Treating delirium in the intensive care unit: No easy answers

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Consider a case of hyperactive delirium in the intensive care unit (ICU): As nurses run to tame flailing arms into restraints, providers turn to quick-acting sedatives to quell agitation and facilitate continuation of ongoing cares. In fact, surveys suggest that 60% to 85% providers treat ICU delirium with pharmacologic therapies, often antipsychotic medications.^{1,2} In the case of hyperactive delirium in which patient distress and agitation may be physically harmful to themselves or others, short-term use of an antipsychotic may be warranted to prevent injury or dislodgement of life-sustaining therapies.³ However, most cases of ICU delirium are likely hypoactive in presentation, represented by a state of inertia or quietude. This phenotype is often under-recognized because of the withdrawn nature of the patient and potential for misdiagnosis as dementia or depression.⁴ In contrast to agitated forms of hyperactive delirium, the role for antipsychotic medication in the treatment of hypoactive delirium is not clear.

Why is the question of optimal management for delirious patients so important? Over the last decade, it has become increasingly recognized that delirium is not transient or fleeting. Rather, the acute onset of delirium may precede and has been consistently associated with both short- and long-term morbidity and mortality, and is a significant burden to patients and the healthcare system. In the short-term, delirium has been associated with medical complications, increased length of hospitalization, and increased cost.^{5,6} Patients are often unable to participate and cooperate with important medical care such as physical or respiratory therapy. In the long-term, patients may experience earlier mortality and long-term cognitive and functional impairment.⁷⁻¹⁰ However, it is unknown how to treat delirious patients to reduce these downstream sequelae and improve overall patient care.

One challenge is that the pathophysiology of delirium is multifactorial and poorly characterized. Leading hypotheses include changes in neurotransmitters, neuro-inflammation, ischemia, immobility, and drugs, but the exact mechanisms

are not known.¹¹ In fact, most of the data describing important patient vulnerabilities and potential perioperative insults have been derived from epidemiologic studies, which are often insufficient to illustrate mechanism. Thus, the syndrome of delirium as currently defined may be a mixed phenotype that is not amenable to any one intervention.

NEED FOR THIS STUDY

When caring for a delirious patient at the bedside, the intensivist is faced with a quandary: how best to manage acute symptoms of hyperactive or hypoactive delirium and prevent important long-term sequelae. Antipsychotic medications are commonly administered in this setting, based on their profile to agonize the cholinergic system, antagonize the dopaminergic system, and provide sedation to hyperactive patients.^{1,12} Worldwide, haloperidol is most commonly used and is the most studied, but atypical antipsychotics (ie, ziprasidone, quetiapine, olanzapine) have demonstrated at least equivalent efficacy to haloperidol, with the additional benefit of reduced extrapyramidal symptoms.¹³

Charles H. Brown IV, MD, MHS (left), and Stephanie Cha, MD (right)

Central Message

Antipsychotics do not appear to be effective in the treatment of hypoactive delirium, a finding relevant to the management of cardiac surgical ICU patients.

The Invited Expert Opinion provides a perspective on this topic based on the following paper: *N Engl J Med*. 2018; 379:2056-2516. <https://doi.org/10.1056/NEJMoa1808217>.

See Commentaries on pages 1899 and 1901.

The authors of the MIND-USA trial note that both hyperactive and hypoactive delirium are commonly managed with antipsychotic medications, despite guidelines that recommend against the routine use of any medication for the treatment of delirium.³

Does the evidence support this common practice, and if so, which class of antipsychotic medication should be used in the setting of delirium? Early placebo-controlled randomized trials have failed to demonstrate consistent and substantial benefits, such as reductions in delirium-free days, improvement in hospital length of stay, or reduced mortality. However, these studies were limited by smaller sample sizes, heterogeneity in design, and variable outcome measures.¹⁴⁻¹⁶ Additionally, studies were conflicting, with at least one trial demonstrating faster delirium resolution, less agitation, and greater rate of discharge to home or rehabilitation with the use of the atypical antipsychotic quetiapine, when added to haloperidol therapy.¹⁷ To address this gap in understanding and practice, the authors of the MIND-USA study designed a large randomized trial comparing a typical and atypical antipsychotic medication with placebo among patients with delirium in the ICU.

SUMMARY OF STUDY

The MIND-USA trial was a masked 1:1:1 randomized trial comparing haloperidol and ziprasidone with placebo in the treatment of delirious patients in the ICU. Patients included medical or surgical ICU patients with acute respiratory failure or shock requiring positive pressure ventilation, vasopressors, or the use of an intra-aortic balloon pump. Patients who screened positive for delirium within 5 days of enrollment using the well-validated CAM-ICU tool were randomized to receive intravenous placebo, haloperidol, or ziprasidone for a total intervention exposure of 14 days. Drugs were titrated such that subsequent doses occurred at 12-hour intervals and were doubled if delirium was still present (to a maximum of haloperidol 10 mg/dose or 20 mg/d and ziprasidone 20 mg/dose or 40 mg/d) or halved if 2 consecutive screens were negative.

Of 566 patients enrolled in this study, 48% were found to have new-onset delirium and randomized. Some 89% were represented by the hypoactive phenotype at randomization. The median duration of medication exposure was 4 days with a mean haloperidol dose of 11.0 mg and a mean ziprasidone dose of 20.0 mg.

The authors found no differences between groups in the primary outcome (duration of delirium-free or coma-free days alive) or secondary outcomes (delirium duration, time to liberation from mechanical ventilation, time to final successful ICU or hospital discharge, ICU readmission rate, and 30-day and 90-day mortality). Additionally, there were no differences in safety end points (incidence of torsades de pointes, neuroleptic malignant syndrome, or severity of extrapyramidal symptoms).

IMPORTANT CONSIDERATIONS

The results of this trial provide important information to guide management of delirium in patients with critical illness and suggest that antipsychotics are ineffective in the management of patients with predominantly hypoactive delirium. Haloperidol and ziprasidone appeared to be safe, with similar occurrence of extrapyramidal symptoms between groups and only 2 patients with torsade de pointes (albeit >4 days after stopping haloperidol). In terms of strength of evidence, the MIND-USA trial is the largest, multicenter randomized trial to investigate the impact of antipsychotics in critically ill patients with delirium. The investigative team are experts in this field and experienced in conducting rigorous trials. The CAM-ICU was used for frequent delirium assessments, and patients, providers, and outcome assessors were masked. In addition, the study was performed in the context of emphasis on best practices in pain and sedation management (ie, "ABCDE" bundled care).

However, there are important limitations to consider in interpreting the results of this study, which highlight the difficulty in treating a heterogeneous syndrome like delirium. Patients with hyperactive delirium were under-represented in this study (11% at randomization and ~37% at any time), and thus there still may be a role for antipsychotic medication in uncontrolled agitation or patients who are difficult to sedate. Indeed, the results of this trial are most broadly applicable to patients with hypoactive delirium. The dose titration protocol was less aggressive than in some clinical practice, and so it is possible that a potential benefit and the true safety profile were missed in hyperactive patients. In addition, the lack of effect may have been clouded by additional medications and crossover between groups—21% of all patients received open-label antipsychotic medications; more than 20% trial drug was withheld because of refusal by medical team, patient, or family; and more than 90% of patients received additional sedation or analgesic medication. Finally, the mechanism of antipsychotic medications is not uniform, so the results of this trial may not hold for all medications in this class.

GENERALIZABILITY TO CARDIAC INTENSIVE CARE UNIT PATIENTS

An important question is how to interpret the results of this study within the context of post-cardiac surgery delirium. The incidence of delirium after cardiac surgery is among the highest of any postoperative population.¹⁸ Patients in the cardiac intensive care unit (CICU) carry a unique risk profile for ICU delirium, including potential cerebral hypoperfusion, high inflammatory response, frequent cerebral emboli, and impaired drug clearance. In addition, the increasingly ageing cardiac surgical population has a high prevalence of preoperative frailty, which is strongly associated with post-cardiac surgery delirium risk.^{19,20} In

noncardiac surgical patients with severe frailty, antipsychotic therapy has also been associated with poorer health outcomes.²¹ Furthermore, concomitant sedation and analgesic needs may be higher in this population (due to such instances as mechanical circulatory support-related hardware) and are often titrated in conjunction with residual neuromuscular blockade and anesthetics. This is significant because polypharmacy of greater than 6 medications has been shown to increase delirium risk in elderly patients hospitalized to acute care.²² In the MIND-USA trial, the majority of patients received additional opioid, benzodiazepines, or propofol (as would be expected in this patient population), but there did not appear to be substantial differences in these medications by group.

Although the studied population of the MIND-USA trial is poorly represented by cardiac (3%) or surgical (28%) patients, the patients in the trial were all critically ill in respiratory failure or shock. The overall and sub-syndromal prevalence of delirium were high and comparable to a CICU population. In the absence of compelling results to the contrary, the results of this trial provide the best evidence to guide the management of delirium in the CICU population.

RELATIONSHIP TO EXISTING GUIDELINES

The results of the MIND-USA trial fit with current guidelines, which recommend against the routine use of any pharmacologic therapy for the prevention or treatment of delirium. This was supported by a systematic review and meta-analysis of randomized control trials published on the impact of haloperidol for the treatment or prevention of ICU delirium, published subsequently to MIND-USA.²³ In addition, guidelines emphasize sedation practice that minimizes the use of benzodiazepine infusions, as well as the routine use of nonpharmacologic multi-component bundles. As an important example, “ABCDE” bundled care is recommended and designed to promote awakening and breathing coordination, delirium monitoring and management, and early exercise mobility.³ Institution of “ABCDE” bundles has been associated with favorable safety/feasibility, reduced delirium incidence, and when expanded to “ABCDEF” (family engagement), reduced mortality and coma- or delirium-free ICU days.^{24,25} The current trial demonstrates high compliance with “ABCDE” bundled care, as well as sedation practice that favors propofol or dexmedetomidine to benzodiazepines, and thus the results reflect a truly best practice scenario.

CONCLUSIONS

The management of ICU delirium is complicated by its heterogeneous expression. Hypoactive delirium is far more common than the hyperactive phenotype in both general ICU and CICU patients. The results of the MIND-USA trial strongly suggest that antipsychotics do not appear to be

effective in the treatment of hypoactive delirium or in the prevention of short-term sequelae. These findings are likely applicable to CICU patients, despite important differences in delirium pathophysiology. Nevertheless, more studies are sorely needed in these patients to better define pathophysiology and appropriate management strategies for post-cardiac surgery delirium. As we wait for more precise characterization of delirium, best practice strategies still include regular delirium screening and minimization of modifiable risk factors of delirium through a multi-component nonpharmacologic program.

Conflict of Interest Statement

Brown has consulted for and has existing data sharing agreements with Medtronic Funding (National Institutes of Health/National Institute on Aging K-76 AG057020). Cha has nothing to disclose with regard to commercial support.

References

- Devlin JW, Bhat S, Roberts RJ, Skrobik Y. Current perceptions and practices surrounding the recognition and treatment of delirium in the intensive care unit: a survey of 250 critical care pharmacists from eight states. *Ann Pharmacother*. 2011;45:1217-29.
- Morandi A, Piva S, Ely EW, Myatra SN, Salluh JIF, Amare D, et al. Worldwide survey of the “Assessing Pain, Both Spontaneous Awakening and Breathing Trials, Choice of Drugs, Delirium Monitoring/Management, Early Exercise/Mobility, and Family Empowerment” (ABCDEF) bundle. *Crit Care Med*. 2017;45:e1111-22.
- Devlin JW, Skrobik Y, Gélinas C, Needham DM, Slooter AJ, Pandharipande PP, et al. Clinical practice guidelines for the prevention and management of pain, agitation/sedation, delirium, immobility, and sleep disruption in adult patients in the ICU. *Crit Care Med*. 2018;46:e825-73.
- Peritogiannis V, Bolosi M, Lixouriotis C, Rizos DV. Recent insights on prevalence and correlations of hypoactive delirium. *Behav Neurol*. 2015;2015:416792.
- Brown CH, La A, Max L, Lymar D, Neufeld KJ, Tian J, et al. The impact of delirium after cardiac surgical procedures on postoperative resource use. *Ann Thorac Surg*. 2016;101:1663-9.
- Ely EW, Gautam S, Margolin R, Francis J, May L, Speroff T, et al. The impact of delirium in the intensive care unit on hospital length of stay. *Intensive Care Med*. 2001;27:1892-900.
- Girard TD, Jackson JL, Pandharipande PP, Pun BT, Thompson JL, Shintani AK, et al. Delirium as a predictor of long-term cognitive impairment in survivors of critical illness. *Crit Care Med*. 2010;38:1513-20.
- Gottesman RF, Grega MA, Bailey MM, Pham LD, Zeger SL, Baumgartner WA, et al. Delirium after coronary artery bypass graft surgery and late mortality. *Ann Neurol*. 2010;67:338-44.
- Saczynski JS, Marcantonio ER, Quach L, Fong TG, Gross A, Inouye SK, et al. Cognitive trajectories after postoperative delirium. *N Engl J Med*. 2012;367:30-9.
- Brown CH, Probert J, Healy R, Parish M, Nomura Y, Yamaguchi A, et al. Cognitive decline after delirium in patients undergoing cardiac surgery. *Anesthesiology*. 2018;129:406-16.
- Inouye SK, Westendorp RGJ, Saczynski JS. Delirium in elderly people. *Lancet*. 2014;383:911-22.
- Maldonado JR. Acute brain failure: pathophysiology, diagnosis, management, and sequelae of delirium. *Crit Care Clin*. 2017;33:461-519.
- Skrobik YK, Bergeron N, Dumont M, Gottfried SB. Olanzapine vs haloperidol: treating delirium in a critical care setting. *Intensive Care Med*. 2004;30:444-9.
- Page VJ, Ely EW, Gates S, Zhao XB, Alce T, Shintani A, et al. Effect of intravenous haloperidol on the duration of delirium and coma in critically ill patients (Hope-ICU): a randomised, double-blind, placebo-controlled trial. *Lancet Respir Med*. 2013;1:515-23.

15. Girard TD, Pandharipande PP, Carson SS, Schmidt GA, Wright PE, Canonic AE, et al. Feasibility, efficacy, and safety of antipsychotics for intensive care unit delirium: the MIND randomized, placebo-controlled trial. *Crit Care Med*. 2010;38:428-37.
16. Neufeld KJ, Yue J, Robinson TN, Inouye SK, Needham DM. Antipsychotic medication for prevention and treatment of delirium in hospitalized adults: a systematic review and meta-analysis. *J Am Geriatr Soc*. 2016;64:705-14.
17. Devlin JW, Roberts RJ, Fong JJ, Skrobik Y, Riker RR, Hill NS, et al. Efficacy and safety of quetiapine in critically ill patients with delirium: a prospective, multi-center, randomized, double-blind, placebo-controlled pilot study. *Crit Care Med*. 2010;38:419-27.
18. Ibrahim K, McCarthy CP, McCarthy KJ, Brown CH, Needham DM, Januzzi JL Jr, et al. Delirium in the cardiac intensive care unit. *J Am Heart Assoc*. 2018;7:1-11.
19. Brown CH, Max L, Laflam A, Kirk L, Gross A, Arora R, et al. The association between preoperative frailty and postoperative delirium after cardiac surgery. *Anesth Analg*. 2016;123:430-5.
20. Jung P, Pereira MA, Hiebert B, Song X, Rockwood K, Tangri N, et al. The impact of frailty on postoperative delirium in cardiac surgery patients. *J Thorac Cardiovasc Surg*. 2015;149:869-75.
21. Stock KJ, Hogan DB, Lapane K, Amuah JE, Tyas SL, Bronskill SE, et al. Antipsychotic use and hospitalization among older assisted living residents: does risk vary by frailty status? *Am J Geriatr Psychiatry*. 2017;25:779-90.
22. Hein C, Forgues A, Piau A, Sommet A, Nourhashémi F, Vellas B. Impact of polypharmacy on occurrence of delirium in elderly emergency patients. *J Am Med Dir Assoc*. 2014;15:850.e11-5.
23. Zayed Y, Barbarawi M, Kheiri B, Banifadel M, Haykal T, Chahine A, et al. Haloperidol for the management of delirium in adult intensive care unit patients: a systematic review and meta-analysis of randomized controlled trials. *J Crit Care*. 2019;50:280-6.
24. Balas MC, Burke WJ, Gannon D, Cohen MZ, Colburn L, Bevil C, et al. Implementing the awakening and breathing coordination, delirium monitoring/management, and early exercise/mobility bundle into everyday care: opportunities, challenges, and lessons learned for implementing the ICU pain, agitation, and delirium guidelines. *Crit Care Med*. 2013;41(9 Suppl 1):S116-27.
25. Barnes-Daly MA, Phillips G, Ely EW. Improving hospital survival and reducing brain dysfunction at Seven California Community Hospitals: implementing PAD guidelines via the ABCDEF bundle in 6,064 patients. *Crit Care Med*. 2017;45:171-8.