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Review Article

# Efficacy and safety of haloperidol for in-hospital delirium prevention and treatment: A systematic review of current evidence

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ABSTRACT

*Objective:* Haloperidol is generally considered the drug of choice for in-hospital delirium management. We conducted a systematic review to evaluate the evidence for the efficacy and safety of haloperidol for the prevention and treatment of delirium in hospitalized patients.

*Methods:* PubMed, Embase, Cumulative Index to Nursing and Allied Health (CINAHL), PsycINFO, and the Cochrane Library were systematically searched up to April 21, 2015. We included English full-text randomized controlled trials using haloperidol for the prevention or treatment of delirium in adult hospitalized patients reporting on delirium incidence, duration, or severity as primary outcome. Quality of evidence was graded. Meta-analysis was not conducted because of between-study heterogeneity.

*Results:* Twelve studies met our inclusion criteria, four prevention and eight treatment trials. Methodological limitations decreased the graded quality of included studies. Results from placebo-controlled prevention studies suggest a haloperidol-induced protective effect for delirium in older patients scheduled for surgery: two studies reported a significant reduction in ICU delirium incidence and one study found a significant reduction in delirium severity and duration. Although placebo-controlled trials are missing, pharmacological treatment of established delirium reduced symptom severity. Haloperidol administration was not associated with treatment-limiting side-effects, but few studies used a systematic approach to identify adverse events.

*Conclusion:* Although results on haloperidol for delirium management seem promising, current prevention trials lack external validity and treatment trials did not include a placebo arm on top of standard nonpharmacological care. We therefore conclude that the current use of haloperidol for in-hospital delirium is not based on robust and generalizable evidence.



## 1. Introduction

Delirium is an acute and fluctuating disturbance in attention, awareness and additionally in cognition (Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, DSM-5) [1] occurring as a frequent complication of acute medical illness and hospitalization in elderly patients. Delirium is a common problem on medical and surgical wards. Based on a recent overview of observational studies by Inouye et al. [2], up to 33% [3] of elderly non-ICU medical patients experience delirium during hospital admission, while reported incidence rates are as high as 51% in elderly hip-fracture patients [4]. The occurrence of delirium is associated with poor patient outcomes and increased health costs [5]. Several studies have demonstrated that delirium predicts worse functional outcomes and institutionalization for different elderly patient populations [6–8]. Furthermore, development of delirium in elderly inpatients has been linked to post-discharge mortality [3,9,10], for which duration of delirium appears to be an important predictor [10,11]. Once delirium has established, it is not always reversible, with prolonged and persisting delirium being associated with even poorer outcomes [12,13]. Therefore, adequate prevention and treatment of delirium is essential.

Management of established delirium primarily includes identifying and treating any underlying cause(s). In addition, nonpharmacological interventions are considered part of standard delirium care, while pharmacological treatments are mostly added to the treatment regimen to reduce the burden of delirium symptoms [14–16]. For prevention of delirium, nonpharmacological interventions are endorsed [17], yet pharmacological treatments are gaining increased attention even though evidence for their efficacy is limited [18]. Among pharmacological delirium treatments, the typical antipsychotic haloperidol generally is considered first choice in varying patient populations [14–16,19], noting that it has not been approved by the US Food and Drug Administration for this indication [20].

To date, no systematic review of randomized controlled trials has merely focused on first-choice haloperidol for the prevention and treatment of delirium in hospitalized adults. We therefore conducted this systematic literature search to study the efficacy and safety of

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haloperidol in terms of reducing delirium incidence, duration and/or severity in adult hospitalized patients.

## 2. Methods

### 2.1. Data sources

We conducted a systematic literature search up to April 21, 2015 in PubMed, Embase, the Cumulative Index to Nursing and Allied Health (CINAHL), PsycINFO, and the Cochrane Library, using the index terms and keywords "haloperidol", "delirium" and "acute confusion". Identified records were imported into Reference Manager 12 for Microsoft Word® 2003. Duplicate references were removed. The full search strategy is included in Appendix A.

### 2.2. Data collection and quality assessment

The titles and/or abstracts of identified records were independently screened by two reviewers. Studies were considered eligible for inclusion in this review if they: (1) were a randomized controlled trial (RCT); (2) included an intervention group with haloperidol (all routes of administration); (3) included one or more comparison group(s) with either no intervention, placebo, or any other drug (all routes of administration); (3) targeted adult (age 18 years or over) hospitalized patients; and (4) targeted incidence, duration, and/or severity of delirium as primary outcome measures. Publications specifically addressing alcohol- or substance-related delirium, patients with schizophrenia, (acute) mania, (psychotic) agitation or aggression were excluded. Only English language full-text articles relevant to the scope of this review and meeting our inclusion criteria were retrieved for detailed evaluation. In case of disagreement between the two reviewers, a third reviewer was consulted. Final article selection was based upon consensus between the investigators. One investigator extracted data on the study design and population, dropout rates, intervention, delirium assessment tools, primary outcome(s), and side-effect reporting. A second investigator checked the acquired data for accuracy and inconsistencies. For each study, p-values and relative risks (RRs) with 95% confidence intervals (CIs) were extracted. If p-values were not reported, these were computed by a statistician using IBM SPSS Statistics 20; p-values less than 0.05 were considered statistically significant. Study characteristics and results were listed by first author, publication year and country. A system based on the Grades of Recommendation, Assessment, Development and Evaluation Working Group (GRADE) and the Cochrane Collaboration's tool for assessing risk of bias were used to evaluate the quality and applicability of the available evidence (Appendix B) [21,22]. To assess the quality of evidence, each study was assessed independently by two reviewers under the supervision of a third reviewer according to the aforementioned criteria. Because all included studies were RCTs they were initially graded as high quality evidence, and thereafter downgraded based on the presence of risk of bias, resulting in four grade categories: high quality, moderate (downgraded), low (double-downgraded), and very low (triple-downgraded). Final quality rating was based upon consensus between the investigators (Appendix B). We initially planned on conducting a meta-analysis of the included studies, but decided this was not possible due to between-study heterogeneity.

## 3. Results

A summary of the search and selection of evidence is provided in Fig. 1. A total of 3597 records were identified through our systematic literature search. After duplicate removal, the titles and/or abstracts of 2872 records were screened for eligibility based on our predefined in- and exclusion criteria. We excluded 2855 articles based on a review of the title and/or abstract, mostly because records were not relevant to the scope of this review or not available as English full-text (abstract, other language). As a result, 17 full-text articles were retrieved for detailed evaluation. Two articles were excluded because they did not include a general in-hospital population [23,24], one article was excluded because delirium incidence, duration and/or severity were not the primary outcome [25], and two articles were excluded because they were not randomized [26,27], resulting in the inclusion of 12 (four prevention, and eight treatment) studies for this review.

### 3.1. Study characteristics

#### 3.1.1. Haloperidol for prevention of delirium

We identified four prophylaxis trials. Three studies included a placebo or saline 0.9% control arm, and one study had a non-intervention control group. Studies were published between 1999 and 2014, and originated from Japan [28,29], The Netherlands [30], and China [31]. Trials included a total of 1088 (range 80–457) patients all admitted for surgical procedures, predominantly orthopedic [29,30] or abdominal [28,29,31] surgery. Two studies were initiated in an ICU setting [28,31]. Two studies specifically excluded patients with profound dementia [30,31]. Primary outcome for all studies was postoperative delirium incidence assessed with the NEECHAM confusion scale [29], or DSM criteria for delirium [28,30,31]. Other reported outcome measures included delirium duration and severity [28–30], adverse events [28–31], time to onset of delirium [31], hospital length of stay (LOS) [30,31], ICU LOS [31], total sleep time [28], and all-cause 28-day mortality [31]. Two studies were graded as high quality evidence [30,31]. A summary of the included study characteristics and results are shown in Table 1A.

#### 3.1.2. Haloperidol for treatment of delirium

Our search yielded eight comparison trials, including a total of 463 (range 28–80) patients. Studies were published between 1996 and 2013, and originated from Turkey [32], USA [33], India [34], Korea [35], Thailand [36], Japan [37], Canada [38], and Greece [39]. Studies compared haloperidol with other typical (chlorpromazine) or atypical (olanzapine, risperidone, quetiapine) antipsychotics, benzodiazepines (lorazepam), tetracyclic antidepressants (mianserin), serotonin 5-$HT_3$ receptor antagonist (ondasetron), and morphine for the treatment of delirium in hospitalized patients. Three studies enrolled patients who were referred to the hospital consultation–liaison psychiatry service [34–36]. Three studies explicitly excluded patients with profound cognitive impairment or dementia [32,34,35]. One study did not use a valid tool for delirium diagnosis [39]. Two trials excluded patients who were diagnosed with hypoactive delirium [32,36]. Primary efficacy outcome was delirium severity assessed with the DI [38], DRS [33,37], DRS-R-98 [34,36], MDAS [35], and RASS respectively [32]. Other outcomes included adverse events [32–38], time to onset of delirium [32], time to response [35,36], delirium duration [32], total sleep time [36], hospital LOS [32], ICU LOS [32], and mortality [32,33,36]. One study was graded as high quality evidence [36]. Study details are provided in Table 1B.

### 3.2. Study results on the primary outcome measures

#### 3.2.1. Delirium incidence

Postoperative delirium incidence ranged from 15.8% [30] to 37.8% [29] across prevention studies. Data from these studies indicated that haloperidol prophylaxis significantly reduced postoperative delirium incidence in patients admitted to the ICU predominantly after abdominal surgery [28,31]. No significant effect was demonstrated after mostly elective abdominal and orthopedic surgery in older, at-risk patients [29,30].