Deprescribing in the Pharmacologic Management of Delirium (de-PMD): A Randomized Trial in the Intensive Care Unit

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Conflict of Interest Checklist:

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Speaker Forum		X		X		X		X		X		X		X		X
Consultant		X		X		X		X		X		X		X		X
Stocks		X		X		X		X		X		X		X		X
Royalties		X		X		X		X		X		X		X		X
Expert Testimony		X		X		X		X		X		X		X		X
Board Member		X		X		X		X		X		X		X		X
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Abstract

OBJECTIVE: Benzodiazepines and anticholinergics are risk factors for delirium in the intensive care unit (ICU). We tested the impact of a deprescribing intervention on short-term delirium outcomes.

DESIGN: Multi-site randomized clinical trial

SETTING: ICU's of three large hospitals

PARTICIPANTS: Two hundred adults aged 18 years admitted to an ICU with delirium according to the Richmond Agitation Severity Scale and the Confusion Assessment Method for the ICU (CAM-ICU). Participants had a contraindication to haloperidol (seizure disorder or prolonged QT interval) or preference against haloperidol as a treatment for delirium, and were excluded for serious mental illness, stroke, pregnancy or alcohol withdrawal. Participants were randomized to a deprescribing intervention or usual care. The intervention included electronic alerts combined with pharmacist support to deprescribe anticholinergics and benzodiazepines.

MEASUREMENTS: Primary outcomes were delirium duration measured by the CAM-ICU, and severity measured by the Delirium Rating Scale Revised-98 (DRS-R-98) and the CAM-ICU-7; secondary outcomes included adverse events and mortality.

RESULTS: Participants had a mean age of 61.8 (standard deviation: 14.3) years, 59% female, and 52% African American with no significant differences in baseline characteristics between groups. No differences between groups were identified in the number exposed to anticholinergics (p=0.219) or benzodiazepines (p=0.566), the median total anticholinergic score (p=0.282), or the median total benzodiazepine dose in lorazepam equivalents (p=0.501). Neither median delirium/coma-free days (p=0.361) nor median change in delirium severity scores (p=0.582 for DRS-R-98; p=0.333 for CAM-ICU-7) were different between groups. No differences in adverse events or mortality were identified.

CONCLUSIONS: When added to state-of-the-art clinical services, this deprescribing intervention had no impact on medication use in ICU participants. Given the age of the population, results of clinical outcomes may not be easily extrapolated to older adults. Nonetheless, improved approaches for deprescribing or preventing anticholinergics and benzodiazepines should be developed to determine the impact on delirium outcomes.

Keywords

Introduction

Deprescribing interventions are hypothesized to reduce the future risk of drug-induced adverse events.[1,2] We previously tested the impact of a deprescribing intervention in an electronic medical record (EMR) system to reduce exposure to anticholinergics among older adults with delirium or dementia in a general medical ward.[3] In hospitalized patients, anticholinergics and benzodiazepines worsen neurotransmitter imbalances of cholinergic deficiency, and dopaminergic and gamma-aminobutyric acid (GABA) excess leading to higher risk of delirium.[4–8] While our initial EMR-based deprescribing intervention did not reduce new orders for anticholinergics, it modestly increased discontinuation orders; however, no impact on clinical outcomes was identified.[3]

Feedback from providers exposed to the EMR-based intervention suggested the intervention failed to change prescribing habits due to a non-interruptive nature of the alert, and lack of human decision support.[3] Based on this feedback, we enhanced the electronic deprescribing intervention by designing an interruptive alert that offered recommendations for alternative (non-anticholinergic) medications with easy-to-order keystrokes, and a pharmacist supporting the intervention through direct clinical support to medical and surgical teams.[9]

Delirium in critically ill adults has been associated with longer hospital stays and higher mortality, and higher rates of long-term cognitive impairment.[10–18] Because no medication is FDA-approved for the treatment of delirium, we developed a multi-component approach to delirium treatment in the intensive care unit (ICU) based on the neurotransmitter models described above, called the pharmacological management of delirium (PMD).[8,9,19] PMD includes deprescribing anticholinergics and benzodiazepines, and prescribing low dose haloperidol for 7 days. However, some patients in the ICU possess contraindications to haloperidol, such as prolonged QT intervals or seizure disorder, or have personal preference against using haloperidol for an off-label indication. Therefore, we performed two parallel, pragmatic randomized trials of the PMD intervention, one that employed all three components of the intervention (PMD),[19] and this trial that employed only the deprescribing interventions (de-PMD). Our hypothesis for both trials was that participants receiving the intervention would have (1) higher number of days without delirium or coma, and (2) lower delirium severity.

Methods:

The Institutional Review Board of Indiana University (IU) Purdue University Indianapolis approved the study. Participants' legally authorized representatives provided informed consent prior to enrollment.[9]

Study Setting:

The study was conducted within the ICU's of Eskenazi Health, Indiana University (IU) Methodist Hospital, and IU University Hospital. Eskenazi hospital hosts three intensive care units: an 8-bed surgical ICU (SICU), a 14-bed medical ICU (MICU) and a 29-bed

progressive ICU (PICU, a step-down unit). IU Methodist Hospital includes 65 mixed MICU and SICU beds, and IU Health University hospital included 36 MICU and SICU beds.

Enrollment, Eligibility and Randomization (See figure 1):

Inclusion criteria consisted of the following: (1) patients admitted to the ICU ward for 24 hours, (2) age 18 years, (3) screen positive for delirium based on the Richmond Agitation-Sedation Scale (RASS)[20] and the Confusion Assessment Method for the ICU (CAM-ICU)[21,22] on any day during the ICU stay, (4) had a contraindication to haloperidol (such as QT prolongation or seizure disorder) or personal preference to avoid exposure to haloperidol as a delirium treatment, and (5) are English-speaking. Patients were excluded if they had 1) history of severe mental illness, 2) delirium due to alcohol intoxication, 3) aphasic stroke, 4) were pregnant or nursing, or 5) previously been enrolled in the study. Randomization of eligible patients occurred in a 1:1 ratio between the intervention and usual care groups utilizing computer-generated allocation in random blocks of four.

Intervention content and delivery:

The intervention consisted of a multi-component decision aid preventing or deprescribing definite anticholinergic medications and benzodiazepines (including the benzodiazepine-receptor agonist zolpidem).[9] Briefly, two methods were employed: 1) a computerized decision support intervention to interrupt orders for strong anticholinergics, and 2) human (pharmacist) decision support that included twice-daily surveillance of medication orders and administration records. After randomization to the intervention, computerized alerts were triggered with new or renewal orders for definite anticholinergics identified according to the Anticholinergic Cognitive Burden (ACB) scale and included in the hospital formularies (see supplemental material for screenshots of computerized alerts and alternatives).[7,23–26] Alerts were interruptive, provided brief education of the risk of anticholinergics, and recommended a non-anticholinergic alternative. The human decision support (intervention pharmacist performing twice daily medication reviews) identified anticholinergics prescribed despite the computerized alerts and communicated directly with the primary medical and surgical ICU teams to offer alternatives.[9] The intervention intended to align prescribing practices with state-of-the-art care for anticholinergics and benzodiazepines in the ICU.[27–29]

Usual Care:

Those randomized to the usual care group received no electronic or human decision support for pharmacologic management of delirium throughout their hospital stay. Low dose haloperidol was not included as part of this intervention, however providers could prescribe haloperidol without restriction on dose, frequency, or duration to those enrolled in either group.

At all study sites, and over the course of the trial, implementation of new standards of care were introduced at each study site.[27] These care bundles include the ABCDE bundle (Awakening and Breathing Coordination, Delirium monitoring and management, and Early mobility). These practices have been shown in prior studies to reduce the duration of mechanical ventilation, length of ICU stay, and mortality.[30–33]

Primary Outcomes:

a) Delirium Duration.—We identified delirium using the Richmond Agitation Sedation Scale (RASS)[20] and the Confusion Assessment Method for the ICU (CAM-ICU).[21,22] The CAM-ICU was chosen based on the recommendation of national guidelines,[27] its practical use in the ICU and its acceptable psychometric properties.[22] The CAM-ICU score was determined by examining (a) acute or fluctuating changes in mental status, (b) inattention, (c) altered level of consciousness, and (d) disorganized or incoherent thinking. CAM-ICU was considered to be positive if the patient displayed both (a) and (b), plus (c) and/or (d). RASS was utilized as a sister instrument to measure level of arousal alongside the CAM-ICU.[20] Patients with a RASS score of −3 to +4 were eligible for delirium assessment, while scores of −4 and −5 were characterized as comatose and not eligible for CAM-ICU assessment. Blinded research assistants conducted twice daily RASS and CAM-ICU assessments after 24 hours of ICU admission and until discharge from the hospital, death, or 30 days after enrollment.

b) Delirium Severity: Delirium severity was assessed using the Delirium Rating Scale-revised (DRS-R-98)[34,35] and the CAM-ICU-7.[36] The DRS-R-98 is a 16-item clinician-rated scale (rated 0 to 3, maximum 39 points) with higher scores indicating greater severity of delirium. The CAM-ICU-7 is a seven point rating scale (0–7, higher scores more severe) that has been derived from the RASS and the CAM-ICU. Severity assessments were performed by trained and blinded research assistants in a similar frequency reported above.

Secondary & Other Outcomes:

Secondary outcomes were collected through direct observation and the EMR, and included mortality rates (up to 30 days after discharge), length of stay (both ICU and total hospital stay) falls, use of physical restraints, pulling out intravenous lines or urinary catheters, re-intubation, and pressure ulcers.[13,37]

We collected baseline demographic and clinical information from the EMR as well as each participant's legally authorized representative. Prior cognitive function was obtained by legally authorized representatives using the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE).[38,39] Activities of daily living and instrumental activities of daily living prior to ICU admission were assessed through Katz[40] and Lawton[41] scales, completed with input from participant's legally authorized representatives. Electronic medical records were used to collect reasons for admission, severity of illness (APACHE II)[42] within 24 hours of admission to the ICU, daily mechanical ventilation status, and the Charlson Comobidity Index.[43] Medication data included drug, dose, time administered, and route was collected manually from hospital administration records. Cumulative or total use by medication or class is reported as a sum of each dose administered.

Sample Size:

Since this trial was conducted in ICU patients with contraindications to haloperidol, we did not set a sample size a priori. Instead, enrollment to the trial occurred concurrently with the PMD trial[19] and was stopped at the end of funding support. Using the two-sample *t*-test for

continuous outcomes, we estimate that the sample size of 100 in each group provides 80% power for detecting a group difference with effect size of 0.4 SD or greater.

Drug-related adverse events:

Adverse effects were monitored using EMRs and direct observation throughout the hospital stay or up to 30 days after enrollment. Likelihood for causality with study interventions was assessed using the Naranjo scale.[44] All adverse events were reported to an independent Data Safety Monitoring Board (DSMB).

Data Analyses:

Baseline differences between groups were assessed using Fisher's exact tests for categorical outcomes and Wilcoxon-Rank sum tests for continuous measures with skewed data. Additionally, we used Fisher's exact test to compare the percentage of patients who received targeted medications, complications, and adverse events. To test for differences in the number of adverse events and total and daily medication doses between groups, we used the Wilcoxon-Rank sum test.

Delirium/coma free days and length of stay were compared using the nonparametric Wilcoxon Rank-Sum test. Two time points were used for delirium/coma free days and for delirium severity: day 8 post-randomization as this was the end of the haloperidol course in the intervention group, and at discharge. Patients who died before day 8 or discharge had their subsequent delirium/coma free days counted as 0. Patients who were discharged before day 8 had the remaining days counted as delirium/coma free. To adjust for length of stay when comparing delirium/coma free days at discharge, we used a Poisson regression model that included an offset equal to the log of length of stay post randomization.

Since delirium severity measured by DRS-R-98 had substantial missing values, we used multiple imputation methods to compare change in DRS-R-98 scores from baseline to day 8 or discharge. We used both regression and propensity-based methods for multiple imputation. The MI procedure in SAS was used to create a set of 30 imputed datasets using the following variables: day post randomization, morning/afternoon assessment, mechanical ventilation, RASS score, coma, delirium, and 4 variables obtained from chart review (hallucinations, delusions, confusion, and disorientation). We used the MIANALYZE procedure in SAS to compare DRS-R-98 scores at baseline, day 8, discharge, and change scores between the two groups. Results were similar for both imputation procedures, therefore, we report the regression-based imputation. A mixed effects model with mean daily CAM-ICU-7 scores as the dependent variable was used to compare the difference in CAM-ICU-7 change from baseline to day 8 or to discharge. The mixed model included randomization group, time, group and time interaction as independent variables and a random effect for patients.

We used Fisher's exact tests to examine differences in mortality at ICU and hospital discharge, and 30 days post discharge. The Wilcoxon-Rank sum test was used to compare length of stay, ICU length of stay, and days on mechanical ventilation post randomization.

All analyses were calculated on an intention-to-treat basis. The analyses were conducted in all patients (including those who withdrew) using available data until time of death, discharge, withdrawal or 30 days after enrollment. Analyses were conducted using SAS v9.4.

Results:

Participants:

The supplemental file (Supplemental Figure) contains the CONSORT diagram shows the flow of participants through screening and study completion. The study screened 12,402 ICU patients for eligibility, with 6,653 never experiencing delirium (53.6%), and 4,183 (33.7%) meeting other exclusion criteria and not eligible for this trial. As described above, this trial occurred in parallel with the PMD delirium treatment trial that included low-dose haloperidol in addition to deprescribing benzodiazepines and anticholinergics; eight participants with prolonged QT intervals were screened for the parallel trail (PMD) but before this trial was initiated and were therefore excluded. Among those eligible, 351 were enrolled in the PMD trial and 200 in this de-PMD trial. Supplemental table 3 reports the distribution of contraindications to haloperidol and the proportions who received haloperidol through routine clinical care.

Participant Characteristics:

As seen in table 1, the mean age of participants was 61.8 (standard deviation (SD) 14.3 years), 59% were female and 52% were African American. Study groups did not differ significantly with respect to age, gender, race, education, comorbidities, acute severity of illness, and discharge diagnosis. The majority of participants were admitted to the medical ICU services (74%) and received mechanical ventilation for at least one day (72%). Almost half were admitted with acute respiratory failure and/or sepsis (49%), while 24% were admitted for altered mental status or other neurological diagnoses.

Primary Outcomes:

No difference in the median number of days without delirium or coma was identified between those randomized to the intervention compared to usual care groups at either day 8 [p=0.361] or 30 days after randomization [p=0.108] (Figure and Supplemental Table 2). Similarly, no difference in the mean reduction in delirium severity scores was seen between groups as measured by either the DRS-R98 or CAM-ICU-7 from baseline to day 8 or discharge (Figure and Supplemental Table 2).

Secondary Outcomes:

No differences in secondary outcomes, including ICU mortality [p=0.794], in-hospital mortality [p=0.478], 30-day mortality [p=0.291], number of days ventilated [p=0.242], number of hospital days post-randomization [p=0.246], and number discharged to home [p=0.447] were identified between groups (Supplemental Table 2). Those randomized to intervention had a higher median number of ICU days after randomization [p=0.019].

Measures of Medication Use:

Table 2 and Supplemental Table 1 describe characteristics of exposure to analgosedatives used in the study population, with benzodiazepines and anticholinergics reported as lorazepam equivalents and anticholinergic burden scores, respectively. Target medication exposure is reported by group and time (defined as prior to enrollment, day-of randomization, and post-randomization periods). The deprescribing intervention did not change the number exposed or median total dose of lorazepam equivalents between groups [intervention: 38.3 mg (IQR 98.6mg) vs. usual care: 37.7 (IQR 115.9mg); p=0.501]. Although the intervention group had a lower mean total ACB score (a cumulative measure of exposure), the difference was not statistically significant [intervention: 4.3 (SD 8.8) vs. usual care: 6.1 (SD 16.6); p=0.282]. The median number of days an anticholinergic was administered among those receiving any anticholinergic was lower but not significantly different between groups [intervention: 3.5 (IQR 1–7) vs. usual care: 4 (IQR 1–15); p=0.32]. To better identify potential subgroups in which the de-PMD intervention reduced anticholinergic use, we explored differences between study group and age, service, and time since enrollment, though we note the study was not powered to detect differences in subgroups. Participants in SICU service teams showed differences approaching statistical significance; the median (IQR) number of anticholinergic doses among SICU participants in the intervention group receiving at least one dose of anticholinergics was 5 (2–8.5) compared to 6 (1–19) in usual care [p=0.114]. The median (IQR) number of doses among those age 65 and over and receiving at least one anticholinergic dose was 4.5 (1–12) in the intervention group and 8 (2–15) [p=0.604] in the usual care group.

Adverse Events:

Twenty-seven participants in the intervention group and twenty-two in the usual care group experienced a serious adverse event (p=0.413). Table 3 describes the distribution of all adverse events recorded by study assessors with no differences between groups observed. Intervention participants experienced a higher rate of pulling out respiratory, gastrointestinal, or intravenous access hardware compared to usual care [p=0.033]. Supplemental Table 4 reports no differences in the distribution of delirium psychomotor subtypes by study group based on RASS scores.

Discussion:

This randomized trial showed that our electronic and pharmacist-based deprescribing intervention had no significant impact on the number exposed, median or total dose of anticholinergics and benzodiazepines, and therefore did not change delirium, length of stay, or mortality outcomes among critically ill adults with delirium. Despite 58% of participants being exposed to at least one dose of benzodiazepines in the post-randomization period, and 30% of participants exposed to strong anticholinergics, the mean and median daily dose of benzodiazepines and anticholinergics was low (table 3). Our combined deprescribing intervention failed to further reduce measures of medication use and therefore could not determine whether deprescribing these medications can reduce delirium outcomes.

The failure of our intervention to influence anticholinergic and benzodiazepine exposure could be attributed to a number of factors related to the design of the intervention as well as the clinical environment in which the study was conducted. First, our intervention employed an interruptive alert and recommendation of alternatives within the EMR at the time of order entry. Our prior experience with approaches in preventing anticholinergic orders also failed to reduce exposure to anticholinergics.[3] Although we included a pharmacist review of medications, our alert was not triggered for pre-existing orders, which may have inflated the number of participants ever exposed to a target medication. Additionally, the intervention did not intend to change sedation practices, which frequently employed benzodiazepines among ventilated participants. During the study, an updated clinical practice guideline for the management of pain, agitation, and delirium in critically ill adults recommended the minimization of benzodiazepines and anticholinergics.[27] This may have resulted in contamination, compromising our ability to influence medication use. We note that medical and surgical ICU teams in each study site received support from clinical pharmacists who have post-graduate training in critical care, participate in rounds with ICU teams on a daily basis, have an influence in sedation and pain management practices, and have access to all clinical data relevant to the care of delirium and other medical illnesses. Therefore our results may be different in healthcare systems without comprehensive clinical pharmacy support.

While we believe the use of electronic medical records offer a scalable opportunity for deprescribing interventions, our experience in this and prior trials suggest that our approach should not be repeated.[3,19] Future deprescribing trials should be improved with attention to the design and timing of alerts as well as the incorporation of behavior change theories including priming and default settings,[45] A successful EMR-based deprescribing intervention could have scalable opportunities not only in acute care environments, but also primary care and rehabilitation or extended care facilities. We note, however, that given the age of the population studied, results of clinical outcomes may not be easily extrapolated to older adults.

Our study had limitations worth noting: 1) this study was conducted in three urban academic hospitals with a diverse population, and consistent clinical pharmacy support and may not be generalizable to other institutions; 2) participants who were not users of benzodiazepine or anticholinergics did not receive any intervention which reduced our ability to measure impact; 3) our design called for randomization of the participant rather than provider or site, therefore contamination among both providers and clinical pharmacists may have compromised the impact of our intervention and results; and 4) the computerized intervention was not triggered for existing medication orders and may have been more effective in the prevention of medication use and ultimately delirium prevention.

Conclusion

This multi-component deprescribing intervention did not significantly reduce benzodiazepine or anticholinergic use compared to usual care among adults admitted to the ICU, and therefore could not influence delirium outcomes. Improving the efficacy of

deprescribing interventions with more attention to the decision processes of deprescribing could improve future research in reducing delirium outcomes in ICU populations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements:

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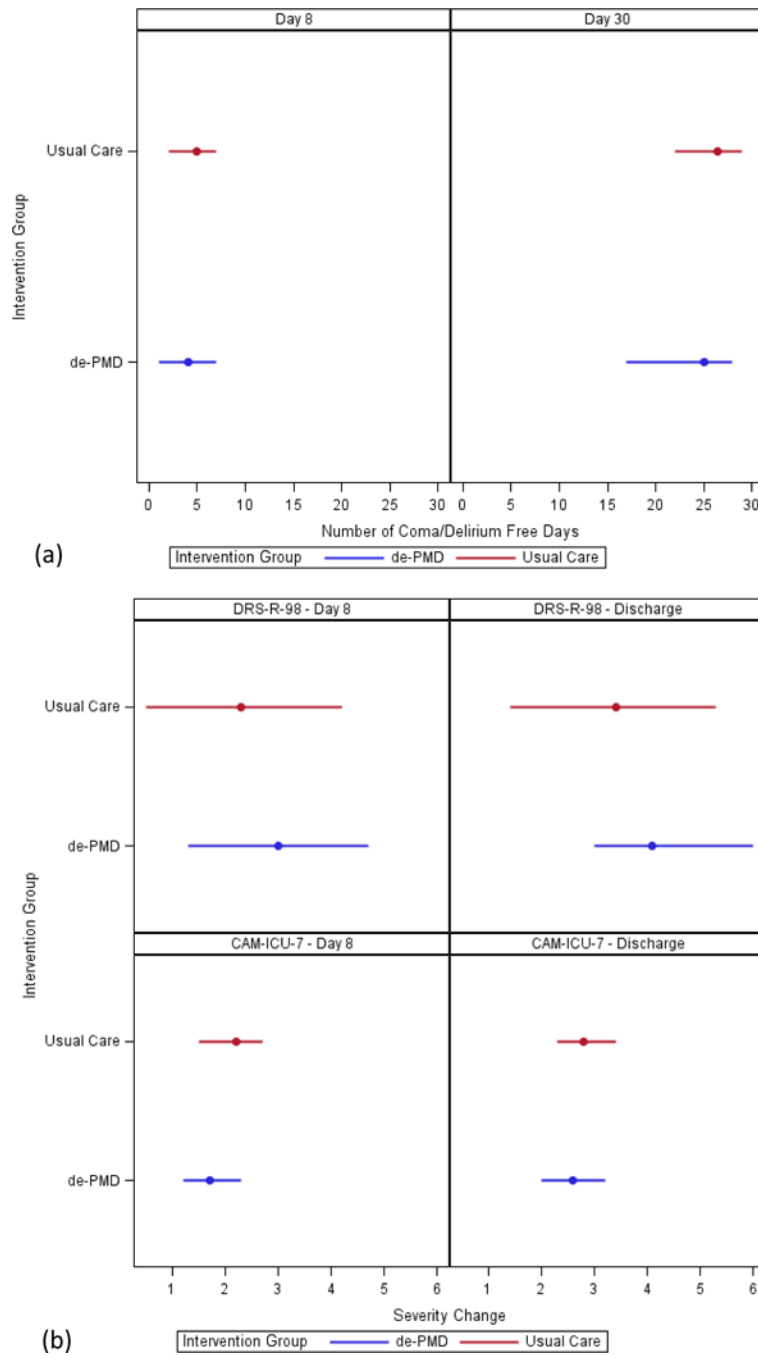
Figure 1: Primary Outcomes of de-PMD: Coma/Delirium Free Days (a) and Change in Delirium Severity Scores (b).

Reporting of primary outcomes of median (interquartile range) number of days alive without delirium or coma at day 8 and day 30 (a), and the mean (standard deviation) reduction from baseline in delirium severity scores at day 8 and discharge according to the Delirium Rating Scale-Revised-1998 and the Confusion Assessment Method for the Intensive Care Unit-7 (b).

Table 1:

Baseline Characteristics of enrolled participants (n=200)

	Overall	de-PMD (N=99)	Usual Care (N=101)
Age	61.8 (14.3)	61.3 (14.6)	62.4 (14.1)
Female n (%)	118 (59.0)	65 (65.7)	53 (52.5)
African-American n (%)	102 (52.0)	54 (55.1)	48 (49.0)
Education (years)	11.6 (2.1)	11.5 (2.1)	11.6 (2.1)
APACHE[a] II	21.2 (8.3)	20.6 (8.2)	21.7 (8.3)
Charlson Comorbidity Index	3.2 (2.5)	3.2 (2.5)	3.2 (2.4)
Activities of Daily Living (ADL)[b]	5.3 (1.4)	5.3 (1.4)	5.3 (1.5)
Instrumental Activities of Daily Living (IADL)[c]	5.6 (2.8)	5.5 (2.8)	5.7 (1.5)
IQCODE[d]	3.3 (0.5)	3.3 (0.4)	3.3 (0.5)
Mechanically Ventilated n (%)	143 (71.9)	73 (73.7)	70 (70.0)
ICU Location			
Medical ICU[e] n (%)	147 (73.9)	72 (72.7)	75 (75.0)
Surgical ICU n (%)	35 (17.6)	20 (20.2)	15 (15.0)
Progressive/step-down ICU n (%)	17 (8.5)	7 (7.1)	10 (10.0)
Diagnoses			
Acute Respiratory Failure/Sepsis	98 (49.0)	50 (50.5)	47 (47.5)
Neurologic/Altered Mental Status	47 (23.5)	23 (23.2)	24 (23.8)
Trauma	16 (8.0)	6 (6.1)	10 (9.9)
Other[f]	39 (19.5)	20 (20.2)	19 (18.8)

Data presented as mean (standard deviation) unless otherwise specified

[a] APACHE: Acute Physiology and Chronic Health evaluation

[b] ADLs assessed by Katz Scale

[c] IADLs assessed by Lawton Scale

[d] IQCODE: Informant Questionnaire on Cognitive Decline in the Elderly

[e] ICU: Intensive Care Unit

[f] Others: Include cardiovascular and gastrointestinal diagnoses

Table 2:

de-PMD Trial Medication Exposures

	Pre-Randomization			Randomization Day			Post-Randomization		
	de-PMD[*] (N=99)	Usual Care (N=100)	P-value	de-PMD (N=99)	Usual Care (N=100)	P-value	de-PMD (N=99)	Usual Care (N=100)	P-value
Haloperidol									
Patients[†] n (%)	7 (7.1)	13 (13.0)	0.238	6.1 (6)	8.0 (8)	0.783	29 (29.3)	20 (20.0)	0.141
Median daily Dose (IQR)	0 (0–0)	0 (0–0)	0.176	0 (0–0)	0 (0–0)	0.575	0 (0–0.2)	0 (0–0)	0.117
Benzodiazepines[‡]									
Patients[†] n (%)	69 (69.7)	58 (58.0)	0.105	37 (37.4)	35.0 (35)	0.769	60 (60.6)	56 (56.0)	0.566
Median daily Dose (IQR)	1.1 (0–10.0)	0.3 (0–3.7)	0.044	0 (0–4)	0 (0–2)	0.550	0.1 (0–1.2)	0.1 (0–1.1)	0.634
Anticholinergic Burden[§]									
Patients[†] n (%)	16 (16.2)	15 (15.0)	0.847	11 (11.1)	12 (12.0)	1.000	34 (34.3)	26 (26.0)	0.219
Median daily score (IQR)	0 (0–0)	0 (0–0)	0.832	0 (0–0)	0 (0–0)	0.823	0 (0–0.3)	0 (0–0.1)	0.266
Olanzapine									
Patients[†] n (%)	3 (3.0)	1 (1.0)	0.369	3 (3.0)	1 (1.0)	0.369	4 (4.0)	2 (2.0)	0.445
Median daily Dose (IQR)	0 (0–0)	0 (0–0)	0.306	0 (0–0)	0 (0–0)	0.306	0 (0–0)	0 (0–0)	0.387
Quetiapine									
Patient[†]s n (%)	4 (4.0)	6 (6.0)	0.748	3 (3.0)	5 (5.0)	0.721	8 (8.1)	9 (9.0)	1.000
Median daily Dose (IQR)	0 (0–0)	0 (0–0)	0.509	0 (0–0)	0 (0–0)	0.461	0 (0–0)	0 (0–0)	0.776
Risperidone									
Patients[†] n (%)	0 (0.0)	1 (1.0)	1.000	0 (0.0)	0 (0.0)		1 (1.0)	1 (1.0)	1.000
Median daily Dose (IQR)	0 (0–0)	0 (0–0)	0.320	0 (0–0)	0 (0–0)	1.000	0 (0–0)	0 (0–0)	0.989
Dexmedetomidine									
Patients[†] n (%)	10 (10.1)	5 (5.0)	0.191	2 (2.0)	2 (2.0)	1.000	6 (6.1)	11 (110)	0.311
Median daily Dose (IQR)	0 (0–0)	0 (0–0)	0.175	0 (0–0)	0 (0–0)	0.992	0 (0–0)	0 (0–0)	0.218
Opioids[‖]									
Patients[†] n (%)	86 (86.9)	76 (76.0)	0.068	68 (68.7)	62 (62.0)	0.372	83 (83.8)	70 (70.0)	0.028
Median daily Dose (IQR)	35.9 (2.5–77.8)	27.5 (0.6–87.2)	0.522	36.8 (0–107.5)	24.1 (0–88.4)	0.460	6.3 (0.8–44.1)	3.5 (0–34.6)	0.078
Propofol									
Patients[†] n (%)	41 (41.4)	45 (45.0)	0.668	22 (22.2)	28 (28.0)	0.414	38 (38.4)	27 (27.0)	0.098

	Pre-Randomization			Randomization Day			Post-Randomization		
	de-PMD* (N=99)	Usual Care (N=100)	P-value	de-PMD (N=99)	Usual Care (N=100)	P-value	de-PMD (N=99)	Usual Care (N=100)	P-value
Median daily Dose (IQR)	0 (0–144)	0 (0–906)	0.304	0 (0–0)	0 (0–229)	0.508	0 (0–199)	0 (0–1)	0.088
Clonidine									
Patients† n (%)	2 (2.0)	3 (3.0)	1.000	1 (1.0)	3 (3.0)	0.621	6 (6.1)	7 (7.0)	1.000
Median daily Dose (IQR)	0 (0–0)	0 (0–0)	0.653	0 (0–0)	0 (0–0)	0.321	0 (0–0)	0 (0–0)	0.780
Propranolol									
Patients† n (%)	2 (2.0)	0 (0.0)	0.246	0 (0.0)	0 (0.0)		3 (3.0)	3 (3.0)	1.000
Median daily Dose (IQR)	0 (0–0)	0 (0–0)	0.154	0 (0–0)	0 (0–0)	1.000	0 (0–0)	0 (0–0)	0.974

*
de-PMD: deprescribing in the Pharmacological Management of Delirium

†
Patients who received the drug during hospitalization

‡
Benzodiazepine data presented as Lorazepam equivalents and includes zolpidem

§
Anticholinergic burden measured by Anticholinergic Burden (ACB) scale

‖
Opioids data presented as morphine equivalents

Haloperidol dose is presented in milligrams (mg)

Table 3.

Comparison of Adverse Events between de-PMD and Usual Care Groups

	de-PMD (n=99)	Usual Care (n=101)	P-value
Patients with Serious Adverse Event	27 (27.3)	22 (21.8)	0.413
Total Number of Serious Adverse Events	37	35	
Event Type [*]			
Death	11 (11.1)	8 (7.9)	0.478
QT prolongation	0 (0)	0 (0)	N/A
Cardiac Arrhythmias	1 (1.0)	1 (1.0)	1.000
Extra Pyramidal Symptoms	0 (0)	0 (0)	N/A
Neuroleptic Malignant Syndrome	0 (0)	0 (0.0)	N/A
Prolonged Hospitalization	5 (5.0)	2 (2.0)	0.277
Other	15 (15.2)	14 (13.9)	0.843
Relationship to Protocol			
Event Definitely related	0 (0)	0 (0)	N/A
Event Probably related	0 (0)	0 (0)	N/A
Event Possibly related	0 (0)	0 (0)	N/A
Organ System			
Central Nervous System	4 (4.0)	2 (2.0)	0.443
Cardiovascular	10 (10.1)	9 (8.9)	0.814
Respiratory	11 (11.1)	12 (11.9)	1.000
Gastrointestinal	3 (3.0)	3 (3.0)	1.000
Genitourinary	0 (0.0)	4 (4.0)	0.121
Skin	1 (1.0)	0 (0.0)	0.495
Hepatic	0 (0)	0 (0)	N/A
Hematologic	3 (3.0)	3 (3.0)	1.000
Endocrine	0 (0)	0 (0)	N/A
Musculoskeletal	1 (1.0)	1 (1.0)	1.000
Delirium-related complications			
Inappropriate attempt to get out of bed, N (%)	8 (8.1)	5 (5.0)	0.407
Verbal agitation, N (%)	5 (5.0)	5 (5.0)	1.000
Fall, N (%)	2 (2.0)	0 (0.0)	0.246
Delayed Procedure, N (%)	0 (0.0)	0 (0.0)	
Pulling Tubes, N (%)	9 (9.1)	2 (2.0)	0.033
Hospital Acquired Pressure Ulcers, N (%)	18 (18.2)	10 (10.0)	0.107

Data presented as N (%) unless otherwise specified

[*] Event types are presented as number of patients with the event. A single patient may have more than one adverse event