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Review

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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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.

Background

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, pharmacological interventions that aim to prevent or decrease the severity of delirium symptoms are important for preventing the sequelae of delirium.

For practical and statistical reasons, pharmacological 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]. Patients with pre-existing cognitive impairment represent a large portion of the patients with delirium, but it is unknown if they are indeed included in pharmacological delirium research. 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 [7,8]. Also, frequently, studies do not include a clear statement explaining why older patients with multimorbidity were not included [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

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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. 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. No other languages were included due to possible translational problems and because we felt bias of the results would be limited as we do not intend to meta-analyze the overall treatment effect in patients with cognitive impairment. Both randomized and non-randomized controlled trials that investigated medication for the prevention and/or treatment of non-alcohol related delirium in adults were included. We excluded studies that did not diagnose delirium by using the criteria in the Diagnostic and Statistical Manual of Mental Disorders (DSM). Secondly, we excluded studies that did not report on incidence/prevalence, severity or duration of delirium as one of the outcome measures. See Fig. 1.

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). We discussed for instance the articles of Hu and Kim and decided that we should not include these articles as they do not fulfill our inclusion criteria [11,12].

Quality assessment

To assess internal validity, all the retrieved articles were scored using the risk of bias tool developed by the Cochrane Collaboration [13]. This tool includes the following items:

1. Random sequence generation (selection bias)
2. Allocation concealment (selection bias)
3. Blinding of participants and personnel (performance bias)
4. Blinding of outcome assessments (detection bias)
5. Completeness of outcome data (attrition bias)
6. 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 (Fig. 1). We screened the titles and the abstracts of 1269 potentially relevant papers and read the full text of 48 papers (Fig. 1). The search ultimately yielded 31 studies that met the inclusion criteria [14–27,27–43].

Quality assessment

Of the 31 included studies, the majority (n = 22) had good methodological quality. Three studies [27,29,41] had moderate methodological quality, and the remaining six studies had low methodological quality [21,33,36,42,44,45] (Fig. 2). Seven studies did not describe the randomization process clearly [21,27,29,33,36,38,44,45], and one study was a controlled clinical trial [21] that had a high risk of allocation concealment and random sequence generation bias. Three studies were open-label studies [23,29,36], four studies had a single-blind design in which only the outcome assessor was blinded [23,27,31,36] and three studies [16,21,44] 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 [42,45]. In total, eight studies did not perform an intention-to-treat analysis, which may have introduced attrition bias [15,17,24,27,33,35,40,42]. 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 [24] (See Tables 3a–4b).

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 1a, 1b and 2a, 2b).

Representation of patients with pre-existing cognitive impairment

Four prophylactic and one treatment study, 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% in the prophylactic studies and were 47% in the treatment study, for a total of 279 patients with cognitive impairment (see Tables 1a, 1b and 2a, 2b). Six prophylactic studies and four treatment studies might have included patients with cognitive impairment; they did not specify cognitive impairment as an exclusion criterion. Nine prophylactic studies and seven treatment 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.

Motivations for not including patients with pre-existing cognitive impairment

Three studies reported the motivation for excluding patients with pre-existing cognitive impairment [35,38,40]. 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 18% of patients who were included in prophylactic delirium trials, and 2% of patients who were included in treatment delirium trials are patients with pre-existing cognitive impairment and/or dementia; 272 (patients with dementia)/1548 (total number of patients in trials that excluded patients with dementia and total number of patients in trials that reported the number of patients with dementia), and 7 (patients with dementia)/376 (total number of patients in trials that excluded patients with dementia 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 [46], it is possible to diagnose delirium by adhering to the DSM criteria, especially for trained health care professionals, and if needed, research assessment tools can be used like the Confusion Assessment Method to distinguish delirium in patients with dementia [25,47,48]. 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