Pharmacological Management of Delirium in the ICU: A Randomized Pragmatic Clinical Trial

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Abstract

Background/Objective: Delirium in the intensive care units (ICU) is prevalent with both delirium duration and delirium severity associated with adverse outcomes. We designed a pragmatic trial to test the efficacy of a pharmacological management of delirium (PMD) bundle in improving delirium/coma free days and reducing delirium severity among ICU patients.

Design: A randomized pragmatic clinical trial.

Setting: Medical, surgical, and progressive ICUs of three tertiary care hospitals.

Participants: 351 critically ill patients.

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Intervention: A multi-component PMD bundle consisting of reducing the exposure to 20 definite anticholinergic medications and benzodiazepines, and prescribing low-dose haloperidol.

Measurements: The primary outcomes were delirium/coma free days measured through Richmond Agitation Sedation Scale and the Confusion Assessment Method for the ICU (CAM-ICU) and delirium severity measured through Delirium Rating Scale Revised-98 (DRS-R-98) and the CAM-ICU-7. Secondary outcomes were in-hospital and post-hospital discharge 30-day mortality, ICU and hospital lengths of stay, and delirium-related hospital complications.

Results: We randomized 351 critically ill delirious patients [mean age=59.3 years (SD 16.9); 52% female, 42% African-Americans] to receive the PMD bundle or usual care. There were no significant differences in median delirium/coma free days at day 8 [PMD: 4 (IQR 2–7) days versus usual care 5 (1–7), p=0.888] or at day 30 [26 (IQR 19–29) days versus 26 (14–29), p=0.991]. There were no significant differences for decrease in delirium severity at day 8, but at hospital discharge, the intervention group showed a greater reduction in delirium severity [PMD: mean decrease in CAM-ICU-7 score=3.2 (SD 3.3) versus usual care: mean decrease=2.5 (SD 3.2); p=0.046]. No differences were observed between groups for ICU and hospital lengths of stay, mortality and delirium-related hospital complications. Similar results were observed when analyses were limited to patients   65 and   75 years.

Conclusion and Relevance: Implementing the PMD Bundle in the ICU did not reduce delirium duration or severity among critically ill patients.

Trial Registration: clinicaltrials.gov Identifier: NCT00842608

Keywords

delirium; haloperidol; benzodiazepine; randomized trial

Introduction

Delirium in the intensive care unit (ICU) is prevalent[1–6] with both delirium duration and severity associated with mortality.[6–10] In a prospective cohort study of 304 ICU patients, duration of delirium was associated with a higher 1-year mortality after adjusting for relevant covariates.[6] Similarly patients with high delirium severity had higher mortality during hospital stay and at 3 and 12 months after discharge.[9,10]

Delirium is a complex pathophysiological process explained through a multi-factorial model.[11] The model posits a dynamic interrelationship between pre-existing vulnerability and the therapeutic and iatrogenic insults acquired during hospitalization.[11] The interaction between the vulnerability and insult factors[12] produces a final common neurotransmission state of relative or absolute cholinergic deficiency, dopaminergic excess and gamma-aminobutyric acid (GABA) overload.[13–15] Based on the neurotransmitter model for delirium, we developed a bundle for pharmacological management of delirium (PMD),[16] with the aim of reducing exposure to benzodiazepines and anticholinergics, and prescribing low-dose haloperidol. We conducted a randomized controlled pragmatic trial to test the effectiveness of our PMD bundle among ICU patients. Our primary hypothesis was that ICU patients receiving the PMD bundle would have (1) higher number of hospital days without

delirium or coma, and (2) reduced delirium severity at one-week post randomization or hospital discharge.

Materials and Methods:

The local Institutional Review Board approved the study and patients' legally authorized representatives provided informed consent.

Study Setting:

We enrolled patients admitted to the ICU services of three Indianapolis hospitals from February 2009-January 2015. Eskenazi hospital is a 457-bed public hospital with an 8-bed surgical ICU (SICU), a 14-bed medical ICU (MICU) and a 29-bed progressive/step-down ICU. University hospital is a 257-bed tertiary care hospital with 36 MICU and SICU beds. Methodist hospital is an 802-bed tertiary center with 65 MICU and SICU beds.

Eligibility and Randomization:

Inclusion criteria: 1) patients admitted to the ICU for 24 hours, 2) age 18 years, 3) screen positive for delirium based on the Richmond Agitation-Sedation Scale (RASS)[17] and the Confusion Assessment Method for the ICU (CAM-ICU)[18] on any day during the ICU stay and 4) English-speaking. Exclusion criteria: 1) history of severe mental illness, 2) Axis 1 psychiatric disorder, 3) severe cognitive impairment preventing study assessments, 4) alcohol-related delirium, 5) aphasic stroke or traumatic brain injury, 6) history of allergic reaction or contraindication to haloperidol, 7) withdrawal of life support, 8) pregnant or nursing, 9) legally blind or deaf, 10) admission for suicide attempt, 11) QTc >500 milliseconds or 12) previously enrolled in the PMD study or enrolled in another study. Randomization occurred in a 1:1 ratio between the PMD bundle and the usual care groups utilizing a computer generated allocation in random blocks of four stratified by enrollment site.

PMD bundle content:

The PMD bundle consisted of a multi-component intervention targeting the imbalance of three neurotransmitters (acetylcholine, dopamine, and GABA), implemented post randomization.[16] The bundle focused on reducing exposure to 20 definite anticholinergic medications identified by the anticholinergic cognitive burden (ACB) scale;[19–21] reducing exposure to benzodiazepines;[22] and prescribing low-dose haloperidol.

Delivery of the PMD bundle:

The reduction in exposure to anticholinergic medications was executed through both computerized decision support and a human clinical expert, a pharmacist. The computerized physician order entry generated automated interruptive messages that alerted providers to the risks of anticholinergics in delirium and offered alternative, non-anticholinergic medications. Ignoring the recommendation prompted the study pharmacist to contact the provider on the same day to discuss reducing or discontinuing the anticholinergic medication. The 20 definite anticholinergics targeted are available in supplementary Table S1. Benzodiazepine reduction was achieved through communications between the ICU teams and the study

pharmacist. The goal was to achieve 20–40% dose reduction on day one with subsequent reductions of 10–25% every 24 hours. Patients ≥ 60 years of age received 0.5 mg of haloperidol, whereas patients aged <60 years received 1 mg every 8 hours intravenously for a total of seven days or until discharged from the hospital, whichever came first. Haloperidol was administered only if the QTc was <500ms. In contrast to the haloperidol component, the other two PMD bundle components (anticholinergic reduction and benzodiazepine reduction) continued throughout the hospital stay for up to 30 days.

Usual Care:

Usual care group received no electronic or human decision support for pharmacologic management of delirium throughout their hospital stay. With our pragmatic design, participants in usual care could receive haloperidol as part of routine care, without restriction on the dose, frequency, or duration.

Primary Outcomes:

a)   Delirium/coma free days: Delirium/coma free days were defined as number of days after randomization patient was alive free of delirium and not in coma. This outcome describes the duration of normal cognitive status where the patient is not comatose and does not have delirium. Patients with a RASS score of −4 or −5 with lack of response to verbal or physical stimuli were characterized as comatose and ineligible for CAM-ICU assessments. Patients with a RASS score of −3 to +4 were considered eligible for CAM-ICU assessments. The CAM-ICU score was determined by examining the patient for (a) acute or fluctuating changes in mental status, (b) inattention, (c) altered level of consciousness and (d) disorganized thinking. Patients were considered delirious if they displayed (a) and (b), plus (c) and/or (d).

b)   Delirium Severity: Delirium severity was assessed using the Delirium Rating Scale-Revised (DRS-R-98)[23] and CAM-ICU-7.[24] DRS-R-98 is a 16-item scale with 13 severity items (rated 0–3, maximum 39 points) with higher scores indicating greater delirium severity.[23] CAM-ICU-7 is a seven-point scale (0–7), derived from the RASS and the CAM-ICU. The CAM-ICU-7 score ranges from 0–7; categorized as 0–2: no delirium, 3–5: mild to moderate delirium, and 6–7: severe delirium.[24] Trained research assistants blinded to randomization assignment conducted twice-daily RASS, CAM-ICU, CAM-ICU-7 and DRS-R-98 assessments after 24 hours of ICU admission until patients' discharge from the hospital or death.

Secondary Outcomes:

In-hospital and 30-days post hospital discharge mortality rates, ICU and hospital lengths of stay, and delirium-related hospital complications[25,26] collected through electronic records and direct daily observation.

Other Data:

Demographics, cognitive function,[27] activities and instrumental activities of daily living, [28,29] admission diagnoses, severity of illness,[30] chronic comorbidities,[31] and medications were collected (Details in supplementary material).

Adverse events:

QT prolongation (QTc >500ms), extrapyramidal and movement related symptoms were reported to an independent data safety monitoring board (DSMB) throughout the study (Details in supplementary material).

Data Analyses:

Baseline differences between groups were assessed using Fisher's exact test for categorical outcomes and Wilcoxon Rank-Sum (also known as Mann-Whitney U) test for continuous measures since the majority of these measures contained skewed data. Additionally, we used the Fisher's exact test to compare the percentage of patients who received targeted medications, complications, and adverse events. To test for difference in the number of adverse events and dose (total and daily) between the randomized groups, we used the Wilcoxon Rank-Sum test.

We conducted intention-to-treat analyses to test the intervention effects on the primary and secondary outcomes. Six patients withdrew from the trial and their data collected up to the date of withdrawal were included in the analyses. 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 delirium severity: day 8 post-randomization as this time was the end of the haloperidol use in the intervention group, and day 30 post-randomization as this was the end of active delirium monitoring. Patients who died or withdrew before day 8 or 30 had their subsequent delirium/coma free days counted as 0. Patients who were discharged alive before day 8 or 30 had the remaining days counted as delirium/coma free.

Since delirium severity measured by DRS-98 had substantial missing values, we used multiple imputation methods to compare change in DRS-98 scores from baseline to day 8 or hospital discharge (Details in supplementary material). 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 scores from baseline to day 8 or hospital 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 in ICU, before hospital discharge, and 30 days post hospital discharge. Logistic regression models were also used to determine group differences in hospital mortality and mortality 30 days post hospital discharge adjusting for baseline variables. Length of stay was compared using the nonparametric Wilcoxon Rank-Sum test. Additionally, we used proportional hazard models to test the effect of the intervention on time to discharge with a competing risk for death.

Patients who withdrew were censored at date of study withdrawal. All analyses were conducted using SAS v9.4.

Sample size and power consideration:

The trial had a planned enrollment of 428 patients with the anticipated sample size of 400 patients completing follow-up thus providing 80% power to detect an effect size of 0.286 between the intervention and control groups in the primary outcomes of delirium severity or delirium/coma free days at 0.05 significance level. Enrollment was stopped in year five of the trial due to the end of funding. The final enrollment of 351 patients provides 76% power for detecting the effect size assumed in the original power estimate. The Data Safety Monitoring Board approved the reduction in sample size.

Results:

Participants Characteristics:

From February 2009-January 2015, 12,402 patients were screened and 351 were enrolled [Eskenazi hospital (n=324), University hospital (n=23), Methodist hospital (n=4)]. Patients were randomly assigned to the PMD intervention (n=174) or usual care groups (n=177) (Figure 1). The mean age was 59.3 years (SD 16.9), 52% were females and 42% African-American. Patients had a mean APACHE-II score of 19.3 (SD 8.1) and a mean Charlson Comorbidity index score of 3.2 (SD 3.0). The majority of patients were admitted to the MICU services (63%), received mechanical ventilation for at least one day (73%), and had sepsis and/or acute respiratory failure as the principal admitting diagnoses (52%). The two randomized groups had similar demographics, severity of illness, chronic comorbidities, prior functional and cognitive status, and admitting diagnoses (Table 1).

Primary Outcomes:

There were no significant differences in median delirium/coma free days at day 8 [PMD: 4 (IQR 2–7) days versus usual care 5 (1–7) days, p=0.888] or at 30 days [26 (IQR 19–29) days versus 26 (14–29), p=0.991] (Figure 2). There were no significant differences for decrease in delirium severity at day 8 on either DRS-R-98 or CAM-ICU-7. At hospital discharge, the intervention group showed a greater reduction in delirium severity as measured by the CAM-ICU-7 [PMD: mean decrease in CAM-ICU-7 score=3.2 (SD 3.3) versus usual care: mean decrease=2.5 (SD 3.2); p=0.046] (Figure 2). In patients ≥ 65 years (n=125), no differences in delirium/coma free days were observed by day 8 [PMD: 4 (IQR 2–7) days versus usual care 4 (1–7) days, p=0.284] or at 30 days [26 (IQR 20–29) days versus 25 (12–29), p=0.331] (Supplementary Table S2). There were no significant differences for decrease in delirium severity at day 8 or at hospital discharge. Similar results were observed in patients ≥ 75 years (Supplementary Table S3).

Secondary Outcomes:

Mortality at both hospital discharge [PMD: 11.5%, usual care: 18.1%, p=0.098, OR=0.61 (0.32–1.16)] and 30-day post hospital discharge [PMD: 14.6%, usual care: 22%, p=0.096, OR=0.62 (0.35–1.12)] was not significantly different between the two groups (Supplementary Table S4).

Patients in both groups had similar lengths of ICU [PMD median: 10 (IQR 5–18) days versus usual care: 9.5 (5–15) days, p=0.208] and hospital stay [PMD: 12 (7–23) days versus usual care: 12 (7–19) days, p=0.731] post randomization. The median ventilator-free days were 9 days (5–18) in the PMD group and 8 days (5–15) in the usual care group (p=0.197) post randomization. There were no differences in the number of patients discharged home [PMD 72 (48%), usual care 58 (40.3%); p=0.198] and no differences in delirium-related hospital complication rates between the two groups (Table 2). When results were limited to patients 65 and 75 years, no differences were observed in any of the secondary outcomes (Supplementary Tables S2 and S3).

Process Measures:

Table 3 describes the use of haloperidol, benzodiazepines, and anticholinergics classified as pre, day-of, and post-randomization periods in both groups. PMD bundle delivery increased the exposure to low dose haloperidol post-randomization as 68% of the PMD group received at least one dose of haloperidol versus 32% of usual care group (p< 0.001). Benzodiazepine median daily exposure was lower post-randomization in the PMD group but did not reach statistical significance (p=0.079). No significant differences in the proportion of participants receiving strong anticholinergics were identified (p=0.248). Prior to randomization, there were no differences in the exposure to haloperidol, benzodiazepines, and anticholinergics. The administration of other anti-psychotics did not differ between groups (Table 3). There were also no differences in exposure to sedatives and anti-psychotics prior to extubation post-randomization (Supplementary Table S5).

Adverse Events:

The rates of serious adverse events were not different between groups [PMD: 44 patients (25.9%), usual care: 57 (32.2%), p=0.200] (Supplementary Table S6). None of the events were definitely or probably related to the protocol as determined by the DSMB.

Other Analyses:

Online supplementary material contains ancillary analyses: per-protocol analyses, proportional hazards model for time to hospital discharge with competing risk of death, and intervention targeted medications exposures (Supplementary Tables S7–S9). Per-protocol analyses limited to subjects with haloperidol exposure in the intervention group showed results similar to the intention to treat analysis (Supplementary Table S7). Proportional hazards model for time to hospital discharge with competing risk of death showed that PMD group did not differ from usual care in time to discharge [HR=1.08 (0.86–1.35)] (Supplementary Table S8).

Discussion:

Our pragmatic randomized controlled trial showed that a multi-component pharmacological management of delirium bundle was not effective in reducing delirium duration and delirium severity at one-week post randomization. The PMD bundle included a combination of de-prescribing benzodiazepines and anticholinergics and prescribing low dose haloperidol. The adherence to the bundle was accomplished by a computerized decision support coupled with

a pharmacist. The PMD trial results are the first to describe the effects of implementing a complex pharmacologic intervention to reduce delirium duration and severity in the ICU. As the intervention was not able to achieve a significant reduction in benzodiazepines and anticholinergics, we cannot ascertain with confidence that the bundle is truly ineffective in delirium reduction and whether our results could have been different if we had achieved high fidelity in all three components of the bundle. Additionally, given the low anticholinergic burden in the ICU this component of the bundle may not be a viable intervention target in future studies.

Our results further expand the findings of the Hope-ICU[32], MIND[33] and REDUCE[34] trials. Some differences are worthy to note: Hope-ICU and MIND both tested higher doses of haloperidol, whereas REDUCE used prophylactic low-dose haloperidol with one of the secondary outcomes being delirium/coma free days. The aforementioned trials tested haloperidol as a sole intervention compared to placebo or another anti-psychotic.[32–34] Rather than focusing on just the dopaminergic pathway, we targeted two additional neurotransmitter imbalances in the cholinergic and the GABA systems. As delirium is a complex pathophysiological process, we hypothesized that a combined approach might be better suited to reduce delirium. The PMD bundle did improve delirium severity at discharge but our process measures did not show a discernible difference in the components intervened. Hence, we can only speculate that continuing the PMD bundle may result in positive outcomes later in the hospital course.

The PMD bundle did not decrease the risk of death and lengths of ICU and hospital stay, nor did it reduce the duration of mechanical ventilation; findings similar to other pharmacologic delirium trials in the ICU setting.[32–34] To improve these outcomes, system-wide changes could be required in addition to the pharmacological approaches to delirium. Programs employing six or more implementation strategies targeting delirium assessment, prevention and treatment with integration of the pain, agitation and delirium guidelines[22] or the ABCDE bundle[35] (Awakening and Breathing coordination, Choice of sedation, Delirium monitoring, and Early Mobility) may be better suited to improve ICU length of stay.[36]

It has been proposed that haloperidol may have direct neuroprotective and immunomodulatory effects and combined with its dopamine blockade activities, it stands to reason that haloperidol could be efficacious in reducing delirium.[37–40] This may explain the positive results as seen in the study by Wang et al. using low-dose haloperidol among surgical ICU patients.[37] The patient population in that study was not as critically ill as expected in a traditional medical or surgical ICU. The high severity of illness as seen in our study and the aforementioned ICU trials[32–34] may render it difficult to control delirium symptoms with a single agent without managing other mechanistic pathways involved in delirium pathophysiology. Even though we focused on three neurotramsitter pathways i.e. dopaminergic, cholinergic, and GABA, we still could not reduce delirium duration and severity. Future interventions incorporating advancements in delirium pathophysiology might be better suited to reduce critical illness delirium.

Our study had limitations. This was a single city study conducted in academic hospitals. Some patients received intervention after 48 hours post-randomization that may have

reduced the intervention efficacy. We were not able to enroll the planned sample size. From 2009–2015, the prevalence of delirium decreased at our institute for unclear reasons. It could have been due to a change in sedation, analgesia practices and implementation of brain care bundles. This also highlights the difficulties in conducting ICU studies. We did not have a placebo-controlled arm. Due to our patient-based randomization instead of provider-based, contamination may have happened between study groups with same physicians taking care of patients in both the arms whose prescribing practices may have been influenced by the study. Utilizing an electronic medical record system for generating computer alerts and the incorporation of a pharmacist to ensure bundle adherence may not be generalizable to other institutions or cost-effective. Strategies to overcome the limitations of PMD that can be employed in future trials could include conducting a placebo controlled double blind trial with a delirium rescue protocol to reduce use of antipsychotics exposure or a cluster randomized trial with interventions focused on ICU units rather than individual patients that may reduce contamination across arms.

The study had several strengths. We had a diverse patient population. Trained research staff assessed sedation and delirium twice daily. Our bundle focused on three neurotransmitter imbalances. We also targeted delirium severity, which few studies have reported. We used a practical delivery method providing recommendations at the time of order entry, suitable for a fast paced ICU environment.

In conclusion, implementation of a multi-component pharmacological bundle of de-prescribing deliriogenic medications coupled with prescribing low dose haloperidol does not reduce delirium burden among critically ill patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

References:

1. Inouye SK, van Dyck CH, Alessi CA, Balkin S, Siegal AP, Horwitz RI. Clarifying confusion: the confusion assessment method. A new method for detection of delirium. Ann of Intern Med, 1990 113(12): p. 941–8 [PubMed: 2240918]

2. Lin SM, Liu CY, Wang CH, et al. The impact of delirium on the survival of mechanically ventilated patients. Crit CareMed 2004; 32 (11): 2254–2259.

3. Ely EW, Shintani A, Truman B, et al. Delirium as a predictor of mortality in mechanically ventilated patients in the intensive care unit. JAMA 2004; 291 (14): 1753–1762. [PubMed: 15082703]

4. Ely EW, Gautam S, Margolin R, et al. The impact of delirium in the intensive care unit on hospital length of stay. Intensive Care Med 2001; 27 (12): 1892–1900. [PubMed: 11797025]

5. Milbrandt EB, Deppen S, Harrison PL, et al. Costs associated with delirium in mechanically ventilated patients. Crit Care Med 2004; 32 (4): 955–962. [PubMed: 15071384]

6. Pisani MA, Kong SYJ, Kasl SV, Murphy TE, Araujo KLB, Van Ness PH.· Days of Delirium Are Associated with 1-Year Mortality in an Older Intensive Care Unit Population. Amer J of Resp and Crit Care Med, 2009 Vol 180 pp. 1092–1097 [PubMed: 19745202] ·

7. Shehabi Y; Riker R; Bokesch P; Wisemandle W; Shintani A; Ely EW: Delirium duration and mortality in lightly sedated, mechanically ventilated intensive care patients. Crit Care Med 2010 Volume 38(12): 2311–2318 [PubMed: 20838332]

8. Marcantonio E, Ta T, Duthie E, Resnick N. Delirium severity and psychomotor types: their relationship with outcomes after hip fracture repair. J Am Geriatr Soc 200250: 850–857 [PubMed: 12028171]

9. Kelly KG, Zisselman M, Cutillo-Schmitter T, Reichard R, Payne D, Denman S. Severity and course of delirium in medically hospitalized nursing facility residents. Amer J of Geriatr Psych 2001 9, 72–77),

10. McCusker J, Cole M, Abrahamowicz M, Prieau F, Belzile E. Delirium predicts 12-month mortality. Archives in Internal Medicine 2002 162, 457–463)

11. Inouye SK, Charpentier PA. Precipitating factors for delirium in hospitalized elderly persons. Predictive model and interrelationship with baseline vulnerability. JAMA 1996;275:852–7. [PubMed: 8596223]

12. Van Rompaey B Schuurmans MJ Shortridge-Baggett LM Truijen S Bossaert L Risk factors for intensive care delirium: a systematic review. Intensive & Critical Care Nursing 2008;24(2):98–107. [PubMed: 17949984]

13. Trzepacz PT. Is there a final common neural pathway in delirium? Focus on acetylcholine and dopamine. Semin Clin Neuropsychiatry 2000;5(2):132–48. [PubMed: 10837102]

14. Trzepacz PT, Bourne R, Zhang S. Designing clinical trials for the treatment of delirium. J of Psychosomatic Research 2008;65(3):299–307.

15. Khan BA, Zawahiri M, Campbell NL, Boustani M. Biomarkers for delirium - a review. J Am Geriatr Soc 2011 11;59 Suppl 2:S256–61 [PubMed: 22091570]

16. Campbell N, Khan B, Farber M, et al. Improving the care of delirium in the ICU: Design of a pragmatic study. Clinical Trials 2011 6 6;12:139

17. 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 [PubMed: 12421743]

18. Ely EW, Inouye SK, Bernard GR, et al.: Delirium in mechanically ventilated the intensive care unit (CAM-ICU). JAMA 2001; 286:2703–2710 [PubMed: 11730446]

19. Campbell NL. Maidment I, Fox C, Khan B, Boustani M. The 2012 Update to the Anticholinergic Cognitive Burden Scale. J Am Geriatr Soc Special Issue: 2013 Volume 61, Issue Supplement s1, pages S142–143

20. Campbell NL, Boustani MA, Lane KA, et al.: Use of anticholinergics and the risk of cognitive impairment in an African American population. Neurology 2010; 75:152–159 [PubMed: 20625168]

21. Cai X, Campbell N, Khan B, et al.: Long-term anticholinergic use and the aging brain. Alzheimers Dement 2013; 9:377–385 [PubMed: 23183138]

22. Barr J, Fraser GL, Puntillo K, et al. Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. Crit Care Med 2013 1;41(1): 263–306 [PubMed: 23269131]

23. Trzepacz PT, Baker RW, Greenhouse J. A symptom rating scale for delirium. Psychiatry Res 1988;23:89–97 [PubMed: 3363018]

24. Khan BA, Perkins AJ, Gao E, et al. The CAM-ICU-7 Delirium Severity Scale: A Novel Delirium Severity Instrument for Use in the ICU. Crit Care Med 2017 5;45(5):851–857. [PubMed: 28263192]

25. Ely EW, Gautam S, Margolin R, et al. The impact of delirium in the intensive care unit on hospital length of stay. Intensive Care Med 2001, 27:1892–1900. [PubMed: 11797025]

26. Pandharipande P, Shintani A, Peterson J, et al. Lorazepam is an independent risk factor for transitioning to delirium in intensive care unit patients. Anesthesiology 2006;104(1):21–6. [PubMed: 16394685]

27. Jorm AF. The Informant Questionnaire on cognitive decline in the elderly (IQCODE): a review. Int Psychogeriatr 2004 9;16(3):275–93. [PubMed: 15559753]

28. Katz S, Ford AB, Moskowitz RW, Jackson BA, Jaffe MW. Studies of illness in the aged. The index of Adl: A standardized measure of biological and psychosocial function. J Am Med Assoc 1963;185:914–919.

29. Lawton MP, Brody EM. Assessment of older people: self-maintaining and instrumental activities of daily living. Gerontologist 1969; 9:179–186. [PubMed: 5349366]

30. Knaus WA, Zimmerman JE, Wagner DP, et al. APACHE – Acute physiology and chronic health evaluation: A physiologically based classification system. Crit Care Med 1981;9:591–597. [PubMed: 7261642]

31. Charlson ME, Pompei P, Ales KL, et al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40:373–38346. [PubMed: 3558716]

32. Page JV, Ely EW, Gates S. et al. Effect of intravenous haloperidol on the duration of delirium and coma in critically ill patients (Hope-ICU): a randomized double-blind placebo controlled trial. Lancet Resp Med 2013; 1: 515–23

33. Girard TD, Pandharipande P, Carson SS. et al. Feasibility, efficiacy, and safety of antipsychotics for ICU delirium: the MIND randomized, placebo-controlled trial. Critical Care Med 2010; 38 (2): 428–437 [PubMed: 20095068]

34. van den Boogaard M, Slooter AJC, Brüggemann RJM et al. Effect of Haloperidol on Survival Among Critically Ill Adults With a High Risk of Delirium. The REDUCE Randomized Clinical Trial. JAMA 2018;319(7):680–690 [PubMed: 29466591]

35. Morandi A, Brummel NE, Ely EW. Sedation, delirium, and mechanical ventilation: the 'ABCDE' approach. Curr Opin Crit Care, 2011; 17 (1): 43–9 [PubMed: 21169829]

36. Troglic Z, van der Jagt M, Bakker J. et al. A systematic review of implementation strategies for assessment, prevention, and management of ICU delirium and their effect on clinical outcomes. Crit Care 2015 4 9; 19:157 [PubMed: 25888230]

37. Wang W, Li HL, Wang DX, et al. Haloperidol prophylaxis decreases delirium incidence in elderly patients after noncardiac surgery: a randomized controlled trial. Crit Care Med 2012; 40: 731–39 [PubMed: 22067628]

38. Song C, Lin A, Kenis G, et al. Immunosuppressive effects of clozapine and haloperidol: enhanced production of the interleukin-1 receptor antagonist. Schizophr Res 2000; 42:157–164 [PubMed: 10742653]

39. Schetz JA, Perez E, Liu R, et al. A prototypical Sigma-1 receptor antagonist protects against brain ischemia. Brain Res 2007; 1181:1–9. [PubMed: 17919467]

40. Khan BA, Farber MO, Campbell N, et al. S100 calcium binding protein B as a biomarker of delirium duration in the intensive care unit - an exploratory analysis. Int J Gen Med 2013 12 2;6:855–61. [PubMed: 24324346]
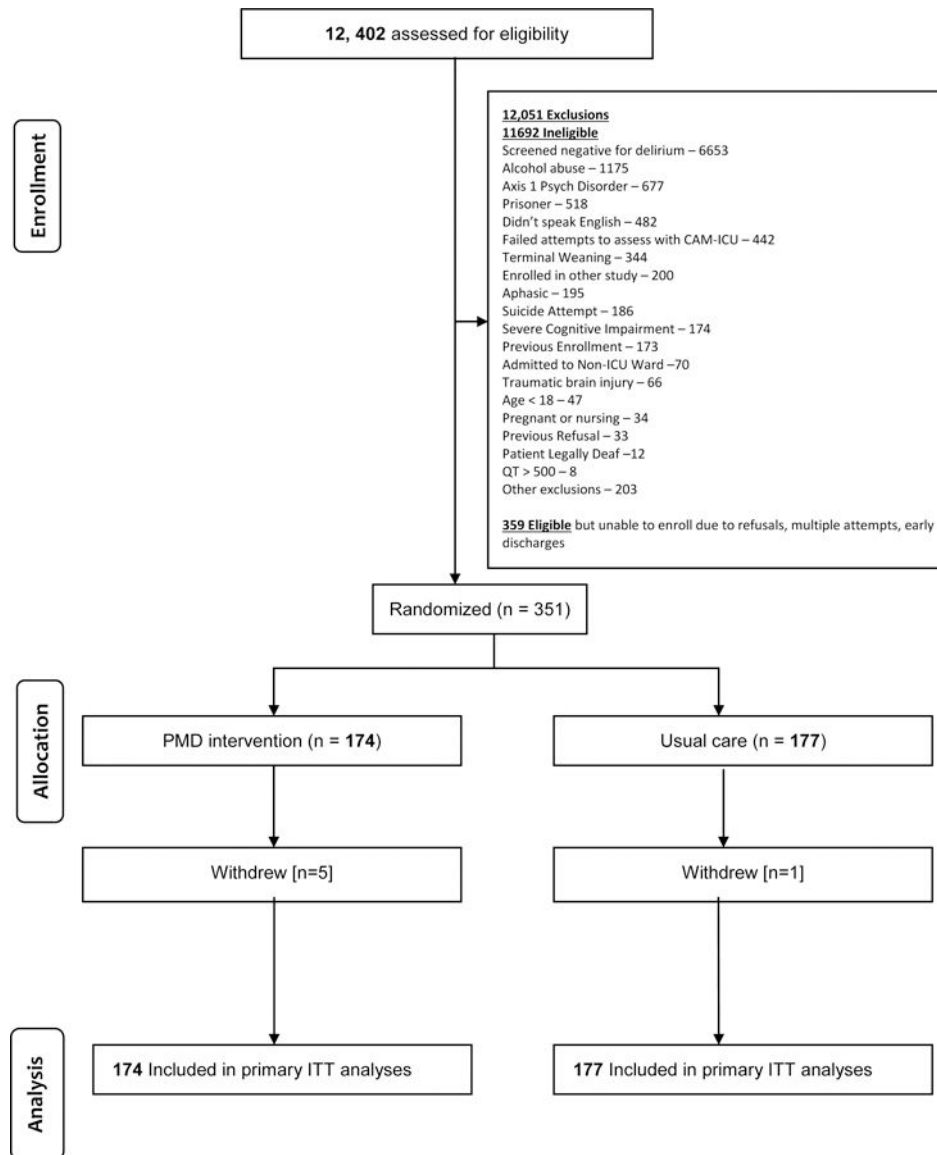
Figure 1.
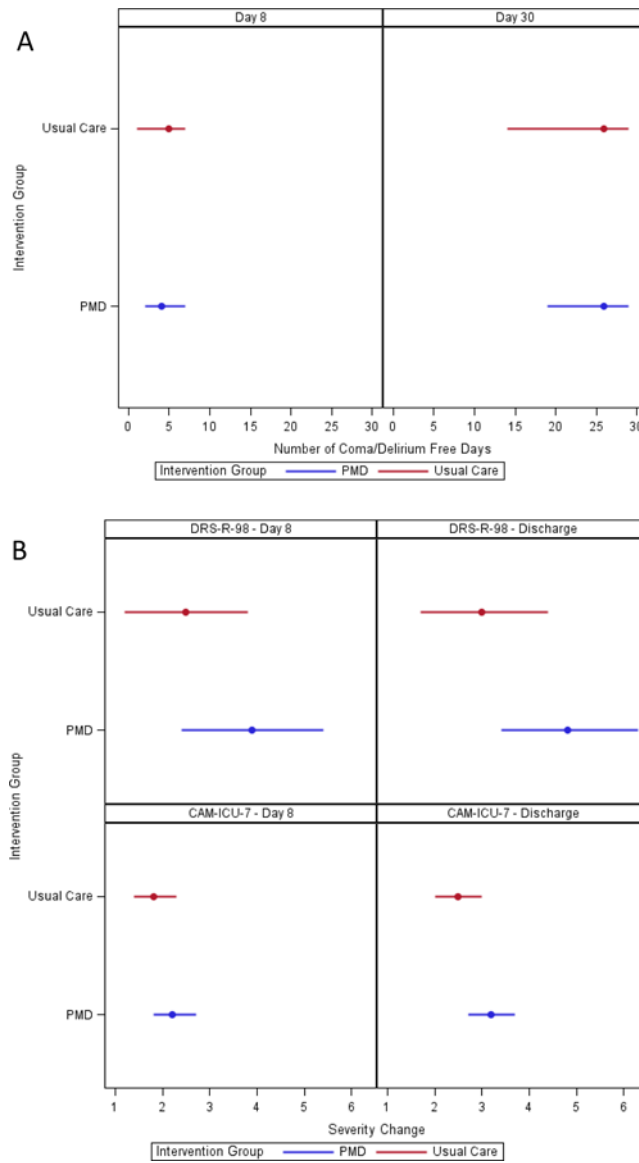Flow of Participants (N= 351) Through Study

Figure 2.
Primary Outcomes of PMD: Coma/Delirium Free Days at Day 8 and Day 30 (A) and
Change in Delirium Severity Scores at Day 8 and Discharge according to Delirium Rating
Scale-Revised-1998 and the Confusion Assessment Method for the Intensive Care Unit-7
(B).

Table 1

Baseline characteristics of patient in the Pharmacological Management of Delirium (PMD) trial (N=351).

	Overall (N=351)	PMD (N=174)	Usual Care (N=177)
Age	59.3 (16.9)	59.5 (16.9)	59.1 (16.9)
Female n (%)	184 (52.4)	98 (56.3)	86 (48.6)
African-American n (%)	146 (41.6)	74 (42.5)	72 (40.7)
Hispanic n (%)	4 (1.1)	2 (1.2)	2 (1.1)
Education (years)	11.3 (2.6)	11.2 (2.8)	11.5 (2.4)
APACHE II	19.3 (8.1)	18.5 (7.5)	20.1 (8.6)
Charlson Comorbidity Index	3.2 (3.0)	3.0 (2.7)	3.3 (3.2)
Activities of Daily Living (ADL)	5.4 (1.3)	5.3 (1.4)	5.5 (1.2)
Instrumental Activities of Daily Living (IADL)	6.4 (2.4)	6.4 (2.4)	6.4 (2.5)
IQCODE	3.2 (0.5)	3.2 (0.5)	3.2 (0.4)
Mechanically Ventilated n (%)	254 (72.8)	128 (74.4)	126 (71.2)
ICU Location			
Medical ICU n (%)	218 (63.0)	105 (61.8)	113 (64.2)
Surgical ICU n (%)	88 (25.4)	44 (25.9)	44 (25.0)
Progressive/step-down ICU n (%)	40 (11.6)	21 (12.3)	19 (10.8)
Diagnoses			
Acute Respiratory Failure/Sepsis	184 (52.4)	90 (51.7)	94 (53.1)
Neurologic/Altered Mental Status	34 (9.7)	19 (10.9)	15 (8.5)
Trauma	39 (11.1)	18 (10.3)	21 (11.9)
Other [*]	94 (26.8)	47 (27.0)	47 (26.5)

Data presented as mean (standard deviation) unless otherwise specified. PMD: Pharmacological Management of Delirium; APACHE: Acute Physiology and Chronic Health evaluation; ADLs assessed by Katz Scale; IADLs assessed by Lawton Scale; IQCODE: Informant Questionnaire on Cognitive Decline in the Elderly; ICU: Intensive Care Unit

[*] Others: Include cardiovascular and gastrointestinal diagnoses

Table 2

Delirium related hospital acquired complications rates in the Pharmacological Management of Delirium Trial (N=351)

Complications	PMD (N=174)	Usual Care (N=177)	P-value
Trying to get out of bed, N (%)	14 (8.2)	9 (5.1)	0.284
Verbal abuse, N (%)	10 (5.8)	4 (2.3)	0.106
Falls, N (%)	1 (0.6)	2 (1.1)	1.000
Delayed Procedure, N (%)	1 (0.6)	1 (0.6)	1.000
Pulling Tubes [*], N (%)	15 (8.8)	11 (6.2)	0.418
Hospital Acquired Pressure Ulcers, N (%)	26 (15.2)	22 (12.4)	0.535

N: Number of subjects

[*] Includes intravenous lines, urinary catheters, nasogastric tubes

Table 3

Pharmacological Management of Delirium Trial Medication Exposures

	Pre-Randomization			Randomization Day			Post-Randomization		
	PMD* (N=170)	Usual Care (N=176)	P-value	PMD (N=170)	Usual Care (N=176)	P-value	PMD (N=170)	Usual Care (N=176)	P-value
Haloperidol									
Patients[†] n (%)	29 (17.1)	32 (18.2)	0.888	41 (24.1)	24 (13.6)	0.014	116 (68.2)	56 (31.8)	<0.001
Median daily Dose (IQR)	0 (0–0)	0 (0–0)	0.723	0 (0–0)	0 (0–0)	0.040	0.5 (0–0.9)	0 (0–0.3)	<0.001
Benzodiazepines[†‡]									
Patients[†] n (%)	122 (71.8)	118 (67.0)	0.353	72 (42.3)	75 (42.6)	1.000	97 (57.1)	116 (65.9)	0.098
Median daily Dose (IQR)	1.3 (0 – 13.1)	1.0 (0–10.5)	0.466	0 (0–3.7)	0 (0–5.4)	0.720	0.1 (0–2.0)	0.3 (0–3.2)	0.079
Anticholinergic Burden[§]									
Patients[†] n (%)	30 (17.6)	29 (16.5)	0.777	17 (10.0)	17 (9.7)	1.000	44 (25.9)	54 (30.7)	0.342
Median daily score (IQR)	0 (0–0)	0 (0–0)	0.706	0 (0–0)	0 (0–0)	0.890	0 (0–0.1)	0 (0–0.2)	0.248
Olanzapine									
Patients[†] n (%)	2 (1.2)	2 (1.1)	1.000	1 (0.6)	2 (1.1)	1.000	3 (1.8)	2 (1.1)	0.680
Median daily Dose (IQR)	0 (0–0)	0 (0–0)	0.982	0 (0–0)	0 (0–0)	0.583	0 (0–0)	0 (0–0)	0.625
Quetiapine									
Patient[†] s n (%)	7 (4.1)	5 (2.8)	0.568	8 (4.7)	7 (4.0)	0.796	10 (5.9)	19 (10.8)	0.121
Median daily Dose (IQR)	0 (0.0)	0 (0.0)	0.519	0 (0.0)	0 (0.0)	0.751	0 (0.0)	0 (0.0)	0.099
Risperidone									
Patients[†] n (%)	0 (0–0)	0 (0–0)		0 (0–0)	0 (0–0)		3 (1.8)	1 (0.6)	0.364
Median daily Dose (IQR)	0 (0–0)	0 (0–0)		0 (0–0)	0 (0–0)		0 (0–0)	0 (0–0)	0.300
Dexmedetomidine									
Patients[†] n (%)	10 (5.9)	14 (8.0)	0.528	7 (4.1)	9 (5.1)	0.799	12 (7.1)	17 (9.7)	0.440
Median daily Dose (IQR)	0 (0–0)	0 (0–0)	0.448	0 (0–0)	0 (0–0)	0.669	0 (0–0)	0 (0–0)	0.375
Opioids[‖]									

	Pre-Randomization			Randomization Day			Post-Randomization		
	PMD* (N=170)	Usual Care (N=176)	P-value	PMD (N=170)	Usual Care (N=176)	P-value	PMD (N=170)	Usual Care (N=176)	P-value
Patients† n (%)	151 (88.8)	141 (80.1)	0027	132 (77.6)	129 (73.3)	0.383	140 (82.4)	144 (81.8)	1.000
Median daily Dose (IQR)	67.1 (9.6–153.9)	51.7 (2.8–138.1)	0.118	65.1 (5–139.3)	33.3 (0 – 145.2)	0.326	16.0 (1.8–55.5)	17.1 (1 – 69.6)	0.683
Propofol									
Patients† n (%)	83 (48.8)	81 (46.0)	0.667	45 (26.5)	41 (23.3)	0.535	52 (30.6)	61 (34.7)	0.425
Median daily Dose (IQR)	0 (0–352.9)	0 (0 –629.4)	0.794	0 (0–33.7)	0 (0–0)	0.559	0 (0–6.8)	0 (0–165.5)	0.358
Clonidine									
Patients† n (%)	4 (2.4)	4 (2.3)	1.000	6 (3.5)	2 (1.1)	0.168	15 (8.8)	7 (4.0)	0.079
Median daily Dose (IQR)	0 (0–0)	0 (0–0)	0.967	0 (0–0)	0 (0–0)	0.145	0 (0–0)	0 (0–0)	0.076
Propranolol									
Patients† n (%)	4 (2.4)	1 (0.6)	0.208	5 (2.9)	1 (0.6)	0.116	9 (5.3)	6 (3.4)	0.438
Median daily Dose (IQR)	0 (0–0)	0 (0–0)	0.165	0 (0–0)	0 (0–0)	0091	0 (0–0)	0 (0–0)	0.390

*
PMD: Pharmacological Management of Delirium

†
Patients who received the drug during hospitalization

‡
Benzodiazepines data presented as Lorazepam equivalents

§
Anticholinergic burden measured by Anticholinergic Burden (ACB) scale

||
Opioids data presented as morphine equivalents

Haloperidol dose is presented in milligrams (mg)

Median number of pre-randomization hospital days: PMD=6 (3–10), Usual care=5 (3–10), p=0.449

Median number of post-randomization hospital days: PMD=12 (7–23), Usual care=12 (7–19.5), p=0.537