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

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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, among participants with life-limiting illness, delirium, and a delirium symptoms score (sum of Nursing Delirium Screening Scale behavioral, communication, and perceptual items) of 1 or more.

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. Five a priori secondary outcomes: delirium severity, midazolam use, extrapyramidal effects, sedation, and survival.

RESULTS Two hundred forty-seven participants (mean [SD] age, 74.9 [9.8] years; 85 women [34.4%]; 218 with cancer [88.3%]) were included in intention-to-treat analysis (82 receiving risperidone, 81 receiving haloperidol, and 84 receiving placebo). In the primary intention-to-treat analysis, participants in the risperidone arm had delirium symptom scores that were significantly higher than those among participants in the placebo arm (on average 0.48 Units higher; 95% CI, 0.09-0.86; $P = .02$) at study end. Similarly, for those 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. Compared with placebo, patients in both active arms had more extrapyramidal effects (risperidone, 0.73; 95% CI, 0.09-1.37; $P = .03$; and haloperidol, 0.79; 95% CI, 0.17-1.41; $P = .01$). Participants in the placebo group had better overall survival than those receiving haloperidol (hazard ratio, 1.73; 95% CI, 1.20-2.50; $P = .003$), but this was not significant for placebo vs risperidone (hazard ratio, 1.29; 95% CI, 0.91-1.84; $P = .14$).

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.

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Delirium is highly prevalent in patients receiving palliative care, with up to 4 in 10 people having delirium on admission to a palliative care unit, and higher rates seen at the end of life.[1] Symptom relief is important to reduce the known distress associated with delirium; thus, effective, evidence-based management strategies that optimally balance benefits and risks are needed.[2]

Management of delirium includes treating remediable causes and nonpharmacologic and pharmacologic interventions, with goals of treatment to reduce distress, maintain safety, and resolve delirium wherever possible.[3] Antipsychotic drugs are widely used for selected symptoms of delirium,[4,5] despite few supporting data.[6] The role of dopamine and cholinergic imbalance in the pathophysiology of delirium underpinned their use.[7] Internationally, there is no approved medication for the symptomatic treatment of delirium, to our knowledge. Clinical guidelines[3] recommend antipsychotic drugs to be reserved for severe distress or behavioral disturbance, when other strategies have been ineffective or are inappropriate, with consideration of patient safety.

Outside the field of palliative care, uncertainty remains about the role of antipsychotic drugs. Randomized clinical trials (RCTs) of antipsychotic drugs for managing established delirium suggest there is potential to improve overall delirium severity[8-14]; however, all the RCTs had significant methodological limitations: one had flawed concealment of allocation,[9] several were inadequately powered,[8-14] and only 3 were placebo-controlled.[9,10,14] Two adequately powered placebo-controlled studies of antipsychotics in critically ill adults (including people with established delirium)[15,16] found no difference in the number of delirium-free days.

In palliative care, an adequately powered comparison is needed to evaluate whether antipsychotic drugs improve the management and resolution of symptoms of delirium in this population. The aim of this study was to determine if risperidone or haloperidol, given in addition to managing precipitants of delirium and providing individualized supportive nursing care, provides additional benefits in reducing target symptoms of delirium associated with distress when compared with placebo. The primary null hypothesis was that there was no difference between risperidone and placebo, and secondarily, no difference between haloperidol and placebo.

Key Points

Question What are the benefits of risperidone or haloperidol in reducing distressing symptoms of delirium in patients receiving palliative care?

Findings In this randomized clinical trial of 247 participants receiving palliative care, distressing behavioral, communication, and perceptual symptoms of delirium were significantly greater in those treated with antipsychotics (risperidone or haloperidol) than in those receiving placebo.

Meaning Antipsychotic drugs are not useful to reduce symptoms of delirium associated with distress in patients receiving palliative care.

Methods

Study Setting

This multi-site, double blind, parallel arm, dose-titrated, placebo-controlled randomized clinical trial was funded by the Australian Government's National Palliative Care Program and conducted by the Australian national Palliative Care Clinical Studies Collaborative in 11 inpatient hospice or palliative care services from August 13, 2008, to April 2, 2014. It was overseen by an Independent Data Safety Monitoring Committee and had relevant approval from the Flinders Clinical Research Ethics Committee (Adelaide, South Australia), Mater Health Services Human Research Ethics Committee (Brisbane, Queensland), Peter MacCallum Cancer Centre Ethics Committee (Melbourne, Victoria), Repatriation General Hospital Research and Ethics Committee (Adelaide, South Australia), South Western Sydney Human Research Ethics Committee, Cancer Institute New South Wales Clinical Research Ethics Committee, Melbourne Health Human Research Ethics Committee, St Vincent's Hospital Melbourne Human Research Ethics Committee, Barwon Health Human Research Ethics Committee (Geelong, Victoria), Alfred Health Human Ethics Committee (Melbourne, Victoria), Queensland Government Guardianship and Administrative Tribunal, and the New South Wales Guardianship Tribunal. Each participant's proxy (defined by Australian state legislation) provided written informed consent. If the participant's delirium resolved, written informed participant consent was obtained from the participant. The trial protocol, which contained the statistical analysis plan, appears in Supplement 1.

Participants

Participants included adult patients receiving hospice or palliative care with advanced, progressive disease that was no longer curable who required inpatient care by a specialist palliative care team. Participants needed to meet the following 3 criteria: delirium diagnosed via criteria from the *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition, Text Revision), Memorial Delirium Assessment Scale (MDAS) score of 7 or more, and presence of the target symptoms of delirium associated with distress, defined as a delirium symptoms score of 1 or more (sum of the scores from items 2 [inappropriate behavior], 3 [inappropriate communication], and 4 [illusions and hallucinations] on the Nursing Delirium Screening Scale [NuDESC] [severity range, 0-6]).

Exclusion criteria included delirium due to substance withdrawal, history of neuroleptic malignant syndrome, regular use of antipsychotic drugs within 48 hours (a single as-needed dose was allowed if administered more than 24 hours before the study for a nondelirium indication), previous adverse reaction to antipsychotic drugs, extrapyramidal disorders, prolonged QT interval, clinician-predicted survival of 7 days or fewer, cerebrovascular accident or seizure in the prior 30 days, and pregnancy or breastfeeding. Participants were required to speak English and be able to swallow liquids.

Randomization and Masking

Site randomization schedules were generated using random number tables at an independent blinded central registry. Participants were randomized in blocks of 6 by site in a 1:1:1 ratio by arm. Allocation concealment was by sealed opaque envelopes. Site clinical trial pharmacists who opened the treatment schedules to prepare the intervention were not otherwise involved in patient care. Study medication was dispensed in opaque screw-top bottles, which were identical in terms of volume, color, and smell and taste of the contents. Treatment assignment was double-blinded: both participants and investigators were masked to treatment group for the duration of the study.

Procedures

Eligible participants were randomly assigned to receive oral risperidone, haloperidol, or placebo solution at diagnosis of delirium for the control of target delirium symptoms (delirium-induced behavior, communication, and/or perceptual disturbance). Dosing was based on prior controlled trials.[11] Participants 65 years or younger received a 0.5 mg loading dose administered with the first dose of 0.5 mg, then 0.5 mg maintenance doses every 12 hours. Doses could be titrated by 0.25 mg on day 1 and by 0.5 mg thereafter to a maximum dose of 4 mg/d. For participants older than 65 years, the loading, initial, and maximum doses were halved. The placebo solution was titrated similarly using matching volumes of solution for each dose level.

Doses were increased if the sum of NuDESC scores for items 2, 3, and 4 (delirium symptoms score) was 1 or more at the most recent assessment, conducted every 8 hours. Dose reduction to the prior dose could occur for adverse effects, resolution of delirium (MDAS score of <7 for 48 hours), or resolution of symptoms (all NuDESC item scores <1 for 48 hours). Study treatment duration was 72 hours, with the last assessment performed 12 hours after the sixth dose. All participants received individualized treatment plans, including treatment of reversible precipitants where clinically indicated and nonpharmacologic measures[3] (hydration, vision and hearing aids, presence of family, and reorientation), as appropriate.

Protocol-defined as-needed subcutaneous midazolam hydrochloride, 2.5 mg, was available (every 2 hours) when participants scored 2 on the NuDESC item for inappropriate behavior or illusions and hallucinations, and were deemed to require immediate intervention for safety or distress. Intravenous benztropine mesylate, 1 to 2 mg, was available for serious extrapyramidal adverse effects. Participants were observed daily, with NuDESC scores measured every 8 hours by trained nurses and MDAS scores, use of rescue midazolam, adverse effects, and vital status assessed daily. Site initiation involved standardized cases and training for calibration of key measures.

The study drug was discontinued if adverse effects became unacceptable, the treating clinician deemed the treatment ineffective, or at onset of dysphagia. Maintenance of blinded study medication was optional for an additional 48 hours if a partial response occurred or to taper the dose with resolution of symptoms.

Outcomes

The a priori primary outcome was the average of the last 2 delirium symptom scores on day 3, using the baseline score (average of the eligibility delirium symptom score and the score before the first dose of the study drug) as a covariate. Secondary outcomes included daily MDAS score, lowest delirium symptoms score, daily use of midazolam use, extrapyramidal symptoms assessed by the Extrapyramidal Symptom Rating Scale, sedation assessed by the Richmond Agitation-Sedation Scale, National Cancer Institute Common Terminology Criteria for Adverse Events, and survival.

Baseline covariates included clinician-identified known prior cognitive impairment (all cause), Informant Questionnaire on Cognitive Decline in the Elderly score, comorbidity burden (Cumulative Illness Rating Scale score), vision or hearing impairment, daily oral morphine and diazepam equivalents, and the Australia-modified Karnofsky Performance Status score.

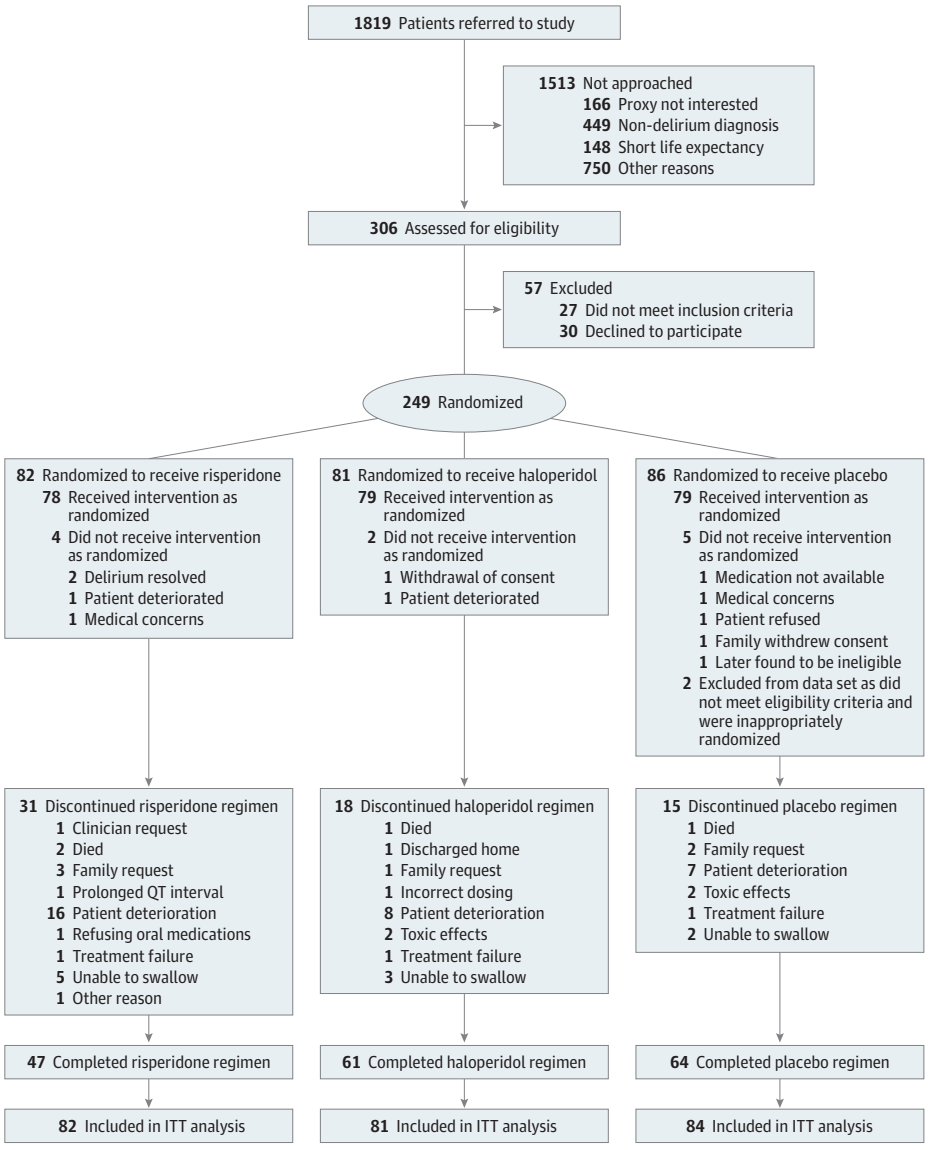
Statistical Analysis

There are no agreed-upon primary outcome measures for assessing changes in symptoms of delirium associated with distress, nor are there agreed-upon minimally important clinical differences for measuring improvement. Prior RCTs have used delirium symptom scores that include symptoms that are not treated with antipsychotic drugs in clinical practice. For our study, palliative care physicians, geriatricians, and geriatric psychiatrists agreed through consensus that the NuDESC-derived total score on items 2, 3, and 4 (delirium symptoms score) was the best available primary end point, with a 1-Unit decrease between baseline and follow-up deemed the minimum clinically significant difference. The choice of target symptoms was informed by qualitative literature of patient distress in delirium, including in palliative care.[17] The measure also needed to allow frequent measurement of symptoms of delirium without undue burden on participants. Fifty-five participants completing the study in the risperidone and placebo arms provides 80% power for a 1-Unit change in NuDESC score,[18] assuming a baseline SD of 1.92 and correlation of 0.5 or more between baseline and follow-up scores. This required 80 randomizations per arm to manage expected attrition.

The primary analysis was conducted from October 2014 through September 2015 on an intention-to-treat basis. Missing scores were imputed using multiple imputation, drawing 50 resamples, with predictive mean matching using age, sex, eligibility delirium symptoms score, Australia-modified Karnofsky Performance Status score, Cumulative Illness Rating Scale score, baseline morphine and diazepam equivalents, and presence of preexisting cognitive impairment and life-limiting illness. The change between baseline and the average of the last 2 observations on day 3 were compared between each active treatment group and placebo using analysis of covariance.

A mixed-effects model using observed data only was conducted for delirium symptom scores, MDAS score, Richmond Agitation Sedation Scale score, and extrapyramidal effects. Each outcome was modeled over time using random

Figure 1. Numbers of Participants Assessed and Enrolled in the Trial



ITT indicates intention-to-treat.

effects mixed modeling, controlling for the same variables used to impute in the primary analysis. Time was measured as hours from the first dose. Participants and site were entered as random effects. The fixed effects comprised covariates (treatment group, sex, age, cancer diagnosis, Australia-modified Karnofsky Performance Status, Cumulative Illness Rating Scale score, prior cognitive impairment, and oral morphine and diazepam equivalents), time, and the product term time by group. Time was reparametized to improve model fit by adding a time squared term in some models. Mixed models were validated by examining the residuals visually for normality, homoscedasticity, and independence, using quantile normal and scatter plots. Overall, difference in survival was modeled using a Cox proportional hazards regression frailty model, clustering over site, having verified that the proportional hazards assumption was met. Differences in the proportion using midazolam and level of use in those who received the drug was assessed using χ^2 and Mann-Whitney tests, respectively. $P < .05$ (2-tailed) was considered significant, with 95% CIs reported. Analyses were conducted using Stata, version 13.1 (StataCorp).

Results

Two hundred forty-nine participants were randomized. Two were removed because they did not meet inclusion criteria, leaving a study sample of 247 participants (82 receiving risperidone, 81 receiving haloperidol, and 84 receiving placebo) (**Figure 1**). The study reached its preplanned sample size, with comparable clinicodemographic baseline data between arms (**Table 1**). The number of observations and mean delirium symptom score, per day and by group, is outlined in the eTable in Supplement 2.

Table 1. Baseline Sample Characteristics by Group

Characteristic	Risperidone (n = 82)	Haloperidol (n = 81)	Placebo (n = 84)
Delirium symptom score, mean (SD)[a]	2.54 (1.23)	2.60 (1.48)	2.54 (1.43)
Female sex, No. (%)	25 (31)	33 (41)	27 (32)
Age, mean, (SD), y	74.5 (10.6)	76.5 (8.2)	73.8 (10.7)
Age <65 y, No. (%)	18 (22)	8 (10)	17 (20)
Cancer diagnosis, No. (%)	76 (93)	67 (83)	75 (89)
Performance status (AKPS) score, median (IQR)	40 (30-50)	50 (40-50)	40 (30-50)
CIRS score, median (IQR)	24 (21-28)	23 (20-26)	25 (21-29)
Cognitive impairment, No. (%)	18 (22)	17 (21)	14 (17)
ESRS score, median (IQR)	5.0 (1.0-8.5)	4.0 (1.0-8.0)	4.5 (2.0-9.0)
MDAS score, median (IQR)	15.1 (5.8)	14.6 (5.0)	13.7 (4.8)
Opioid dose, median (IQR)[b]	6.9 (0-88.2)	33.0 (0-153.5)	15.0 (0-86.4)
Patients receiving opioids, No. (%)	39 (48)	31 (38)	35 (42)
Benzodiazepine dose, median (IQR)[c]	0 (0-0.63)	0 (0-0)	0 (0-0)
IQCODE score, median (IQR)	4.1 (3.0-4.9)	4 (3.2-4.6)	4.2 (3.5-4.7)

Abbreviations: AKPS, Australia-modified Karnofsky Performance status; CIRS, Cumulative Illness Rating Scale; ESRS, Extrapyramidal Symptoms Rating Scale; IQCODE, Informant Questionnaire on Cognitive Decline in the Elderly; IQR, Interquartile range; MDAS, Memorial Delirium Assessment Scale.

[a] Scores of items 2, 3, and 4 of the Nursing Delirium Screening Scale. For further description of primary outcome, see the Statistical Analysis subsection in the Methods section.

[b] Oral morphine equivalents (in milligrams).

[c] Oral Diazepam equivalents (in milligrams).

In primary intention-to-treat analyses between risperidone and placebo (n = 166), those in the risperidone arm had significantly greater delirium symptom scores that were, on average, 0.48 Units (95% CI, 0.09-0.86; $P = .02$) higher than those in the placebo group at study end. Similarly, patients in the haloperidol arm also experienced significantly greater delirium symptoms than those in the placebo arm at study end that were, on average, 0.24 Units higher (95% CI, 0.06-0.42; $P = .009$).

Secondary multivariable mixed-model analysis of delirium corroborates these results (**Table 2** and **Figure 2**). Delirium symptom scores per day were higher in patients taking risperidone relative to those receiving placebo on average by 0.24 Units (95% CI, 0.11-0.38; $P < .001$). Similarly, patients receiving haloperidol had delirium symptom scores that were, on average 0.21 Units (95% CI, 0.08-0.34; $P = .002$) higher per day than those receiving placebo.

Participants receiving risperidone also had a significantly higher MDAS score (delirium severity) per day than those in the placebo arm, with a mean difference of 0.96 (95% CI, 0.16-1.77; $P < .001$) (eFigure 1 in Supplement 2). Memorial Delirium Assessment Scale scores were higher per day in those receiving haloperidol vs placebo, but did not reach statistical significance (0.75; 95% CI, −0.03 to 1.51; $P = .06$).

In a post hoc multivariable mixed-model analysis, no statistically significant difference between groups was seen for the lowest delirium symptom score achieved during the study period (after baseline). The mean lowest achieved score was 0.15 Units higher in the risperidone group compared with those receiving placebo (95% CI, -0.16 to 0.48; $P = .31$) and 0.01 Units lower in the haloperidol group compared with those receiving placebo (95% CI, −0.41 to 0.43; $P = .95$).

There were statistically significantly greater mean extrapyramidal effects in the risperidone vs placebo arms each day (0.73; 95% CI, 0.09-1.37; $P = .03$) and in the haloperidol vs placebo arms (0.79; 95% CI, 0.17-1.41; $P = .01$). There were no differences in subscale scores for parkinsonism and akathisia and no serious extrapyramidal adverse effects.

For those taking risperidone compared with placebo, there were no significant differences in the Richmond Agitation Sedation scores per day (-0.05; 95% CI, −0.19 to 0.09; $P = .52$), but a significant difference between scores per day for those taking haloperidol vs placebo (-0.14; 95% CI, −0.28 to −0.00; $P = .048$). A greater proportion of participants in the placebo group (39 of 62 [62.9%]) had a Richmond Agitation-Sedation Scale score of 0 (no sedation or agitation) at study end than in either the risperidone (25 of 46 [54.3%]) or haloperidol (33 of 61 [54.1%]) groups, but this was not statistically significant (χ^2; $P = .55$).

Thirty-four participants died during the study period (9 in the placebo group, 9 in the haloperidol group, and 16 in the risperidone group). For overall survival, those receiving risperidone were 29% more likely to die vs those receiving placebo (hazard ratio, 1.29; 95% CI, 0.91-1.84; $P = .14$), while those receiving haloperidol were 73% more likely to die (hazard ratio, 1.73; 95% CI, 1.20-2.50; $P = .003$) vs those receiving placebo (**Figure 3**). Median survival for all participants in the placebo group was 26 days compared with 17 days for those in the risperidone arm and 16 days for those in the haloperidol arm. In a post hoc analysis, those receiving an antipsychotic drug were approximately 1.5 times more likely to die (hazard ratio, 1.47; 95% CI, 0.18-2.01; $P = .01$).

In post hoc analysis, for those older than 65 years, there was no significant difference between arms in mean dose at study end ($P = .09$) (eFigure 2A in Supplement 2). In those 65 years or younger, those in the placebo arm had less titration, with a lower mean dose ($P = .01$) (eFigure 2B in Supplement 2).

Midazolam use was significantly lower among those in the placebo arm compared with the risperidone and haloperidol arms combined on each study day (13 of 75 [17.3%] vs 50 of 144 [34.7%] on day 1; $P = .007$; 11 of 68 [16.8%] vs 40 of 121 [33.1%] on day 2; $P = .01$; and 9 of 66 [13.6%] vs 32 of 108 [29.6%] on day 3; $P = .02$). For those who needed rescue midazolam, the median (interquartile range) dosage during the study was 2.5 mg (2.5-5.0 mg) for those receiving placebo, 2.5 mg (2.5-5.0

Table 2. Variables Associated With Delirium Symptoms at 72 Hours Using Multivariable Random Effects Mixed-Model Analysis[a]

Delirium Symptom Score	β (95% CI) Univariable	Multivariable
Changes between groups at 72 h		
Placebo [reference][b]	0	0
Risperidone	0.66 (0.11 to 1.20)[c]	0.64 (0.10 to 1.19)[c]
Haloperidol	0.68 (0.16 to 1.20)[c]	0.70 (0.17 to 1.23)[c]
Female	−0.05 (−0.33 to 0.23)	−0.25 (−0.51 to 0.02)
Age, y	0.01 (0.24 to 0.43)	0.00 (−0.02 to 0.01)
Cancer diagnosis	−0.74 (−1.16 to −0.33)[d]	−0.70 (−1.13 to −0.27)[e]
AKPS score	−0.19 (−0.29 to −0.09)[d]	−0.17 (−0.27 to −0.08)[d]
CIRS score	−0.01 (−0.03 to 0.02)	−0.01 (−0.03 to 0.01)
Cognitive impairment	−0.01 (−0.35 to 0.32)	−0.13 (−0.44 to 0.19)
Oral morphine equivalent[f]	−0.01 (−0.02 to −0.00)[c]	−0.010 (−0.02 to −0.00)[c]
Oral diazepam equivalent	−0.00 (−0.02 to 0.02)	−0.00 (−0.02 to 0.02)

Abbreviations: AKPS, Australia-modified Karnofsky Performance status; CIRS, Cumulative Illness Rating Scale.

[a] The dependent variable was delirium symptom score at each day. The independent variables also included interaction terms, time × risperidone, and time × haloperidol. The relative difference in improvement between groups at 72 hours was determined using Stata's lincom function.

[b] Absolute reduction in delirium symptom score in placebo group at 72 hours is 1.79 (95% CI, 1.43-2.16).

[c] $P < .05$.

[d] $P < .001$.

[e] $P < .01$.

[f] Effect is for a 10-Unit increase.

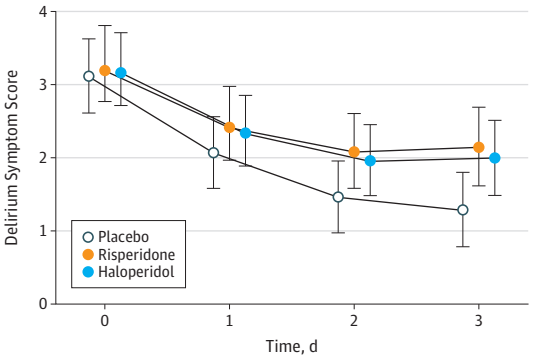
mg) for those receiving risperidone, and 4 mg (2.5-5.0 mg) for those receiving haloperidol. There was no difference in the median dosage between arms on any day or overall ($P > .20$).

Discussion

This RCT has demonstrated that behavioral, communication, and perceptual symptoms of delirium associated with distress in patients receiving palliative care were greater in those treated with antipsychotic drugs than in those receiving placebo. This finding was mirrored in delirium severity, with higher MDAS scores in patients in both antipsychotic arms compared with those receiving placebo. There was also no difference in the mean lowest delirium symptom score achieved between the 3 groups. There were no significant differences in baseline characteristics between the arms, including delirium symptom scores and delirium severity (MDAS scores). Better symptom control occurred in patients in the placebo arm without increased use of rescue midazolam, and less dose titration for those 65 years or younger. More important, the outcomes and direction of findings in the haloperidol and risperidone groups for key measures were similar, suggesting that this may be an antipsychotic class effect, limiting any likelihood of a type II error. Poorer overall survival in the haloperidol group compared with those in the placebo group warrants further study given the association of antipsychotic drugs and premature death in patients with dementia[19] and widespread use of haloperidol for delirium.[4] Possible mechanisms for this poorer survival include persistent delirium or longer-term exposure to antipsychotic drugs after the study period. These data suggest that approaches that identify delirium early, treat underlying precipitant(s) if appropriate, and provide other evidence-based supportive measures provide better reduction in symptoms of delirium associated with distress.[3,20,21] This finding is aligned with those of prior studies that have demonstrated that even in palliative care inpatient or hospice settings, delirium is reversible in up to half of patients.[22,23]

Open-label, single-arm studies of antipsychotics in patients with cancer or receiving palliative care[24] have demon-

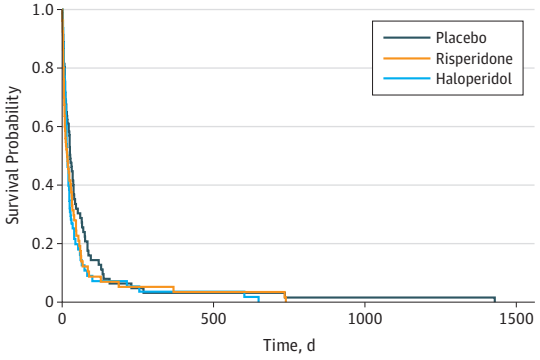
Figure 2. Secondary Multivariable Mixed-Model Analysis of Delirium



No. at risk				
Placebo	84	63	59	55
Risperidone	82	58	49	39
Haloperidol	81	64	55	51

The dependent variable was delirium score at each day. The independent variables comprise the covariates in Table 2, group, time, and 2 interaction terms, time × risperidone and time × haloperidol. The relative difference in improvement between groups at 72 hours was determined using the *lincom* function in Stata. Placebo vs risperidone: $P < .001$; placebo vs haloperidol: $P = .002$. Error bars indicate 95% CIs.

Figure 3. Kaplan-Meier Survival of Participants Who Died at 6 Months



No. at risk				
Placebo	81	2	1	0
Risperidone	80	2	0	0
Haloperidol	79	2	0	0

Overall survival modeled using multivariable Cox regression. Risperidone vs placebo: $P = .14$; haloperidol vs placebo: $P = .003$.

strated that delirium severity is reduced over time, but failed to compare that reduction with the natural history of delirium resolution by including a placebo arm. The findings of our adequately powered RCT conflict with those of 3 prior RCTs in established delirium; however, these studies were underpowered, 1 was not adequately blinded, and all were conducted outside the field of palliative care and oncology.[9,10,14] Prior adequately powered RCTs in patients in the intensive care unit included participants with and without delirium but did not find differences in days without delirium; however, owing to significant differences between populations receiving palliative care and those in the intensive care unit, direct comparison is not possible.[15,16] A recent meta-analysis that combined evidence for antipsychotic drugs for the treatment or prevention of delirium in hospitalized patients and those in the intensive care unit also did not demonstrate an effect in reducing the severity or duration of delirium.[25] Furthermore, exploring improvements in delirium symptom scores captures a range of symptoms that would not be target symptoms in palliative care clinical practice, and achieving complete resolution of delirium in patients receiving palliative care is often not possible.

Two prior studies outside the field of palliative care demonstrated that multicomponent management of delirium, including early detection with screening, medication review, optimizing hydration, orientation strategies, and mobilization, can alleviate symptoms of delirium earlier, but the studies were of low to moderate quality and did not assess these interventions independent of antipsychotic management.[20,21] Further studies are needed to determine which elements of multicomponent management strategies are most efficacious and can be delivered in patients receiving palliative care to reduce symptoms of delirium and associated distress. In our study, regular screening for potential participants might have also fostered earlier identification of delirium with fewer delays in delivery of effective treatment, but this does not explain the differences between study arms.

The dose used in our study was informed by a prior RCT of haloperidol and risperidone[11] that demonstrated a reduction in delirium severity scores at 7 days with a mean (SD) daily dose of 1.71 (0.84) mg of haloperidol (range, 1-3) and 1.02 (-0.41) mg of risperidone (range, 0.5-2.0). Lower doses were used for those 65 years or older based on a recommendation in the intervention product information to use caution for dosing in older people. The doses used in our study were conservative compared with doses reported in practice settings,[4,5,26] and therefore may underestimate adverse consequences of using antipsychotic drugs to treat delirium in routine practice. Chlorpromazine equivalents were used to determine dose equivalence, as the dopamine antagonist action is likely the key mode of action in delirium.[27] A loading dose achieved steady state levels of the drugs rapidly during the early period of delirium when symptoms were likely to be more florid, followed by dose titration if symptoms persisted.

To our knowledge, this is the first adequately powered RCT of delirium treatment that has specifically aimed to assess control of symptoms of delirium that are associated with distress in patients receiving palliative care. The study reflected populations seen in palliative care clinical practice and did not exclude participants who had irreversible causes of delirium. It was not possible to determine the proportion of participants deemed to have irreversible delirium (without or despite medical intervention) during the 72-hour study period, as treatment of underlying precipitants was often ongoing, and there is currently no risk prediction model for prospectively classifying patients at delirium diagnosis for probability of recovery. Another strength of the study was systematic measurement of extrapyramidal adverse effects and other expected adverse effects.

The study population was recruited through palliative or hospice services, but findings can inform symptomatic treatment of people with advanced progressive illnesses that are no longer curable in other settings. To assist in comparison outside the field of palliative care, evaluation of illness severity (eg, Acute Physiological and Chronic Health Evaluation II) would be helpful, but this requires investigations that are often inappropriate in patients receiving palliative care. Most participants had mild to moderate delirium severity (MDAS scores at baseline), limiting generalizability of our findings to people with severe delirium. The primary outcome was at 72 hours and, although resolution of symptoms of delirium can take up to 5 to 7 days,[11] an intervention for symptom relief with no effect on symptoms within 72 hours is unlikely to be of benefit in this patient population.

Limitations

The use of an oral solution was a limitation, leading to ineligibility of some potential participants or subsequent withdrawal of those who developed dysphagia during the study period. It is also possible that the target symptoms of delirium may not have been distressing for the participant. Imputation was also required owing to missing data. In the haloperidol arm, fewer participants were younger than 65 years, the median oral morphine equivalent at baseline was higher, and there were fewer participants with a cancer diagnosis, but these were not statistically significant differences.

The study had 2 main comparisons: placebo vs risperidone and placebo vs haloperidol. We did not allow for multiple comparisons in the protocol, but the *P* values for each primary comparison are both below 0.025 and so would remain significant by any multiple comparison procedure.

Conclusions

Antipsychotic drugs should not be added to manage specific symptoms of delirium that are known to be associated with distress in patients receiving palliative care who have mild to moderately severe delirium. Rather, management relies on ensuring systematic screening (given that two-thirds of people with delirium are not diagnosed on referral to palliative care[28]), reversing the precipitants of delirium, and providing supportive interventions.[29] Further studies are needed to understand how to tailor, implement, and embed screening for delirium and multicomponent supportive interventions into palliative care settings. It is increasingly understood that in-

formed family caregivers are essential, and our trial gave family caregivers information about delirium and its management[30] and, plausibly, this facilitated their better advocacy for care.

Developing more efficacious therapies for prevention and management of delirium is needed. Our study illustrates that adequately powered RCTs of therapies for delirium are feasible and acceptable and can be undertaken even in patients receiving palliative care, while satisfying ethical and legislative requirements. Survival outcomes must be measured, controlling for delirium (persistent or recurrent) and cumulative psychotropic use (antipsychotics and benzodiazepines).

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Invited Commentary

Medicating Distress

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Chlorpromazine hydrochloride first became available in Europe and the United States in the early 1950s. A large, double-blind, placebo-controlled trial that was conducted within the US Veterans Affairs system and included nearly 700 patients (all men aged ≤50 years) helped establish its efficacy for treating schizophrenia.[1] The use of chlorpromazine is credited with large decreases in psychiatric inpatient populations around the world, as well as prompting a widespread search for other antipsychotic drugs.

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However, before the study on schizophrenia was published in 1960,[1] advertisements marketing chlorpromazine (as Thorazine) appeared in the late 1950s for a host of indications and populations, ranging from "prompt control of senile agitation" (featuring a white-haired older man wielding an upraised cane) to "prompt control of nausea and vomiting in children" (with a child leaning over a sink) to "relief from the suffering and mental anguish of cancer." But why stop there? Advertisements also touted Thorazine for the treatment of arthritis, acute alcoholism, and the "psychic stress" of severe asthma. For all varieties of distress, apparently chlorpromazine and similar antipsychotic drugs were the solution.

By 1990, more than 40 antipsychotic drugs had been marketed worldwide,[2] although the indications for use had been narrowed since the 1950s. Although severe asthma is not a common reason for use of antipsychotic drugs in 2016, they are still used for perceived benefit in reducing "psychic stress" or distress. As such, antipsychotic drugs have a long history of use for treating delirium associated with severe or terminal medical illness, although rigorous evidence supporting this use is sparse.[3] In this issue of *JAMA Internal Medicine*, Agar and colleagues[4] provide critical evidence to help guide the use of antipsychotic drugs for delirium in patients receiving palliative care. The short answer is: don't.

The study targeted symptoms of delirium that are associated with distress: inappropriate behavior, inappropriate communication, and illusions or hallucinations. Haloperidol and risperidone were not only not better than placebo but these symptoms actually worsened in patients randomized to receive the antipsychotic drugs, while the patients' overall delirium also worsened. As would be expected, patients receiving the antipsychotic drugs experienced more extrapyramidal effects. Perhaps most concerning, median time to survival was shorter for patients taking antipsychotic drugs, and these patients were approximately 1.5 times more likely to die. This finding is remarkable in a placebo-controlled trial in which patients received just 6 doses of study medication (or placebo) in 72 hours. Hopefully, the study by Agar et al[4] will help convince health care professionals that, in using antipsychotic drugs to treat delirium in terminally ill patients, not only are they not reducing distress but they are in fact worsening patients' symptoms.

What happens now with the use of antipsychotic drugs in this patient population? It may be useful to consider the use of antipsychotic drugs in patients with dementia as a potential guide. The advertisement for Thorazine with the white-haired gentleman wielding a cane illustrates that, since their development, antipsychotic drugs have been seen as useful to treat the distressing behavioral and psychological symptoms of dementia (BPSD). However, as manufacturers sought approval to use the newer atypical antipsychotic drugs specifically for distressing BPSD, it became clear that their use caused an increased risk of death relative to placebo.[5] In 2005, the US Food and Drug Administration issued a black box warning regarding the increased risk of mortality associated with the use of atypical antipsychotic drugs to treat BPSD.

Although the use of atypical antipsychotic drugs did decrease after this warning was issued, the use of conventional antipsychotic drugs, which had been declining up to that point, plateaued. In addition, the use of other psychotropic drugs that were not antipsychotics, with even less evidence of benefit but lacking definitive evidence of harms, grew.[6] And today, despite more than a decade of evidence about the harms of using antipsychotic drugs to treat distressing BPSD, their use per-