Efficacy of Oral Risperidone, Haloperidol, or Placebo for Symptoms of Delirium Among Patients in Palliative Care: A Randomized Clinical Trial.

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Abstract (abbreviated from original text)**:**

Importance: Antipsychotics are widely used for distressing symptoms of delirium, but efficacy has not been established in placebo-controlled trials in palliative care.

Objective: To determine efficacy of risperidone or haloperidol relative to placebo in relieving target symptoms of delirium associated with distress among patients receiving palliative care.

Design, Setting, and Participants: A double-blind, parallel-arm, dose-titrated randomized clinical trial was conducted at 11 Australian inpatient hospice or hospital palliative care services between August 13, 2008, and April 2, 2014…

Interventions: Age-adjusted titrated doses of oral risperidone, haloperidol, or placebo solution were administered every 12 hours for 72 hours, based on symptoms of delirium. Patients also received supportive care, individualized treatment of delirium precipitants, and subcutaneous midazolam hydrochloride as required for severe distress or safety.

Main Outcome and Measures: Improvement in mean group difference of delirium symptom score (severity range, 0-6) between baseline and day 3 …

Results: 247 participants were included (82 risperidone, 81 haloperidol, and 84 placebo). In the primary intention-to-treat analysis, participants in the risperidone arm had delirium symptom scores that were significantly higher than the placebo arm (on average 0.48 Units higher; 95% CI, 0.09-0.86; $P = .02$) at study end. Similarly, in the haloperidol arm, delirium symptom scores were on average 0.24 Units higher (95% CI, 0.06-0.42; $P = .009$) than in the placebo arm …

Conclusions and Relevance: In patients receiving palliative care, individualized management of delirium precipitants and supportive strategies result in lower scores and shorter duration of target distressing delirium symptoms than when risperidone or haloperidol are added.

Strengths: Publicly funded, prospective, multi-centre, double-blinded, placebo-controlled randomized trial that was powered to detect clinically relevant differences. Findings are

applicable to palliative in-patients with mild-moderate delirium symptoms. Study period and drug dosing were relevant to clinical practice. Randomized patients had comparable baseline.

Weaknesses: Possible selection bias as 750 of 1819 referred patients were not approached for "other reasons". Significant discontinuation rates in treatment arms (22%-38%) and missing data was imputed. Findings do not apply to severe or terminal delirium. Primary outcomes were statistically different but did not reach clinical significance as defined by the authors (0.48 vs 1).

<u>Relevance to palliative care:</u> Antipsychotic are commonly prescribed for delirium in palliative patients. This study suggests antipsychotics do not reduce the severity or duration of delirium in palliative in-patients compared to placebo. Further studies are required to confirm whether antipsychotics lead to increased mortality in this population.