>
<th>Sample Size</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aizawa K (2002)</td>
<td>Prophylactic</td>
<td>Gastric or colon cancer laparotomy patients</td>
<td>40</td>
<td>Diazepam (0.1 mg/kg) iv bolus and a continuous infusion of flunitrazepam 0.04 mg/kg and pethidine 1 mg/kg over 8 h during the night vs. care as usual</td>
</tr>
<tr>
<td>Devlin JW (2010)</td>
<td>Treatment</td>
<td>Intensive care unit patients</td>
<td>36</td>
<td>Quetiapine 50 mg twice daily vs. placebo</td>
</tr>
<tr>
<td>Grover S (2011)</td>
<td>Treatment</td>
<td>Patients referred to consultation-liaison psychiatry</td>
<td>64</td>
<td>Olanzapine, risperidone and haloperidol at flexible dosages</td>
</tr>
<tr>
<td>Hakim SM (2012)</td>
<td>Treatment</td>
<td>On-pump cardiac surgery patients</td>
<td>101</td>
<td>Risperidone 0.5 mg vs. placebo</td>
</tr>
<tr>
<td>Han CS (2004)</td>
<td>Treatment</td>
<td>Medical and ICU patients</td>
<td>24</td>
<td>Flexible dosages of haloperidol (starting with 0.75 mg) vs. risperidone (starting with 0.5 mg) twice a day</td>
</tr>
<tr>
<td>Hudetz JA (2009)</td>
<td>Prophylactic</td>
<td>Male cardiac surgery patients</td>
<td>58</td>
<td>Single dose (0.5 mg/kg, intravenous) of ketamine during anesthetic induction vs. placebo</td>
</tr>
<tr>
<td>Kim SW (2010)</td>
<td>Treatment</td>
<td>Hospital patients</td>
<td>32</td>
<td>Flexible dosages of risperidone vs. olanzapine</td>
</tr>
<tr>
<td>Larsen KA (2010)</td>
<td>Prophylactic</td>
<td>Elective knee or hip replacement patients</td>
<td>400</td>
<td>Olanzapine 5 mg per day vs. placebo</td>
</tr>
<tr>
<td>Lee KU (2005)</td>
<td>Treatment</td>
<td>Patients referred to the psychiatric consultation service</td>
<td>31</td>
<td>Flexible dosages of amisulpride vs. quetiapine</td>
</tr>
<tr>
<td>Leung JM (2006)</td>
<td>Prophylactic</td>
<td>Spine surgery patients requiring general anesthesia</td>
<td>21</td>
<td>Gabapentin 900 mg vs. placebo</td>
</tr>
<tr>
<td>Liptzin B (2005)</td>
<td>Prophylactic</td>
<td>Elective knee or hip surgery patients</td>
<td>80</td>
<td>Donepezil 5 mg vs. placebo</td>
</tr>
<tr>
<td>Prakanrattana U (2007)</td>
<td>Prophylactic</td>
<td>Cardiopulmonary bypass patients</td>
<td>103</td>
<td>Risperidone 1 mg vs. placebo</td>
</tr>
<tr>
<td>Sampson EL (2007)</td>
<td>Prophylactic</td>
<td>Elective total hip replacement patients</td>
<td>126</td>
<td>Donepezil 5 mg vs. placebo</td>
</tr>
<tr>
<td>Shehabi Y (2009)</td>
<td>Prophylactic</td>
<td>Pump cardiac surgery patients</td>
<td>33</td>
<td>Dexmedetomidine (0.1–0.7 g·kg⁻¹·ml⁻¹) vs. Morphine (10–70 g·kg⁻¹·ml⁻¹)</td>
</tr>
<tr>
<td>Skrobik YK (2004)</td>
<td>Treatment</td>
<td>Surgical ICU patients</td>
<td>73</td>
<td>Olanzapine (5 mg) vs. haloperidol (2.5 - 5 mg) every 8 h (both starting dosages) adjusted when needed</td>
</tr>
<tr>
<td>Sultan SS (2010)</td>
<td>Prophylactic</td>
<td>Hip arthroplasty patients</td>
<td>222</td>
<td>Placebo vs. melatonin 5 mg vs. midazolam 7.5 mg vs. clonidine 100 μg</td>
</tr>
</tbody>
</table>
Motivations for not including patients with pre-existing cognitive impairment

Three studies reported the motivation for excluding patients with pre-existing cognitive impairment (34, 37, 39). We contacted the authors of the other thirteen articles that excluded patients with cognitive impairment, and seven responded. The reasons for excluding cognitively impaired patients (some mentioned more than one reason) were the expected legal burden (2), issues related to the study medication (2), issues related to the research design (2), and issues directly related to dementia (14). The dementia-related issues were difficulty judging treatment effect (7); interference with the treatment effect (2); the belief that these patients were not present in the eligible patient group (4); and the belief that these patients were more likely to be excluded or to decline participation (1).

DISCUSSION

This systematic review clearly states that only 14% of patients who were included in delirium trials are patients with pre-existing cognitive impairment and/or dementia; 274 (patients with dementia) / 1930 (total number of patients in trials that excluded patients with delirium and total number of patients in trials that reported the number of patients with dementia). The stated motivations for excluding patients with cognitive impairment varied and were frequently related to dementia. The researchers indicated that cognitive impairment/dementia hampered a clear assessment of the incidence, severity or resolution of delirium. Although we acknowledge that delirium and dementia share many symptoms (47), it is possible to diagnose delirium by adhering to the DSM criteria, especially for trained health care professionals (24). Furthermore, the researchers indicated that ‘dementia interferes with the treatment effect’ (i.e., the effect of the intervention for patients with a high risk of delirium might be different from the effect for low-risk patients). This is possible but excluding high-risk patients hampers the external validity of the trial results.

Another motivation was that ‘these patients are not expected to be in the eligible patient group’ (e.g., in the ICU). It is not possible to investigate this statement, especially because acutely admitted patients may not be fully conscious; therefore, cognitively impaired patients might have been included without the researchers’ knowledge. Another researcher reported that ‘these patients were more likely to be excluded or to decline participation in this study’. However, this statement is not supported by the studies that are included in this review; the fifteen studies that did include patients with cognitive impairment (or may have included them) did not report any dropouts that occurred because of cognitive impairment.

None of the four studies that reported the percentages of patients with cognitive impairment that were included, performed a subgroup analysis for patients with cognitive impairment (the fifth study included only patients with dementia). The underrepresentation of patients with pre-existing cognitive impairment limits the external
validity of these studies and thus the applicability of many trial results to delirious patients with pre-existing cognitive impairment. In the field of delirium research, many patient groups or settings are underrepresented, e.g. patients aged 85 and over or palliative care. However, it is of particular importance to include patients with pre-existing cognitive impairment in pharmaceutical trials as these patients are in the highest risk group for developing delirium and they have a high risk of pharmacological side effects. Furthermore, all studies on atypical antipsychotics, except for one, excluded patients with cognitive impairment. However, treatment with atypical antipsychotics can lead to serious cerebrovascular side effects and higher mortality, especially in patients with dementia (48, 49). Therefore, the U.S. Food and Drug Administration (FDA) discourages clinicians from prescribing antipsychotics to delirious dementia patients and from using these medications prophylactically (50).

Because of the lack of evidence about the preventive effect of antipsychotics for delirium, the NICE guideline does not recommend prophylactic treatment in patients with an increased risk of delirium (10, 51). In addition, the NICE guideline recommends reserving antipsychotics for treating delirium only in patients for whom verbal and non-verbal de-escalation techniques are ineffective or inappropriate. There are no recommendations specifically for patients with cognitive impairment, and it is not explicitly stated that the available evidence was not derived from the group for which the treatment will be prescribed. Thus, clinicians are left with limited evidence about pharmacological treatment for cognitively impaired patients with delirium or an increased risk for delirium.

CONCLUSION
This review shows that a minority of the total population of patients in clinical trials concerning the pharmacological prevention or treatment of delirium had known cognitive impairment. These findings indicate that the current evidence has limited applicability for daily clinical practice. Researchers should be more aware of the underrepresentation of patients with pre-existing cognitive impairment so that future delirium research includes this specific group. Clinicians should recognize that there is a gap in the evidence about the possible effects and side effects of medication for treating delirium, especially for vulnerable patients.
Patients with cognitive impairment in delirium trials

Appendix 1

The following search strategy was applied in MEDLINE:

The search strategy of the NICE guideline:
1
deliri$.ti,ab.
2
(acute adj2 (confusion$ or "brain syndrome" or "brain failure" or "psycho-organic syndrome" or "organic psychosyndrome").mp.
3
(terminal$ adj restless$).mp.
4
toxic confus$.mp.
5
delirium/
6
confusion/
7
or/1-6
8
*psychoses, alcoholic/ or *alcohol withdrawal delirium/
9
*substance withdrawal syndrome/
10
8 or 9
11
7 not 10
AND:
1 randomized controlled trial$.pt,sh.
2 clinical trial$.pt,sh.
3 random allocation/
4 double blind method/
5 single blind method/
6 ((clin$ or control$) adj5 trial$).ti,ab.
7 ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.
8 placebo/
9 placebo$.ti,ab.
10 random$.ti,ab.
16 DELIRIUM APPENDICES
11 (volunteer$ or "control group" or controls or prospective$).ti,ab.
12 research design/
13 or/1-12
14 animals/ not humans/
15
13 not 14
Patients with cognitive impairment in delirium trials

Reference List

(1) Inouye SK. Predisposing and precipitating factors for delirium in hospitalized older patients. Dement Geriatr Cogn Disord 1999 Sep;10:393-400.
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Patients with cognitive impairment in delirium trials