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Review Article

The Mortality Risk of Conventional Antipsychotics in Elderly Patients: A Systematic Review and Meta-analysis of Randomized Placebo-Controlled Trials

Tessa A. Hulshof RN, MSc [a,b], Sytse U. Zuidema MD, PhD [a], Raymond W.J.G. Ostelo PhD [b,c], Hendrika J. Luijendijk MPH, MD, PhD [a,d,*]

[a] University of Groningen, University Medical Center Groningen, Department of General Practice, Groningen, The Netherlands
[b] Department of Health Sciences and the EMGO Institute for Health and Care Research, VU University, Amsterdam, The Netherlands
[c] Department of Epidemiology and Biostatistics, VU University Medical Center, Amsterdam, The Netherlands
[d] Department of Geriatric Psychiatry, BAVO Europoort, Rotterdam, The Netherlands

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A B S T R A C T

Background: Numerous observational studies have reported an increased risk of mortality for conventional antipsychotics in elderly patients, and for haloperidol in particular. Subsequently, health authorities have warned against use of conventional antipsychotics in dementia. Experimental evidence is lacking.
Objective: To assess the mortality risk of conventional antipsychotics in elderly patients with a meta-analysis of trials.
Methods: Original studies were identified in electronic databases, online trial registers, and hand-searched references of published reviews. Two investigators found 28 potentially eligible studies, and they selected 17 randomized placebo-controlled trials in elderly patients with dementia, delirium, or a high risk of delirium. Two investigators independently abstracted trial characteristics and deaths, and 3 investigators assessed the risk of bias. Deaths were pooled with RevMan to obtain risk differences and risk ratios.
Results: Data of 17 trials with a total of 2387 participants were available. Thirty-two deaths occurred. The pooled risk difference of 0.1% was not statistically significant (95% confidence interval (CI) −1.0%−1.2%). The risk ratio was 1.07 (95% CI 0.54−2.13). Eleven of 17 trials tested haloperidol (n = 1799). The risk difference was 0.4% (95% CI −0.9%−1.6%), the risk ratio was 1.25 (95% CI 0.59−2.65).
Conclusions: This meta-analysis of placebo-controlled randomized trials does not show that conventional antipsychotics in general or haloperidol in particular increase the risk of mortality in elderly patients. It questions the observational findings and the warning based on these findings.

Haloperidol and other conventional antipsychotics are commonly used to reduce hallucinations, delusions, and aggression in elderly patients with dementia or delirium despite their well-known extrapyramidal and cardiac side effects.[1] However, in 2005, a meta-analysis of randomized trials suggested that use of haloperidol in patients with dementia increased the risk of mortality compared with placebo (odds ratio 1.68; 95% confidence interval [CI] 0.72−3.92).[2] Multiple large cohort studies have since confirmed that conventional antipsychotics are associated with a higher risk of mortality than atypical antipsychotics and no use.[3] The association was present in general elderly populations, residents of nursing homes, and in patients with and patients without dementia. In several studies, haloperidol in particular increased the risk of mortality.[4,5] In 2008, the US Food and Drug Administration and the UK Commission for Drug Safety warned against use of conventional antipsychotics in elderly patients with dementia.[6,7] Health care professionals were advised to consider other, nonpharmacological, management options.

The cohort studies that reported the mortality risk of conventional antipsychotics used extensive administrative databases incorporating sociodemographic data, medical diagnoses, and filed prescriptions.

The authors declare no conflicts of interest.

* Address correspondence to Hendrika J. Luijendijk, MPH, MD, PhD, University Medical Center Groningen, Department of General Practice, Postbus 196, 9700 AD Groningen, The Netherlands.
E-mail address: h.j.luijendijk@umcg.nl (H.J. Luijendijk).

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Some studies applied advanced statistical techniques to adjust for confounders. Nevertheless, results of observational studies may be biased, even if the studies are of high quality. One source of bias might be that none of the studies took severity of illness into account.[8] This is a potentially strong confounder because haloperidol and chlorpromazine are often used to treat the symptoms of delirium in terminally ill patients.[9,10] These 2 drugs accounted for more than half of the conventional antipsychotics used.[8]

Evidence from experimental data is scarce. Two meta-analyses of randomized controlled trials (RCTs) have reported the risk of various adverse effects of conventional antipsychotics in patients with dementia, but not the risk of mortality.[1,11] Moreover, the risk of mortality presented in the 2005 meta-analysis was based on an unplanned subanalysis of 2 trials.[2] More trials that tested haloperidol and other conventional antipsychotics in patients with dementia have been published.[1,11] Information from trials in delirium may be valuable as well. Delirium, like dementia, is characterized by cognitive impairment and is indicative of frailty in an elderly patient. Many patients with delirium have a history of premorbid cognitive disorders or dementia, and patients with behavioral or psychological symptoms in dementia may have delirium.[12,13] Also, the use of haloperidol to prevent delirium in frail elderly patients has been advocated in recent years, and tested in trials.[14]

In general, the study period of trials is too short and the number of participants too small to detect infrequent adverse events such as deaths. However, the observational studies have suggested that deaths due to conventional antipsychotic use are rather common during the first 180 days of use (4.2%–7.3% of users),[3] and the relative risk of dying is highest in the first month when compared with atypical antipsychotics.[8] Trials to test antipsychotics for neuropsychiatric symptoms of dementia usually last 3 months or longer. The aim of this study was to perform a systematic review and meta-analysis of randomized trials to establish the mortality risk of conventional antipsychotics compared with placebo in elderly patients with dementia or delirium. We investigated (1) the conventional antipsychotics that were available in the study periods of the cohort studies (1994–2010), and (2) haloperidol, because this drug is the most popular conventional antipsychotic for psychosis and aggression related to dementia and delirium.

Methods

We set out to perform a systematic review and meta-analysis of RCTs using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) method to rate the quality of the evidence.[15]

Setting and Participants

We included RCTs that tested the efficacy of a conventional antipsychotic compared with placebo in participants aged 65 years or older who had diagnosed dementia, or delirium, or were frail and at risk of delirium. We excluded RCTs among patients with schizophrenia, advanced cancer, or terminal illness, and studies with multiple drugs in an intervention arm.

Intervention

The following drugs were considered to be conventional antipsychotics[16]: chlorpromazine, chlorprothixene, droperidol, flupentixol, fluphenazine, haloperidol, levomepromazine, loxapine, mesoridazine, molindone, pericyazine, perphenazine, pimozide, prochlorperazine, thioridazine, thiothixene, trifluoperazine, and zuclopenthixol.

Outcome Measure

Primary outcome measure was the number of participants who died between the start and the end of the study. Deaths of participants after the end of the study were excluded from the analyses.

Search Strategy

Two investigators performed the literature search and selected the studies (TAH, HJL). Three sources were used to identify studies: (1) electronic databases, (2) references of published systematic reviews and meta-analyses, and (3) trial registration Web sites. The electronic databases covered PubMed, CINAHL, and Embase. To search RCTs, the search strings ['generic name conventional antipsychotic' AND trial] and [dementia OR delirium] were used to find studies. Second, published systematic reviews and meta-analyses also were identified with PubMed, CINAHL, and Embase databases. The references in these systematic reviews were hand-searched. Title and abstract of potentially eligible studies were retrieved in PubMed. Third, RCTs were searched in the trial registries clinicaltrials.gov and controlled-trials.com for all the conventional antipsychotics mentioned previously. There were no restrictions with respect to publication date, language, or duration of the study.

If studies seemed potentially eligible given title and abstract, full articles of published studies and online protocols of unpublished studies were retrieved. These articles and protocols were reviewed for definitive eligibility.

Data Extraction

Two reviewers (TAH, HJL) independently extracted the following data from the included studies: setting, type of patients, treatment groups, number of randomized patients in each treatment group, mean dose and range of administered haloperidol, study period, dropouts per group, and number of deaths per group. When mortality rates or other data were not reported, the corresponding author was contacted by e-mail and asked to provide the missing information. Only data from the first part of crossover studies (before actual crossover) was included.

GRADE and Risk of Bias

We followed the GRADE recommendation to rate the quality of overall evidence according to 5 items: risk of bias, inconsistency, indirectness, imprecision, and other considerations.[15] The items are to be graded as either "serious risk" or "no serious risk."

Three reviewers (TAH, SUZ, HJL) independently assessed the risk of bias in the RCTs with the Cochrane Collaboration risk of bias assessment tool.[17] This tool covers 6 items: (1) random sequence generation; (2) allocation concealment; (3) blinding of participants, health care personnel, and outcome assessors; (4) incomplete outcome data addressed adequately; (5) absence of selective reporting; and (6) absence of other potential sources of bias such as commercial funding. The reviewers also assessed (7) absence of baseline differences between treatment groups, because lack of baseline differences is the goal of randomization (items 1 and 2). Characteristics that predict risk of dying, such as age, sex, race, and history of (cerebro)vascular disease, were of particular interest to the aim of our study. The last item was (8) low overall dropout (<20%)[18] and comparable dropout across treatment arms (<5% difference). Each item was scored as low, high, or unclear risk of bias. Disagreements were resolved by consensus.