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Proportional Sedation for Persistent Agitated Delirium in Palliative Care
A Randomized Clinical Trial

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IMPORTANCE Neuroleptic and benzodiazepine medications are often considered for patients with persistent agitated delirium in the last days of life; however, the risk-to-benefit ratio of these medications is ill-defined and benzodiazepine medications have not been compared to placebo.

OBJECTIVE To compare the effect of scheduled haloperidol, lorazepam, haloperidol plus lorazepam, and placebo on patients with advanced cancer and delirium and experiencing restlessness and/or agitation in the palliative care setting.

DESIGN, SETTINGS, AND PARTICIPANTS This multicenter randomized clinical trial was conducted at 3 acute palliative care units in Taiwan and the US with patients with advanced cancer experiencing persistent restlessness and/or agitation despite nonpharmacologic therapies and standard-dose haloperidol. Among 245 eligible patients, 111 were enrolled, and 75 received blinded treatments. Participants were randomized in a 1:1:1:1 ratio (stratified by site and Richmond Agitation-Sedation Scale [RASS] score). The study period was from July 16, 2019, to June 8, 2023, with a 30-day follow-up after medication administration. Data analysis was performed from October 10, 2023, to April 11, 2025.

INTERVENTIONS Scheduled intravenous haloperidol, lorazepam, haloperidol plus lorazepam, or placebo every 4 hours until discharge, death, or withdrawal from study. Medications in all 4 groups had identical volume and appearance.

MAIN OUTCOMES AND MEASURES Change in RASS scores during the first 24 hours. Secondary outcomes included the use of rescue neuroleptics or benzodiazepines for breakthrough restlessness or agitation during the first 24 hours, delirium severity, perceived patient comfort, and adverse events.

RESULTS The primary outcome was assessed in 72 patients (mean [SD] age, 64 [12] years, 42 male [58%]) with a median (IQR) MDAS score of 24 (18-29). The lorazepam group had significantly lower RASS scores than the haloperidol group (mean difference, −2.1; 95% CI, −3.4 to −0.9; $P < .001$) and the combination group had significantly lower RASS scores than the haloperidol group (−2.0; 95% CI, −3.2 to −0.8; $P = .002$); however, there was no difference observed between haloperidol and placebo groups (−0.5; 95% CI, −1.7 to 0.7; $P = .42$) nor between the combination and lorazepam groups (0.2; 95% CI, −1.1 to 1.4; $P = .79$). The combination and lorazepam groups required fewer rescue medications for breakthrough restlessness or agitation compared to the haloperidol and placebo groups (32%, 37%, 56%, 83%, respectively; $P = .006$). Adverse events or survival did not differ between groups.

CONCLUSIONS AND RELEVANCE The results of this randomized clinical trial indicate that proactive use of scheduled sedatives, particularly lorazepam-based regimens, may reduce persistent restlessness and/or agitation in patients with advanced cancer and delirium in the palliative care setting.

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Visual Abstract
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Delirium is a common and highly distressing neuropsychiatric syndrome that affects more than 90% of patients in the last days or weeks of life.[1-6] Approximately 50% to 70% of patients with delirium develop restlessness and/or agitation, which can be highly distressing to patients, caregivers, and health care professionals and may pose a safety risk for patients.[1,7,8] Unlike delirium in other settings, delirium in the last days of life (ie, end-of-life delirium) is typically irreversible, and many patients continue to have persistent restlessness and/or agitation despite nonpharmacologic measures; thus, effective pharmacologic measures for palliation of delirium symptoms are necessary.[9-11] Neuroleptics and benzodiazepines are often prescribed for persistent restlessness and/or agitation in patients with end-of-life delirium; however, there is much debate regarding their risks and benefits in the palliative care setting due to the paucity of high-quality data and mixed findings.[12-16]

While deep, continuous palliative sedation may be necessary for selected patients with refractory restlessness and/or agitation, proportional sedation with scheduled medications titrated to effect is often considered for patients with persistent agitated delirium who do not respond to standard-dose neuroleptics.[17-20] The options for proportional sedation may include (1) neuroleptic dose escalation; (2) rotation to another medication class, such as benzodiazepines; and (3) combination of neuroleptic and benzodiazepine.[21] To our knowledge, no randomized trial has assessed these strategies against a placebo as control. An improved understanding of the risks and benefits of these strategies may inform the management of this distressing syndrome. The objective of the Rotation, Escalation, Combination or Reduction for Delirium (RECORD) randomized clinical trial was to compare the effect of haloperidol dose escalation, rotation to lorazepam, combination therapy with both lorazepam and haloperidol, and placebo on restlessness and agitation intensity in patients with cancer and delirium admitted under palliative care.

Key Points

Question What is the impact of haloperidol and/or lorazepam on restlessness and agitation in patients with advanced cancer and persistent agitated delirium in the palliative care setting?

Findings In this 4-parallel group, double-blind, randomized clinical trial including 72 patients, the lorazepam group had significantly lower Richmond Agitation-Sedation Scale (RASS) scores compared to the haloperidol alone group; the haloperidol plus lorazepam group also had significantly lower RASS scores compared to the haloperidol group. RASS scores did not differ significantly between haloperidol and placebo groups; however, the placebo group required significantly more rescue doses for breakthrough restlessness and agitation.

Meaning These results indicate that for these patients, proactive use of scheduled sedatives, particularly lorazepam-based regimens, may reduce breakthrough restlessness and agitation.

Methods

The institutional review boards of the 3 participating institutions approved this study protocol and the MD Anderson Cancer Center's Data Safety Monitoring Board provided yearly review (the trial protocol is available in Supplement 1). Each participant's medical power of attorney or legal representative provided written surrogate informed consent. This study adhered to the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline.

Study Design and Participants

The RECORD trial was a randomized, multicenter, double-blind, double-dummy, parallel-group trial conducted from July 16, 2019, to June 8, 2023, with a 30-day follow-up after medication administration. The following were the inclusion criteria: age 18 years or older; advanced cancer diagnosis; admission to an acute palliative care unit (APCU); having delirium as defined by the *Diagnostic and Statistical Manual of Mental Disorders,* 5th edition; having a history of hyperactivity, with Richmond Agitation-Sedation Scale[22,23] (RASS) score of 1 or greater; and taking scheduled haloperidol or required 4 mg/d or more of rescue haloperidol for agitation in the past 24 hours. Patients were excluded if they had myasthenia gravis, acute narrow angle glaucoma, neuroleptic malignant syndrome, active seizure disorder, Parkinson disease, Alzheimer dementia, Lewy Body dementia, QTc prolongation, hypersensitivity to haloperidol or lorazepam, or were taking scheduled lorazepam within the 48 hours prior to study enrollment. Regarding demographic characteristics, sex, race, and ethnicity were collected from patients' electronic health record and were self-reported.

In the APCUs, the specialist palliative care team routinely assessed and treated any underlying causes of delirium and provided nonpharmacologic measures whenever feasible. In previous trials using similar eligibility criteria, patients in the APCU with persistent delirium had days of survival.[14,15]

Randomization and Blinding

Immediately after enrollment, patients were randomized by a study pharmacist and assigned in a 1:1:1:1 ratio to 1 of 4 treatment groups: (1) dose escalation of haloperidol; (2) rotation to lorazepam; (3) combination therapy with lorazepam and haloperidol; and (4) placebo. A total of 2888 patients admitted to the APCU from July 16, 2019, to June 8, 2023, were screened for eligibility. Of the 245 patients (8%) who were fully eligible, 111 (45%) were enrolled and randomized (haloperidol n = 27; lorazepam n = 29; combination n = 28; placebo n = 27). Of these, 75 patients (68%) developed breakthrough restlessness and/or agitation during the open-label haloperidol phase and proceeded to blinded treatment (**Figure 1**). In 3 participants, delivery of the blinded study medication in relation to time 0 was delayed; therefore, their data could not be properly analyzed.

Study medications were continued until death, discharge, or withdrawal. This was done via a centralized website, using permuted block sizes of 4 and 8 and stratified by study site and RASS score at the time of enrollment (≤1 vs ≥2). To ensure allocation concealment, only the study pharmacists had access to the secure website.

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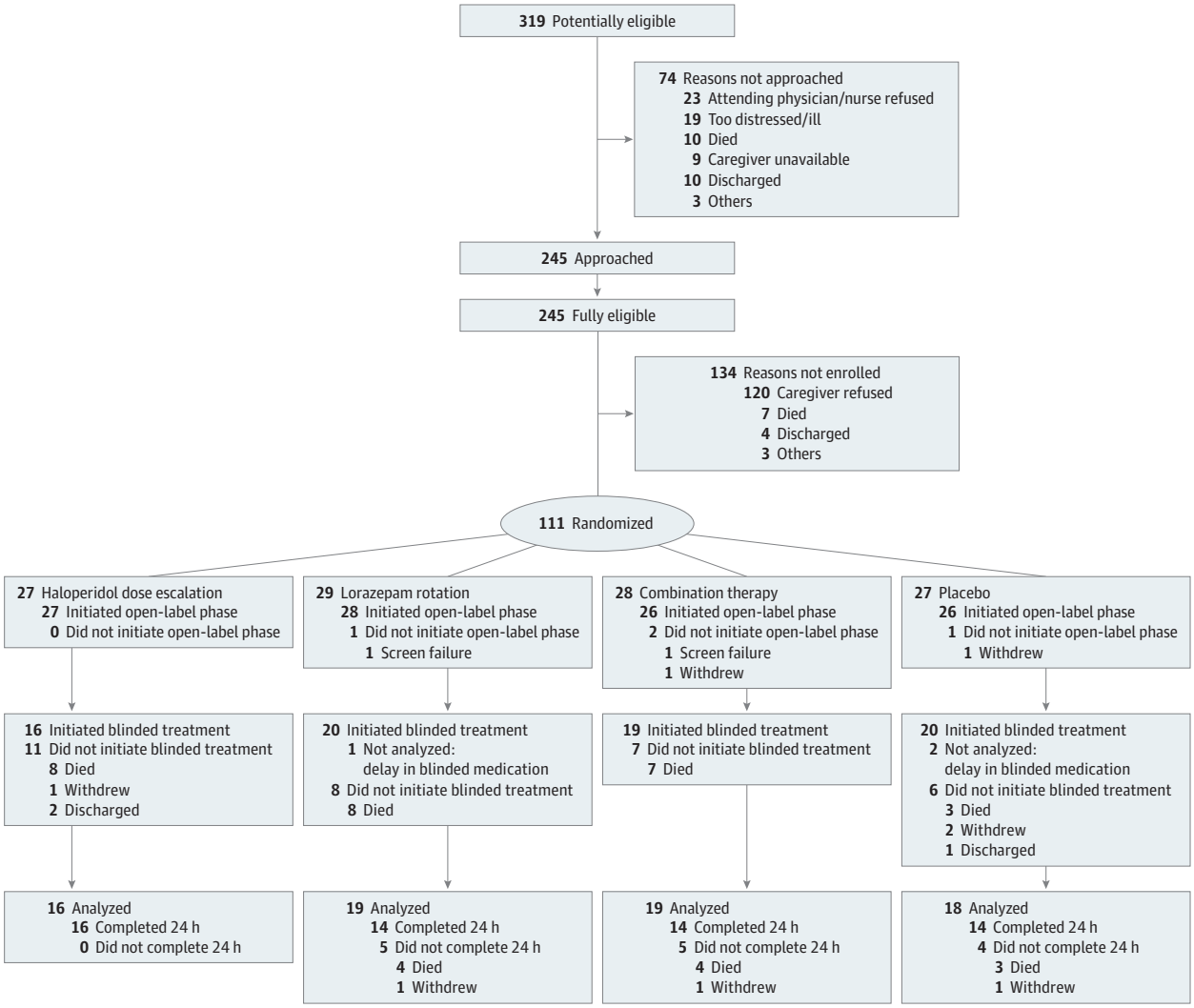
Figure 1. Participant CONSORT Flow Diagram



At enrollment, patients were randomized to haloperidol, lorazepam, haloperidol plus lorazepam, or placebo. All enrolled patients immediately started taking a standardized regimen of haloperidol, 2 mg, every 6 hours intravenously and haloperidol, 2 mg, every 1 hour as needed for restlessness and agitation. Because of the fluctuating nature of delirium, we monitored patients' scores on the Richmond Agitation-Sedation Scale every 2 hours until a score of 1 was reached and required rescue medication according to the bedside nurse's judgment.

We used a double-dummy design with identical-appearing administration bags (lorazepam or placebo) and syringes (haloperidol or placebo) to ensure proper blinding (eTable 1 in Supplement 3). Medications in all 4 groups had identical volume and appearance. Patients, caregivers, research staff conducting study assessments, and the clinical team, including bedside nurses and attending physicians, were blinded to treatment assignment. Blinded caregivers and nurses were asked to identify the treatment assignment after 24 hours.

Trial Procedures

At enrollment, all patients immediately started taking open-label haloperidol, 2 mg, intravenously every 6 hours and 2 mg intravenously every hour as needed, and the nonpharmacologic therapies were implemented (Supplement 3). The open-label phase was designed to standardize the dose of first-line haloperidol and to ensure that patients had persistent restlessness and/or agitation before beginning the blinded study interventions. Patients were monitored regularly until they had a RASS score of 1 or higher and the study medication arrived in the APCU, at which time they started the blinded phase immediately.

During the blinded phase, patients received scheduled medication intravenously every 4 hours plus rescue medication intravenously every hour as needed (RASS score ≥ 1 and the bedside nurse determined that an as-needed dose was warranted). We selected a RASS of 1 as the threshold for initiating second-line therapy because persistent restlessness is distressing and may rapidly evolve into severe agitation;

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Table 1. Patient Characteristics at Time of Enrollment, by Study Group

Variables	Study group, No. (%)[a]			
	Haloperidol (n = 16)	Lorazepam (n = 19)	Combination (n = 19)	Placebo (n = 18)
Age, mean (SD), y	61 (11)	72 (8)	63 (13)	62 (12)
Female[b]	6 (38)	9 (47)	8 (42)	7 (39)
Male	10 (62)	10 (53)	11 (58)	11 (61)
Race[b]				
Asian	4 (25)	4 (21)	4 (21)	4 (22)
Black	1 (6)	4 (21)	5 (26)	3 (17)
White	11 (69)	11 (58)	10 (53)	11 (61)
Ethnicity[b]				
Not Hispanic	13 (81)	18 (95)	17 (90)	16 (89)
Hispanic	3 (19)	1 (5)	2 (11)	2 (11)
Education				
Some high school or less	4 (25)	3 (16)	1 (5)	2 (11)
Completed high school	4 (25)	7 (37)	8 (42)	6 (33)
Some college	4 (25)	6 (32)	5 (26)	8 (44)
Completed college	3 (19)	2 (11)	4 (21)	2 (11)
Advanced degree	1 (6)	1 (5)	1 (5)	0
Cancer type				
Breast	0	0	0	3 (17)
Gastrointestinal	4 (27)	5 (26)	5 (26)	5 (28)
Genitourinary	1 (7)	2 (11)	4 (21)	2 (11)
Gynecological	1 (7)	0	4 (21)	0
Hematological	3 (20)	1 (5)	1 (5)	3 (17)
Respiratory	5 (33)	3 (16)	1 (5)	3 (17)
Other site	0	4 (21)	3 (16)	2 (11)
Metastatic advanced-stage cancer	15 (94)	17 (90)	19 (100)	17 (94)
Karnofsky Performance Status, %[c]				
10	1 (6)	2 (11)	1 (5)	0
20	9 (56)	10 (53)	7 (37)	10 (56)
30	5 (31)	5 (26)	7 (37)	7 (39)
40	1 (6)	2 (11)	4 (21)	1 (5)
Reason(s) for acute palliative care unit admission[d]				
Delirium	13 (81)	14 (74)	16 (84)	16 (89)
Pain	14 (88)	16 (84)	17 (90)	16 (89)
Dyspnea	6 (38)	11 (58)	8 (42)	8 (44)
Others	0	3 (16)	0 (0.0)	2 (11)
Memorial Delirium Assessment Scale, median (IQR)[e]	25 (19-29)	22 (19-25)	25 (18-30)	23 (17-26)
Medication use in 24 h before enrollment				
Haloperidol, scheduled	15 (94)	14 (74)	15 (79)	15 (83)
Haloperidol, as needed	14 (88)	16 (84)	16 (84)	16 (89)
Chlorpromazine, scheduled	1 (6)	1 (5)	1 (5)	0
Chlorpromazine, as needed	5 (31)	10 (53)	5 (26)	6 (33)
Benzodiazepine, scheduled	0	1 (5)	0	0
Benzodiazepine, as needed	4 (25)	8 (42)	7 (37)	2 (11)
Haloperidol use in the 24 h before enrollment, median (IQR), mg				
Scheduled	4.0 (1.0-7.5)	4.5 (2.8-5.5)	4.0 (0.0-6.0)	3.0 (1.0-6.0)
Rescue	5.0 (2.0-8.0)	2.0 (1.5-2.8)	4.0 (2.0-5.0)	4.5 (2.0-8.0)
Rescue doses	2.0 (1.0-4.0)	1.5 (1.0-2.0)	2.0 (1.0-3.0)	2.0 (2.0-3.0)

(continued)

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Table 1. Patient Characteristics at Time of Enrollment, by Study Group (continued)

Variables	Study group, No. (%)[a]			
	Haloperidol (n = 16)	Lorazepam (n = 19)	Combination (n = 19)	Placebo (n = 18)
Communication Capacity Scale, mean (SD)[f]				
Conscious level	2.4 (1.2)	3.3 (1.5)	3.3 (0.9)	2.2 (1.0)
Open-ended questions	2.3 (0.8)	2.5 (0.8)	2.3 (0.9)	2.2 (1.0)
Close-ended questions	1.8 (1.0)	2.2 (1.1)	1.8 (1.2)	1.3 (1.0)
Voluntary communication	2.3 (0.9)	2.4 (1.0)	2.3 (0.9)	1.9 (0.9)
Voluntary movement	2.1 (1.0)	2.3 (0.9)	2.2 (1.0)	1.5 (0.9)
RASS score at 0 h, mean (95% CI)[g]	1.7 (1.2-2.2)	1.6 (1.2-1.9)	1.3 (1.1-1.5)	1.6 (1.2-1.9)

Abbreviation: RASS, Richmond Agitation-Sedation Scale.

[a] Unless otherwise specified.

[b] Sex, race, and ethnicity were collected from patients' electronic health record and were self-reported.

[c] A validated assessment of performance status that ranges from 0% (dead) to 100% (normal, no complaints).

[d] Some patients had multiple reasons for admission.

[e] A 10-item clinician-rated assessment scale validated for assessment of delirium in patients with cancer.[24,25] It examines the level of consciousness, disorientation, memory, recall, attention, disorganized thinking, perceptual disturbance, delusions, psychomotor activity and sleep, assigning a score between 0 to 3, for a total score between 0-30. A score of 13 or higher indicates delirium; and a score of 30 was assigned to patients who were not arousable.

[f] Communication Capacity Scale consists of 5 questions examining patients' level of consciousness (0-5), ability to answer an open-ended question (0-3), ability to answer a closed-ended question (0-3), voluntary communication (0-3), and voluntary movement (0-3). A higher score indicates lower ability to communicate.

[g] The Richmond Agitation-Sedation Scale is a validated 10-point numeric rating scale that ranges from −5 (unarousable) to 4 (combative), in which 0 indicates that a patient is alert and calm. Ratings were assessed by the bedside nurse immediately prior to study medication administration (time 0) and then at 0.5, 1, 1.5, 2.0, 4.0, 6.0, 8.0, 10, 12, 14, 16, 18, 20, 22, and 24 h. The primary outcome was change in RASS score from 0 to 24 h.

additionally, previous studies have shown that proactive management of RASS score of 1 is associated with improved perceived patient comfort.[15] A rescue dose was also given with the first dose of scheduled medication (eAppendix 1 in Supplement 3).

Study medication dose escalation and reduction were permissible according to preestablished thresholds in the study protocol (eTable 1 in Supplement 3). Patients received other scheduled or as-needed medications outside of the study for agitated delirium as subsequent-line options following the APCU team's judgment.

Data Collection

Bedside nurses assessed RASS immediately prior to starting study medication administration (time 0), every 30 minutes for the first 2 hours, every 2 hours for the next 22 hours, and every 4 hours thereafter. We also collected daily data on rescue medications use for breakthrough restlessness and agitation, delirium severity (Memorial Delirium Assessment Scale [MDAS] score[24,25]), perceived patient comfort from nurses and caregivers, and adverse events (eAppendix 2 in Supplement 3 provides further details).

Outcome Measures

The primary outcome was change in RASS score between time 0 (immediately before initiation of blinded treatment) and 24 hours. RASS is a validated measure to assess agitation and sedation in patients with delirium.[14,15,26] A key secondary outcome was use of rescue neuroleptic or benzodiazepine medications during the first 24 hours, a clinically relevant marker of breakthrough restlessness and agitation.[27] Other secondary outcomes were proportion of patients in the target RASS score range between −2 and 0 during the first 24 hours; proportion of patients who achieved a treatment response—defined as RASS score reduction of 1.5 points or more—at 1, 4, 8, and 24 hours; change in MDAS between baseline and day 1; proportion of patients who were perceived as comfortable by caregivers and nurses independently, in which strongly agree and agree were combined for reporting; and adverse events based on the US National Cancer Institute's Common Toxicity Criteria Adverse Effects, version 5.0,[28] and Udvalg for Kliniske Undersogelser scale.[29,30] Overall survival from the time of blinded medication administration was also documented. Other secondary outcomes including Edmonton Symptom Assessment System,[31,32] Delirium Experience Questionnaire,[33] and bereaved caregivers' data will be reported elsewhere.

Statistical Analysis

To assess the RASS score change between 0 and 24 hours after study medication administration in the 4 prespecified pairwise comparisons (lorazepam vs haloperidol, combination vs haloperidol, placebo vs haloperidol, and lorazepam vs combination), we initially calculated that 206 patients would provide 86% power to detect a difference of 1.5 (effect size, 0.79) in mean RASS score change at a 2-sided 0.0125 nominal significance level for each of the comparisons, assuming 20% attrition. In 2022, because enrollment was lower than expected during the COVID-19 pandemic, we revised the sample size in consultation with the granting agency. Instead of relying on only 2 RASS data points (at 0 and 24 hours), we took advantage of the 16 repeated RASS measures during the first 24 hours using a linear mixed model, with treatment as a between-patient factor, time as a within-patient factor and a treatment × time interaction. With this more efficient model, we determined that 72 patients would provide 90% power to detect a difference of 1.5 in mean RASS change over a 24-hour period, assuming an interaction effect 0.1

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times that of the time effect and an intracluster correlation coefficient of 0.2. With 30% expected attrition, 104 patients (26 per group) were required. Trial recruitment was stopped after target enrollment was reached.

Baseline characteristics were summarized by descriptive statistics. Primary analysis was conducted with a mixed model as described. Because many patients died or were discharged during the open-label phase, before they received the blinded study medication, we conducted a post hoc modified intention-to-treat analysis including all patients who started the blinded study interventions when RASS score was 1 or higher. $P \leq .05$ was considered to be statistically significant for the primary outcome. Pairwise comparisons were only assessed when the omnibus test was statistically significant.

For secondary outcomes, we compared continuous variables at 24 hours (ie, rescue medication doses and MDAS) and performed a comparison among the 4 study groups using analysis of variance (ANOVA), followed by selected contrasts; the Kruskal-Wallis test followed by pairwise Wilcoxon rank-sum tests was performed if the data violated assumptions for ANOVA. We compared categorical outcomes and compared the proportions across all 4 treatment groups with a Fisher exact or χ^2 test, followed by selected pairwise comparisons. Survival distributions were estimated using the Kaplan-Meier method and compared across all 4 treatment groups using a log-rank test. Survival plots, probabilities at selected times with 95% CIs, and median survival times with 95% CIs were computed for each treatment group. Bonferroni adjustment was applied for the key secondary outcome (ie, number of rescue doses). To avoid issues with multiple testing, results for the remaining secondary outcomes were considered to be hypothesis-generating.

We also conducted post hoc worst-case sensitivity analysis by replacing missing RASS scores with the worst RASS assessments carried forward. Missing data were not imputed for secondary outcomes. Statistical analyses were performed from October 10, 2023, to April 11, 2025, using SAS, version 9.4 (SAS Institute) and R, version 3.6.3 (R Foundation for Statistical Computing). The statistical analysis plan is available in Supplement 2.

Results

Study Sample

The primary outcome analysis included 72 patients: 16 of 16 patients treated with haloperidol, 19 of 20 patients treated with lorazepam, 19 of 19 patients treated with combination therapy, and 18 of 20 patients treated with placebo (Figure 1). The characteristics of enrolled patients who started the blinded phase are shown in **Table 1**. The mean (SD) age of the total sample was 64 (12) years and included 30 female (42%) and 42 male (58%) patients, with a median (IQR) MDAS score of 24 (18-29). Except for age, baseline characteristics were similar across groups.

Primary Outcome

The RASS score significantly decreased within the first hour in all 4 groups (**Table 2**) and remained low during the next 24 hours. Specifically, the mean RASS change at 24 hours was −2.3 (95% CI, −3.2 to −1.5) for haloperidol, −4.5 (95% CI, −5.3 to −3.6) for lorazepam, −4.3 (95% CI, −5.2 to −3.4) for combination, and −2.8 (95% CI, −3.7 to −1.9) for placebo, with a significant difference among groups (mixed-model omnibus test, time-treatment interaction; $P < .001$; Table 2; **Figure 2**A).

In a preplanned pairwise comparison shown in **Table 3**, we found that the lorazepam group had a significantly greater reduction of RASS score at 24 hours than the haloperidol group (mean difference, −2.1; 95% CI, −3.4 to −0.9; $P < .001$). Similarly, the combination of lorazepam plus haloperidol was significantly more effective than haloperidol alone in reducing RASS score (mean difference, −2.0; 95% CI, −3.2 to −0.8; $P = .002$). We did not detect a significant difference between haloperidol and placebo (−0.5; 95% CI, −1.7 to 0.7; $P = .42$), nor combination and lorazepam (0.2; 95% CI, −1.1 to 1.4; $P = .79$) for the primary outcome.

Secondary Outcomes

As shown in Table 2, patients in the combination group required fewer rescue doses for breakthrough restlessness and agitation in the first 24 hours compared to the lorazepam, haloperidol, and placebo groups (mean [SD], 0.47 [0.77] vs 0.74 [1.2], 1.1 [1.3], and 1.4 [1.4]; $P = .04$, respectively); however, this was not considered statistically significant after Bonferroni correction. Significantly fewer patients in the combination and lorazepam groups required any rescue medications for breakthrough restlessness or agitation compared to the haloperidol and placebo groups (32%, 37%, 56%, and 83%, respectively; $P = .006$; Table 2; Figure 2B; eFigure in Supplement 3).

We found no significant difference in the change in MDAS scores (Table 2). Compared to the haloperidol group and placebo group, patients assigned to the combination group and lorazepam group were perceived by nurses to be significantly more comfortable (60% vs 68% vs 92% vs 100%; $P = .009$, respectively) and less agitated (67% vs 68% vs 92% vs 100%; $P = .02$, respectively) after starting study medication (Table 2). Caregiver-perceived comfort and agitation did not differ among the 4 groups (Table 2). Fourteen of 46 caregivers (30%) and 27 of 61 nurses (44%) correctly identified blinded medication (eTable 2 in Supplement 3 provides further details).

Adverse Events and Overall Survival

The most commonly documented severe adverse events (per the Common Toxicity Criteria Adverse Effects, version 5) were hypotension (19 [26%]) and hypoxia (19 [26%]) (eTable 3 in Supplement 3). There were no significant differences among the 4 groups in neuroleptic-related adverse events between days 0 and 3 or in overall survival (eTable 4 in Supplement 3).

Sensitivity Analysis

Worst-case sensitivity analysis of the primary outcome post hoc revealed findings similar to those of the primary analysis. Tables 2 and 3 provide further details.

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Table 2. Changes in RASS, Medication Use, Delirium Scores, and Caregiver and Nurse Outcomes in the First 24 Hours, by Study Group

	Participants by group								
	Haloperidol		Lorazepam		Combination		Placebo		
Time period	No.	Mean difference (95% CI)[a]	No.	Mean difference (95% CI)[a]	No.	Mean difference (95% CI)[a]	No.	Mean difference (95% CI)[a]	*P* value
Change in RASS scores (primary outcome) during the time period[b]									
0-1 h	16	−2.2 (−3.0 to −1.3)	19	−4.1 (−4.8 to −3.3)	19	−4.0 (−4.8 to −3.2)	18	−3.0 (−3.8 to −2.2)	Treatment: *P* < .001 Time: *P* = .002 Interaction: *P* < .001
0-4 h	16	−2.4 (−3.3 to −1.6)	19	−3.3 (−4.1 to −2.5)	17	−3.9 (−4.7 to −3.1)	18	−3.4 (−4.2 to −2.6)	
0-8 h	16	−2.8 (−3.7 to −2.0)	19	−3.8 (−4.6 to −3.0)	17	−4.2 (−5.1 to −3.4)	17	−2.7 (−3.5 to −1.8)	
Between 0 and 24 h	16	−2.3 (−3.2 to −1.5)	14	−4.5 (−5.3 to −3.6)	14	−4.3 (−5.2 to −3.4)	14	−2.8 (−3.7 to −1.9)	
Proportion of patients with RASS ≥1 anytime within time period, % (95% CI)[c]									
1 h	16	44 (23 to 67)	19	16 (5.5 to 38)	19	0.0 (0.0 to 17)	18	44 (25 to 66)	.01
4 h	16	50 (28 to 72)	19	32 (15 to 54)	19	5.3 (0.9 to 25)	18	50 (29 to 71)	
8 h	16	56 (33 to 77)	19	37 (19 to 59)	19	11 (2.9 to 31)	18	56 (34 to 75)	
24 h	16	81 (57 to 93)	19	58 (36 to 77)	19	37 (19 to 59)	18	83 (61 to 94)	
Proportion of patients in the target RASS range of −2 and 0 within time period, % (95% CI)[d]									
1 h	16	63 (39 to 82)	19	53 (32 to 73)	19	58 (36 to 77)	18	61 (39 to 80)	.02
4 h	16	63 (39 to 82)	19	37 (19 to 59)	17	47 (26 to 69)	18	56 (34 to 75)	
8 h	16	56 (33 to 77)	19	37 (19 to 59)	17	47 (26 to 69)	17	59 (36 to 78)	
24 h	16	69 (44 to 86)	14	14 (4.0 to 40)	14	43 (21 to 67)	14	57 (33 to 79)	
Proportion of patients who achieved a treatment response (RASS reduction of ≥1.5 points), by time, % (95% CI)									
At 1 h	16	56 (33 to 77)	19	90 (69 to 97)	19	95 (75 to 99)	18	83 (61 to 94)	.08
At 4 h	16	50 (28 to 72)	19	74 (51 to 88)	17	88 (66 to 97)	18	89 (67 to 97)	
At 8 h	16	75 (51 to 90)	19	84 (62 to 95)	17	94 (73 to 99)	17	77 (53 to 90)	
At 24 h	16	69 (44 to 86)	14	93 (69 to 99)	14	100 (79 to 100)	14	78 (52 to 92)	
No. of rescue doses within time period, mean (SD)[e]									
1 h	16	0	19	0	19	0	18	0.06 (0.24)	.04
4 h	16	0.06 (0.25)	19	0.11 (0.32)	19	0.05 (0.23)	18	0.17 (0.38)	
8 h	16	0.38 (0.62)	19	0.21 (0.42)	19	0.05 (0.23)	18	0.56 (0.86)	
24 h	16	1.1 (1.3)	19	0.74 (1.2)	19	0.47 (0.77)	18	1.4 (1.4)	
Proportion of patients who required any rescue medication within time period, No. (%)[f]									
1 h	16	0	19	0	19	0	18	1 (5.6)	.006
4 h	16	1 (6.3)	19	2 (11)	19	1 (5.3)	18	3 (17)	
8 h	16	5 (31)	19	4 (21)	19	1 (5.3)	18	7 (39)	
24 h	16	9 (56)	19	7 (37)	19	6 (32)	18	15 (83)	

(continued)

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Table 2. Changes in RASS, Medication Use, Delirium Scores, and Caregiver and Nurse Outcomes in the First 24 Hours, by Study Group (continued)

	Participants by group								
	Haloperidol		Lorazepam		Combination		Placebo		
Time period	No.	Mean difference (95% CI)[a]	No.	Mean difference (95% CI)[a]	No.	Mean difference (95% CI)[a]	No.	Mean difference (95% CI)[a]	*P* value
Change in Memorial Delirium Assessment Scale between baseline and 24 h									
Mean (SD)	14	0.36 (6.1)	13	2.9 (6.5)	12	2.4 (3.6)	16	2.8 (4.5)	.55
Improvement in patient comfort between baseline and day 1[g]									
Bedside nurse agrees/strongly agrees	15	9 (60)	16	16 (100)	13	12 (92)	18	13 (68)	.009
Caregiver agrees/strongly agrees	15	12 (80)	13	10 (83)	9	6 (67)	16	12 (75)	.84
Improvement in agitation between baseline and day 1[g]									
Bedside nurse agrees/strongly agrees	15	10 (67)	16	16 (100)	13	12 (92)	18	13 (68)	.02
Caregiver agrees/strongly agrees	15	13 (87)	13	10 (83)	9	6 (67)	16	12 (75)	.67
Sensitivity analysis, worst-case change in RASS over time[h]									
0-24 h	16	−2.3 (−3.3 to −1.4)	19	−3.3 (−4.2 to −2.4)	19	−3.0 (−3.9 to −2.1)	18	−2.1 (−3.0 to −1.2)	Treatment: *P* = .02 Time: *P* < .001 Interaction: *P* = .02
0-1 h	16	−2.2 (−3.1 to −1.2)	19	−4.1 (−4.9 to −3.2)	19	−4.0 (−4.9 to −3.1)	18	−3.0 (−3.9 to −2.1)	
0-4 h	16	−2.4 (−3.4 to −1.5)	19	−3.3 (−4.1 to −2.4)	19	−3.4 (−4.3 to −2.5)	18	−3.4 (−4.3 to −2.5)	
0-8 h	16	−2.8 (−3.8 to −1.9)	19	−3.8 (−4.7 to −2.9)	19	−3.7 (−4.6 to −2.8)	18	−2.5 (−3.4 to −1.6)	

Abbreviation: RASS, Richmond Agitation-Sedation Scale.

[a] Within-group difference.

[b] A linear mixed model was used to examine treatment effect across all time points. *P* for treatment effect <.001; *P* for time effect = .002; *P* for interaction × time effect <.001; intraclass correlation coefficient = 0.45. Adjusted for the baseline RASS at time 0.

[c] Fisher exact tests were used for comparison among the 4 groups.

[d] Proportion of patients in whom at least 50% of RASS scores in the specified time period needed to be between −2 and 0. Fisher exact tests were used for comparisons among the 4 study groups; odds ratios and Fisher exact tests were calculated for pairwise differences.

[e] The mean number of doses was shown; the Kruskal-Wallis test was used for comparison among the 4 groups.

[f] All patients received 1 scheduled and 1 as-needed dose at time 0. The rescue dose at time 0 was not included in the count for this variable because we were interested in what medications were needed after the initial doses.

[g] Perceived level of comfort and level of agitation in the patient were assessed by asking the bedside nurses and caregivers to independently rate the following statements daily: "In my opinion, the patient was more comfortable since starting the study medication" and "In my opinion, the patient was less restless/agitated after starting the study medication." Responses were provided on a 5-point Likert scale from strongly agree to strongly disagree.

[h] Missing RASS assessments were replaced with worst-case carried forward RASS scores. A linear mixed model was used to examine treatment effect across all time points.

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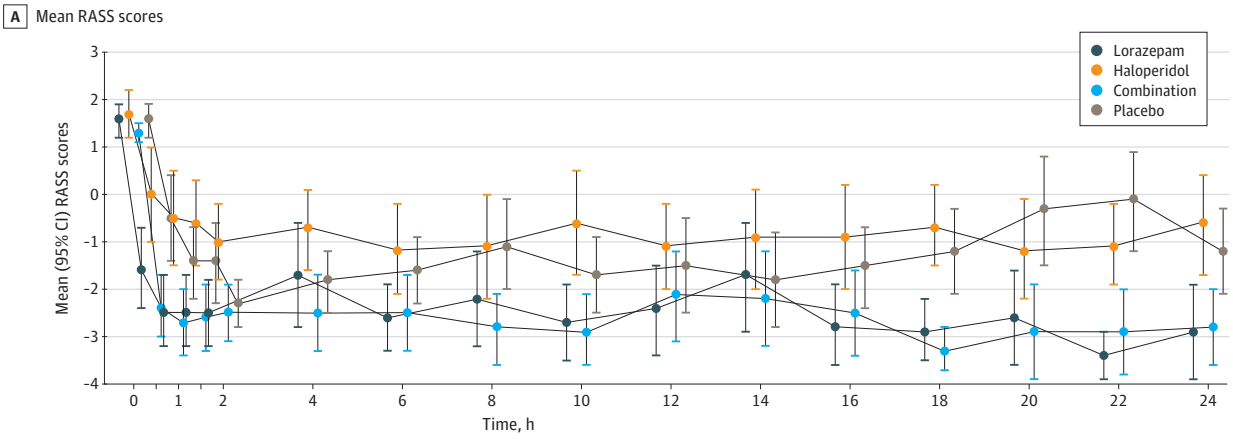
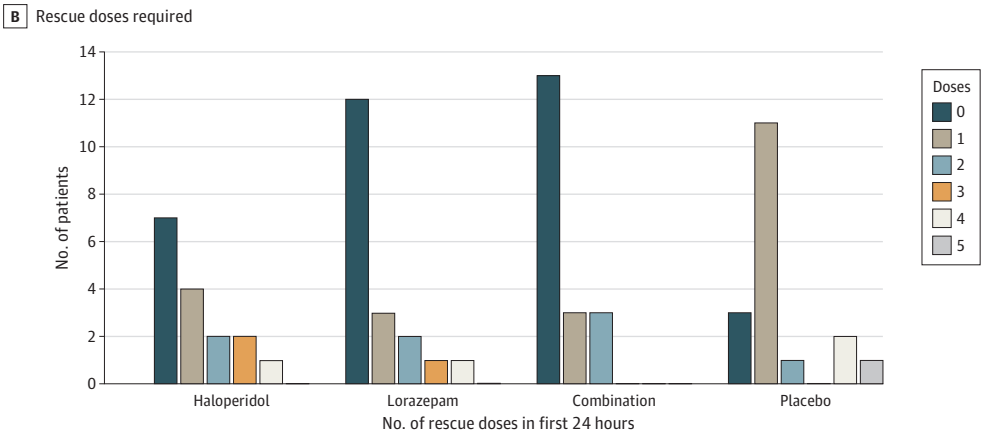
Figure 2. Level of Agitation in First 24 Hours, by Study Group



No. at risk													
Haloperidol	16 16 16 16 16	16	16	16	16	16	16	16	16	16	16	16	16
Lorazepam	19 19 19 19 19	19	19	19	19	18	18	17	16	15	15	14	
Combination	19 19 19 18 18	17	17	17	15	15	15	15	15	14	14	14	
Placebo	18 18 18 18 18	18	18	17	16	16	16	15	15	15	14	14	



No. of patients	Haloperidol	Lorazepam	Combination	Placebo
0 Dose	7 (44)	12 (63)	13 (68)	3 (17)
1 Dose	4 (25)	3 (16)	3 (16)	11 (61)
2 Doses	2 (13)	2 (11)	3 (16)	1 (6)
3 Doses	2 (13)	1 (5)	0	0
4 Doses	1 (6)	1 (5)	0	2 (11)
5 Doses	0	0	0	1 (6)

A, The mean Richmond Agitation-Sedation Scale (RASS) scores are plotted for each study group starting at time 0 (ie, immediately before blinded study medication administration) over the next 24 hours, with error bars indicating 95% CIs. The haloperidol group had a significant reduction in RASS score over time; both the lorazepam group and the combination group showed greater reduction than the haloperidol group. The RASS score in placebo group also decreased initially after a single dose of rescue lorazepam but then increased slightly after a few hours. B, In the first 24 hours, patients in the placebo group required the highest number of rescue medications for breakthrough restlessness and agitation, followed by those in the haloperidol group, lorazepam group and combination group. The data pattern from RASS scores and rescue medication use suggests how the 4 medication options provide varying levels of sedation and ability to reduce agitation, in descending order: combination, lorazepam alone, haloperidol alone, and placebo.

Discussion

The RECORD study found that lorazepam alone and in combination with haloperidol was superior to haloperidol alone in reducing persistent restlessness and agitation in patients with end-of-life delirium. Moreover, patients who received scheduled medications, including haloperidol alone, received significantly fewer rescue medications for breakthrough restlessness and agitation compared to placebo. Taken together, these study findings highlight 3 options with light (haloperidol), moderate (lorazepam), and heavy (combination) sedation for persistent restlessness and agitation in the end-of-life setting.

We included a placebo group in this study because of clinical equipoise and the ongoing debate on the efficacy and safety of benzodiazepine and neuroleptic medication.[9,34,35] For ethical reasons, the placebo group also included lorazepam as a rescue medication, which was administered once at the start of the blinded phase when

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Table 3. Pairwise Comparison of RASS in the First 24 Hours

Time period	Lorazepam vs haloperidol		Combination vs haloperidol		Placebo vs haloperidol		Combination vs lorazepam	
	Mean difference (95% CI)[a]	*P* value	Mean difference (95% CI)[a]	*P* value	Mean difference (95% CI)[a]	*P* value	Mean difference (95% CI)[a]	*P* value
Change in RASS score over time[b]								
0-1 h	−1.9 (−3.0 to −0.7)	<.001	−1.8 (−3.0 to −0.6)	.002	−0.8 (−2.0 to 0.4)	.42	0.1 (−1.1 to 1.2)	.79
0-4 h	−0.8 (−2.0 to 0.3)		−1.4 (−2.6 to −0.3)		−1.0 (−2.1 to 0.2)		−0.6 (−1.8 to 0.5)	
0-8 h	−1.0 (−2.1 to 0.2)		−1.4 (−2.6 to −0.2)		0.2 (−1.0 to 1.4)		−0.4 (−1.6 to 0.7)	
0-24 h	−2.1 (−3.4 to −0.9)		−2.0 (−3.2 to −0.8)		−0.5 (−1.7 to 0.7)		0.2 (−1.1 to 1.4)	
No. of patients with RASS score ≥1 within time period, odds ratio[c]								
1 h	0.36 (0.11 to 1.2)	NA	NA	NA	1.0 (0.48 to 2.2)	NA	NA	NA
4 h	0.63 (0.28 to 1.4)		0.11 (0.01 to 0.75)		1.0 (0.51 to 2.0)		0.17 (0.02 to 1.3)	
8 h	0.65 (0.32 to 1.4)		0.19 (0.05 to 0.74)		0.99 (0.54 to 1.8)		0.29 (0.07 to 1.2)	
24 h	0.71 (0.45 to 1.1)		0.45 (0.24 to 0.85)		1.0 (0.75 to 1.4)		0.64 (0.32 to 1.3)	
Sensitivity analysis, worst-case change in RASS over time, h[d]								
0-1 h	−1.9 (−3.2 to −0.6)	NA	−1.8 (−3.1 to −0.5)	NA	−0.8 (−2.1 to 0.5)	NA	0.1 (−1.2 to 1.3)	NA
0-4 h	−0.8 (−2.1 to 0.5)		−0.9 (−2.2 to 0.4)		−1.0 (−2.3 to 0.4)		−0.1 (−1.4 to 1.1)	
0-8 h	−1.0 (−2.3 to 0.3)		−0.9 (−2.2 to 0.4)		0.3 (−1.0 to 1.6)		0.1 (−1.1 to 1.4)	
0-24 h	−1.0 (−2.3 to 0.3)		−0.7 (−2.0 to 0.6)		0.2 (−1.1 to 1.5)		0.3 (−0.9 to 1.6)	

Abbreviations: NA, not available; RASS, Richmond Agitation-Sedation Scale.

[a] Between-group difference, unless otherwise specified.

[b] Contrasts were created from a linear mixed model examining treatment effect across all time points. A negative number indicates that the first treatment group had a greater effect on sedation than the second treatment group, and vice versa. *P* values refer specifically to the total time period (0-24 hours).

[c] Fisher exact test was used for comparison between groups; odds ratios were used for pairwise comparisons. An odds ratio <1 indicates that the first treatment group had fewer patients with RASS ≥1 compared to the second treatment group, and vice versa.

[d] Missing RASS assessments were replaced with worst RASS assessments carried forward. A linear mixed model was used to examine treatment effect across all time points. A negative number indicates that the first treatment group had a greater effect on sedation than the second treatment group and vice versa.

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patients had RASS score of 1 or greater and only as needed afterwards. This likely contributed to the initial reduction in RASS score, which subsequently increased as the effect of lorazepam wore off. Although the placebo group eventually achieved similar RASS scores as the haloperidol group, it required more rescue medications, suggesting these patients had more breakthrough restlessness and agitation. Taken together, our findings suggest that scheduled medications represent a more proactive approach to preventing breakthrough restlessness and agitation in this setting.

Similar to other studies outside of the end-of-life delirium setting, we found that haloperidol had no significant association with delirium severity compared to placebo.[13,36,37] Unlike these studies, our study focused on restlessness and/or agitation as the primary outcome, which is more specific. We found that even when standard-dose haloperidol (<8 mg/d) was unable to control agitation, a dose escalation (scheduled haloperidol, 12 mg/d) may be comparable to multiple doses of as-needed lorazepam. The potential benefit of haloperidol is supported by the rapid initial reduction in RASS scores with the first 4-mg dose, the fewer rescue doses required during the subsequent 24 hours, and the greater efficacy when haloperidol was added to lorazepam. Taken together, our data support the use of haloperidol for palliation of restlessness and agitation.

Patients in both scheduled lorazepam groups had better control of their agitation than those in the scheduled haloperidol and scheduled placebo groups as indicated by lower RASS scores, fewer breakthrough restlessness and agitation episodes, fewer rescue doses, and greater perceived comfort levels. Our findings are consistent with a pilot trial and network meta-analysis.[15,38] Benzodiazepine medications are often avoided because they could precipitate or worsen delirium; however, in patients with end-of-life delirium and persistent agitation under the care of a specialist palliative care team, lorazepam may be a reasonable option to reduce restlessness, agitation, and distress.

Hypotension and hypoxia were the most commonly observed adverse events in this study; however, these were also characteristic changes with impending death.[39,40] Extrapyramidal adverse effects were rarely documented despite the relatively high doses of haloperidol.[41] However, the short duration of medication use may explain this finding.

Limitations

This study has several limitations. First, this study was conducted in the end-of-life delirium setting, where the justification for use of pharmacologic measures is high. Our findings are not generalizable to other settings, and further studies are needed. Second, this study was conducted in Taiwan and in the US. Some of the secondary outcomes were based on caregiver assessments, and although we conducted back translation of the questionnaires, we were not able to do full psychometric translations. Third, we adjusted the sample size partly due to challenges during COVID-19 pandemic. Specifically, the APCUs had restricted visitation policies, making it difficult for our research teams to contact or interact with caregivers. Although this study enrolled 72 patients with primary outcome as planned, the haloperidol group comprised 16 rather than 18 patients. Fourth, 30% of caregivers and 44% of nurses were able to correctly identify the assignment after 1 day of treatment; this may be related to the clear clinical effect of lorazepam-based regimens. Fifth, we did not examine other medication options, such as chlorpromazine,[42-44] olanzapine,[44-47] or nonneuroleptic medications.[48] Future studies may assess these options. Sixth, we only examined intravenous medications because of their rapid onset and reliable administration; however, the subcutaneous route is more commonly used in APCUs outside of the US.[49,50] Further studies may evaluate other routes of administration and home health and/or community settings.

Conclusions

The results of the randomized clinical trial highlight 3 levels of sedation to personalize the management of agitated end-of-life delirium, with haloperidol, lorazepam, or both to provide light, moderate, and heavy sedation, respectively. Although some clinicians may choose to prescribe proportional sedation with stepwise titration (ie, from light to heavy), others may elect a more goal-directed approach (ie, start with heavy sedation if personalized sedation goal is RASS score of −4). Future studies should assess how effectively these strategies reduce restlessness and agitation and their effects on communication capacity and caregiver outcomes.

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REFERENCES

1. Hui D, Reddy A, Palla S, Bruera E. Neuroleptic prescription pattern for delirium in patients with advanced cancer. *J Palliat Care*. 2011;27(2):141-147. doi:10.1177/082585971102700210

2. Solano JP, Gomes B, Higginson IJ. A comparison of symptom prevalence in far advanced cancer, AIDS, heart disease, chronic obstructive pulmonary disease and renal disease. *J Pain Symptom Manage*. 2006;31(1):58-69. doi:10.1016/j.jpainsymman.2005.06.007

3. Hui D, De La Cruz M, Bruera E. Palliative care for delirium in patients in the last weeks of life: the final frontier. *J Palliat Care*. 2014;30(4):259-264. doi:10.1177/082585971403000403

4. Lawlor PG, Bush SH. Delirium in patients with cancer: assessment, impact, mechanisms and management. *Nat Rev Clin Oncol*. 2015;12(2):77-92. doi:10.1038/nrclinonc.2014.147

5. Fang CK, Chen HW, Liu SI, Lin CJ, Tsai LY, Lai YL. Prevalence, detection and treatment of delirium in terminal cancer inpatients: a prospective survey. *Jpn J Clin Oncol*. 2008;38(1):56-63. doi:10.1093/jjco/hym155

6. Centeno C, Sanz A, Bruera E. Delirium in advanced cancer patients. *Palliat Med*. 2004;18(3):184-194. doi:10.1191/0269216304pm879oa

7. Morita T, Akechi T, Ikenaga M, et al. Terminal delirium: recommendations from bereaved families' experiences. *J Pain Symptom Manage*. 2007;34(6):579-589. doi:10.1016/j.jpainsymman.2007.01.012

8. Finucane AM, Lugton J, Kennedy C, Spiller JA. The experiences of caregivers of patients with delirium, and their role in its management in palliative care settings: an integrative literature review. *Psychooncology*. 2017;26(3):291-300. doi:10.1002/pon.4140

9. Bush SH, Leonard MM, Agar M, et al. End-of-life delirium: issues regarding recognition, optimal management, and the role of sedation in the dying phase. *J Pain Symptom Manage*. 2014;48(2):215-230. doi:10.1016/j.jpainsymman.2014.05.009

10. de la Cruz M, Ransing V, Yennu S, et al. The frequency, characteristics, and outcomes among cancer patients with delirium admitted to an acute palliative care unit. *Oncologist*. 2015;20(12):1425-1431. doi:10.1634/theoncologist.2015-0115

11. Bramati P, Bruera E. Delirium in palliative care. *Cancers (Basel)*. 2021;13(23):5893. doi:10.3390/cancers13235893

12. Finucane AM, Jones L, Leurent B, et al. Drug therapy for delirium in terminally ill adults. *Cochrane Database Syst Rev*. 2020;1(1):CD004770. doi:10.1002/14651858.CD004770.pub3

13. Agar MR, Lawlor PG, Quinn S, et al. Efficacy of oral risperidone, haloperidol, or placebo for symptoms of delirium among patients in palliative care: a randomized clinical trial. *JAMA Intern Med*. 2017;177(1):34-42. doi:10.1001/jamainternmed.2016.7491

14. Hui D, De La Rosa A, Wilson A, et al. Neuroleptic strategies for terminal agitation in patients with cancer and delirium at an acute palliative care unit: a single-centre, double-blind, parallel-group, randomised trial. *Lancet Oncol*. 2020;21(7):989-998. doi:10.1016/S1470-2045(20)30307-7

15. Hui D, Frisbee-Hume S, Wilson A, et al. Effect of lorazepam with haloperidol vs haloperidol alone on agitated delirium in patients with advanced cancer receiving palliative care: a randomized clinical trial. *JAMA*. 2017;318(11):1047-1056. doi:10.1001/jama.2017.11468

16. Hui D, Cheng SY, Paiva CE. Pharmacologic management of end-of-life delirium: translating evidence into practice. *Cancers (Basel)*. 2024;16(11):2045. doi:10.3390/cancers16112045

17. Surges SM, Brunsch H, Jaspers B, et al. Revised European Association for Palliative Care (EAPC) recommended framework on palliative sedation: an international Delphi study. *Palliat Med*. 2024;38(2):213-228. doi:10.1177/02692163231220225

18. Thomas C, Alici Y, Breitbart W, Bruera E, Blackler L, Sulmasy DP. Addressing challenges with sedation in end-of-life care. *J Pain Symptom Manage*. 2024;67(4):346-349. doi:10.1016/j.jpainsymman.2023.12.016

19. Heijltjes MT, van Thiel GJMW, Rietjens JAC, van der Heide A, de Graeff A, van Delden JJM. Changing practices in the use of continuous sedation at the end of life: a systematic review of the literature. *J Pain Symptom Manage*. 2020;60(4):828-846.e3. doi:10.1016/j.jpainsymman.2020.06.019

20. Imai K, Morita T, Yokomichi N, et al. Efficacy of proportional sedation and deep sedation defined by sedation protocols: a multicenter, prospective, observational comparative study. *J Pain Symptom Manage*. 2021;62(6):1165-1174. doi:10.1016/j.jpainsymman.2021.06.005

21. Heijltjes MT, Morita T, Mori M, et al. Physicians' opinion and practice with the continuous use of sedatives in the last days of life. *J Pain Symptom Manage*. 2022;63(1):78-87. doi:10.1016/j.jpainsymman.2021.07.012

22. Sessler CN, Gosnell MS, Grap MJ, et al. The Richmond Agitation-Sedation Scale: validity and reliability in adult intensive care unit patients. *Am J Respir Crit Care Med*. 2002;166(10):1338-1344. doi:10.1164/rccm.2107138

23. Hui D, Hess K, Dibaj SS, et al. The minimal clinically important difference of the Richmond Agitation-Sedation Scale in patients with cancer with agitated delirium. *Cancer*. 2018;124(10):2246-2252. doi:10.1002/cncr.31312

24. Breitbart W, Rosenfeld B, Roth A, Smith MJ, Cohen K, Passik S. The Memorial Delirium Assessment Scale. *J Pain Symptom Manage*. 1997;13(3):128-137. doi:10.1016/S0885-3924(96)00316-8

25. Fadul N, Kaur G, Zhang T, Palmer JL, Bruera E. Evaluation of the memorial delirium assessment scale (MDAS) for the screening of delirium by means of simulated cases by palliative care health professionals. *Support Care Cancer*. 2007;15(11):1271-1276. doi:10.1007/s00520-007-0247-6

26. Ely EW, Truman B, Shintani A, et al. Monitoring sedation status over time in ICU patients: reliability and validity of the Richmond Agitation-Sedation Scale (RASS). *JAMA*. 2003;289(22):2983-2991. doi:10.1001/jama.289.22.2983

27. Tang M, Chen M, Bruera E, Hui D. Association among rescue neuroleptic use, agitation, and perceived comfort: secondary analysis of a randomized clinical trial on agitated delirium. *Support Care Cancer*. 2021;29(12):7887-7894. doi:10.1007/s00520-021-06384-6

28. US National Institutes of Health, National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE), version 5.0. 2017. Accessed October 18, 2024. https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf.

29. Lingjaerde O, Ahlfors UG, Bech P, Dencker SJ, Elgen K. The UKU side effect rating scale. A new comprehensive rating scale for psychotropic drugs and a cross-sectional study of side effects in neuroleptic-treated patients. *Acta Psychiatr Scand Suppl*. 1987;334(suppl):1-100. doi:10.1111/j.1600-0447.1987.tb10566.x

30. Lindström E, Lewander T, Malm U, Malt UF, Lublin H, Ahlfors UG. Patient-rated versus clinician-rated side effects of drug treatment in schizophrenia. Clinical validation of a self-rating version of the UKU Side Effect Rating Scale (UKU-SERS-Pat). *Nord J Psychiatry*. 2001;55(suppl 44):5-69.

31. Bruera E, Kuehn N, Miller MJ, Selmser P, Macmillan K. The Edmonton Symptom Assessment System (ESAS): a simple method for the assessment of palliative care patients. *J Palliat Care*. 1991;7(2):6-9. doi:10.1177/082585979100700202

32. Hui D, Bruera E. The Edmonton Symptom Assessment System 25 years later: past, present, and future developments. *J Pain Symptom Manage*. 2017;53(3):630-643. doi:10.1016/j.jpainsymman.2016.10.370

33. Breitbart W, Gibson C, Tremblay A. The delirium experience: delirium recall and delirium-related distress in hospitalized patients with cancer, their spouses/caregivers, and their nurses. *Psychosomatics*. 2002;43(3):183-194. doi:10.1176/appi.psy.43.3.183

34. Hui D, Agar M, Maeda I. Should neuroleptics be used in patients with delirium seen by palliative care? *J Pain Symptom Manage*. 2023;65(1):e81-e85. doi:10.1016/j.jpainsymman.2022.09.015

35. Gaertner J, Eychmueller S, Leyhe T, Bueche D, Savaskan E, Schlögl M. Benzodiazepines and/or neuroleptics for the treatment of delirium in palliative care? a critical appraisal of recent

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randomized controlled trials. *Ann Palliat Med*. 2019;8(4):504-515. doi:10.21037/apm.2019.03.06

36. Girard TD, Exline MC, Carson SS, et al; MIND-USA Investigators. Haloperidol and ziprasidone for treatment of delirium in critical illness. *N Engl J Med*. 2018;379(26):2506-2516. doi:10.1056/NEJMoa1808217

37. Andersen-Ranberg NC, Poulsen LM, Perner A, et al; AID-ICU Trial Group. Haloperidol for the treatment of delirium in ICU patients. *N Engl J Med*. 2022;387(26):2425-2435. doi:10.1056/NEJMoa2211868

38. Wu YC, Tseng PT, Tu YK, et al. Association of delirium response and safety of pharmacological interventions for the management and prevention of delirium: a network meta-analysis. *JAMA Psychiatry*. 2019;76(5):526-535. doi:10.1001/jamapsychiatry.2018.4365

39. Bruera S, Chisholm G, Dos Santos R, Crovador C, Bruera E, Hui D. Variations in vital signs in the last days of life in patients with advanced cancer. *J Pain Symptom Manage*. 2014;48(4):510-517. doi:10.1016/j.jpainsymman.2013.10.019

40. Hwang IC, Ahn HY, Park SM, Shim JY, Kim KK. Clinical changes in terminally ill cancer patients and death within 48 h: when should we refer patients to a separate room? *Support Care Cancer*. 2013;21(3):835-840. doi:10.1007/s00520-012-1587-4

41. Kurz M, Hummer M, Oberbauer H, Fleischhacker WW. Extrapyramidal side effects of clozapine and haloperidol. *Psychopharmacology (Berl)*. 1995;118(1):52-56. doi:10.1007/BF02245249

42. Tiefenthaler CM, Hirst JM, Edmonds KP, Atayee RS. Chlorpromazine's potential role in palliating distressing symptoms associated with hyperactive delirium in patients at end of life. *J Palliat Med*. 2023;26(6):826-830. doi:10.1089/jpm.2022.0308

43. Hasuo H, Kanbara K, Fujii R, Uchitani K, Sakuma H, Fukunaga M. factors associated with the effectiveness of intravenous administration of chlorpromazine for delirium in patients with terminal cancer. *J Palliat Med*. 2018;21(9):1257-1264. doi:10.1089/jpm.2017.0669

44. Shin SH, Hui D, Chisholm G, et al. Frequency and outcome of neuroleptic rotation in the management of delirium in patients with advanced cancer. *Cancer Res Treat*. 2015;47(3):399-405. doi:10.4143/crt.2013.229

45. Skrobik YK, Bergeron N, Dumont M, Gottfried SB. Olanzapine vs haloperidol: treating delirium in a critical care setting. *Intensive Care Med*. 2004;30(3):444-449. doi:10.1007/s00134-003-2117-0

46. Lyu XJ, Kan AD, Chong PH, Lin K, Koh YH, Yeo ZZ. An open-label clinical trial of oral transmucosal haloperidol and oral transmucosal olanzapine in the treatment of terminal delirium at home. *Trials*. 2022;23(1):311. doi:10.1186/s13063-022-06238-4

47. Boettger S, Jenewein J, Breitbart W. Haloperidol, risperidone, olanzapine and aripiprazole in the management of delirium: a comparison of efficacy, safety, and side effects. *Palliat Support Care*. 2015;13(4):1079-1085. doi:10.1017/S1478951514001059

48. Bush SH, Lawlor PG, Ryan K, et al; ESMO Guidelines Committee. Delirium in adult cancer patients: ESMO Clinical Practice Guidelines. *Ann Oncol*. 2018;29(suppl 4):iv143-iv165. doi:10.1093/annonc/mdy147

49. Tang M, Abdelaal M, Lau J, et al. subcutaneous vs intravenous administration of medications and fluids for patients with cancer in the US and Canada. *JAMA Oncol*. 2023;9(5):717-719. doi:10.1001/jamaoncol.2023.0239

50. Storey P, Hill HH Jr, St Louis RH, Tarver EE. Subcutaneous infusions for control of cancer symptoms. *J Pain Symptom Manage*. 1990;5(1):33-41. doi:10.1016/S0885-3924(05)80007-7

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