Has the Drug of Choice for Treating Critical Illness Delirium Been Established?

THE "PRO" SIDE

Critical illness delirium (hereafter simplified to "delirium") is an acute confusional state seen in up to 80% of adult patients admitted to the intensive care unit (ICU).[1] It is characterized by an altered level of consciousness, changes in cognition, perceptual disturbances, a fluctuating course, disturbances of the sleep–wake cycle, disorientation, psychomotor agitation or retardation, and hallucinations or delusions.[1] As a constellation of symptoms and signs that commonly occur together, delirium should not be considered in and of itself a disease, but rather should be thought of as a syndrome,[2] specifically one of acute brain dysfunction that can typically be traced back to one or more inciting causes.

The mainstay of therapy, therefore, must aim to address the underlying causes of the syndrome and not simply treat the symptoms. Just as for a patient presenting with new-onset congestive heart failure it would be inappropriate to treat the symptoms by administering furosemide and oxygen without looking for and treating the underlying cause (e.g., an acute coronary syndrome), the drug of choice for delirium cannot simply be the one that best treats the symptoms; rather, it must address the underlying cause. Therefore, the drug of choice to treat any given case of delirium will be patient- and cause-specific. It could be the antibiotic that targets the patient's infection, the free water that addresses the patient's hypernatremia, the laxatives that resolve the patient's constipation, the benzodiazepine that counters the patient's alcohol withdrawal, or the correct treatment that addresses any of the myriad other causes of delirium. The number of potential drivers of delirium is immense, and the reader is encouraged to consult other sources for further information on their assessment and treatment.[1,3,4]

Of course, although it is essential to address the underlying etiology of delirium, its symptoms cannot be ignored, as they have the potential to cause significant harm to both the patient and the patient's care team. Anyone who has worked in an ICU for any period of time will have seen a patient with delirium self-extubate or pull out a Foley catheter with the balloon up! Such adverse events can result in significant morbidity and potentially even death.[5] Additionally, patients experiencing delirium can pose a danger to the care team if they become aggressive to the point of striking and injuring care providers. What may be less obvious is that these agitated patients are also at increased risk of morbidity through reactive oversedation by the care team (to keep themselves safe), with the oversedation leading to increased risk of prolonged mechanical ventilation, ventilator-associated pneumonia, and possibly death.[6]

The drug of choice to treat a patient's delirium symptoms must be focused toward the particular issues that are causing other aspects of treatment to fall short of defined care goals. With careful understanding of the goals of therapy and the pharmacology and therapeutic effect of the treatment options for delirium symptoms, the clinician can anticipate and plot the best therapeutic course. Since we are purely targeting symptom control with this aspect of delirium therapy, each patient becomes his or her own unique "*n* of 1" trial, with the agent(s) that ultimately work for that patient becoming the specific drug(s) of choice.

Neuroleptic and antipsychotic medications have the longest history of clinical experience in managing delirium; however, the lack of rigorously conducted placebo-controlled studies of haloperidol or any other neuroleptic agent precludes our knowing for sure whether these agents alter the natural course of delirium.[1] The closest evidence available is from a small pilot study of quetiapine versus placebo, added to as-needed haloperidol for ICU patients with delirium.[7] In this trial of 36 patients, the mean time to resolution of delirium symptoms declined from 4.5 days with placebo to 1 day with quetiapine ($p = 0.001$).[7] This very small trial provides a hint that there may be a standardized approach that will work for all patients, but until larger confirmatory studies are published, we are left to approach delirium from a symptom-based perspective.

It is well appreciated that antipsychotic medications have different effects, which are based on their relative receptor affinities.[4] For example, haloperidol is a potent antagonist of the dopamine receptor, with minimal interactions with other receptors, whereas methotrimeprazine is a relatively weak antagonist of the dopamine receptor but a potent blocker of the histamine and α_1 receptors, providing strong sedative and hemodynamic properties. Depending on the patient's symptoms, the clinician selects a particular drug to address one or more of the patient's predominant symptoms. If the patient is frankly hallucinating and exhibiting hypoactivity, haloperidol may be optimal, given its potent effect on the dopaminergic system (which is thought to drive the hallucinations) and its minimally sedating effects (because of weak histamine blockade). Conversely, in a young patient with hypertension who is exhibiting combativeness, a more sedating approach, such as methotrimeprazine or quetiapine, may yield the best results.

Dexmedetomidine is a relatively new sedative in Canada, with a unique, non–benzodiazepine-like mechanism (acting as an agonist at the central α_2 receptors, which in turn leads to inhibition of central sympathetic outflow).[8] Because of its unique pharmacology, it is being widely explored as a potential therapeutic option for both reducing the risk of delirium, through avoidance of benzodiazepines for sedation, and treating delirium when it does occur. In a small, randomized open-label study of 20 intubated patients with delirium, the time to extubation was reduced from 42.2 h in the haloperidol group to 19.9 h in the dexmedetomidine group (p = 0.016),[9] indicating that dexmedetomidine may be beneficial in facilitating extubation of patients with delirium. As larger and more rigorous studies are conducted and published, it is possible that dexmedetomidine will become the drug of choice for treating delirium.

In summary, delirium is a common syndrome in critically ill patients, one that has significant negative effects on outcomes. The drugs of choice to treat delirium are the case-specific agents that will resolve the underlying cause of the delirium, along with a carefully selected neuroleptic targeted to minimize the patient's particular delirium symptoms and potentially dexmedetomidine if future studies support the results of pilot research to date.

References

1. Barr J, Fraser GL, Puntillo K, Ely EW, Gélinas C, Dasta JF, 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;41(1):263-306.
2. Syndrome [definition]. In: *Merriam-Webster dictionary.* Springfield (MA): Merriam-Webster; 2015 [cited 2015 May 27]. Available from: www.merriam-webster.com/dictionary/syndrome
3. Girard TD, Pandharipande PP, Ely EW. Delirium in the intensive care unit. *Crit Care.* 2008;12 Suppl 3:S3.
4. Hipp DM, Ely EW. Pharmacological and nonpharmacological management of delirium in critically ill patients. *Neurotherapeutics*. 2012;9(1):158-75.
5. Atkins PM, Mion LC, Mendelson W, Palmer RM, Slomka J, Franko T. Characteristics and outcomes of patients who self-extubate from ventilatory support: a case–control study. *Chest.* 1997;112(5):1317-23.
6. Sessler CN, Varney K. Patient-focused sedation and analgesia in the ICU. *Chest.* 2008;133(2):552-65.
7. 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, multicenter, randomized, double-blind, placebo-controlled pilot study. *Crit Care Med.* 2010;38(2):419-27.
8. Gerlach AT, Murphy CV, Dasta JF. An updated focused review of dexmedetomidine in adults. *Ann Pharmacother*. 2009;43(12):2064-74.
9. Reade MC, O'Sullivan K, Bates S, Goldsmith D, Ainslie WR, Bellomo R. Dexmedetomidine vs. haloperidol in delirious, agitated, intubated patients: a randomised open-label trial. *Crit Care.* 2009;13(3):R75.

Jerrold Perrott, BSc(Pharm), ACPR, PharmD
Clinical Pharmacy Specialist – Critical Care (ICU)
Royal Columbian Hospital
New Westminster, British Columbia
Clinical Instructor
University of British Columbia
Vancouver, British Columbia

Competing interests: None declared.

THE "CON" SIDE

Of every 10 patients in the intensive care unit (ICU), 4 to 9 will experience delirium during their admission.[1] The development and validation of delirium screening tools specific to the critically ill population, including those receiving mechanical ventilation, has enabled a greater understanding of the prevalence of delirium in the ICU and its considerable impact on patient outcomes. Patients with delirium have increased mortality, prolonged duration of mechanical ventilation and hospital and ICU length of stay, more long-term cognitive impairment, and increased likelihood of transfer to chronic care facilities.[2-4] Although effective prevention of delirium is paramount, it also remains imperative to identify effective treatment strategies for patients who experience the syndrome.

The pathophysiology of delirium is not fully understood but is considered complex and multifaceted. Multiple contributory mechanisms have been proposed, including direct neurotoxic effects (e.g., inflammation), alterations in cerebral oxidative metabolism and glucose regulation, and imbalances of numerous neurotransmitters (e.g., acetylcholine, dopamine, serotonin, γ-aminobutyric acid, tryptophan).[5] Despite the plethora of studies that have investigated diverse drugs targeting these different pathways, no single drug treatment has been proven to consistently and favourably alter delirium outcomes. The most recent iteration of the American College of Critical Care Medicine's guidelines for pain, agitation, and delirium,[6] published in 2013, summarized the scarcity of data to support delirium treatment for ICU patients and highlighted how some drugs may in fact be harmful to critically ill patients. Specifically, these guidelines recommend against the use of rivastigmine, a cholinergic agent used for mild to moderate dementia. This recommendation statement is based on a double-blind, randomized placebo-controlled trial (RCT) that was terminated prematurely because the rivastigmine-treated group displayed prolonged and more severe delirium, in addition to a near 3-fold increase in mortality rate, relative to placebo.[7]

The guidelines for pain, agitation, and delirium further state that there is no evidence to support the use of haloperidol to reduce the duration of delirium.[6] Despite the fact that only limited evidence exists to support the benefit of treatment with antipsychotics, these agents are commonly used in clinical practice to manage the symptoms of delirium.[8,9] The Hope-ICU trial,[10] which is to date the largest trial of antipsychotic therapy for critically ill patients with delirium or at high risk of delirium (n = 141), found no difference in days alive without delirium between participants treated with haloperidol and those treated with placebo, nor were any significant differences found in other important clinical outcomes. With regard to the use of atypical antipsychotic drugs, the guidelines for pain, agitation, and delirium suggest that these *may* be beneficial,[6] based on the results of one pilot RCT (n = 36) comparing the outcomes of ICU patients with delirium managed with either quetiapine or placebo.[11] In that study, the time to first resolution of delirium

was shorter for the group receiving quetiapine, and this group also had reduced duration of delirium.[11] However, there was no difference in the duration of mechanical ventilation, duration of ICU length of stay, mortality rate, or use of open-label haloperidol. The much larger MIND RCT,[12] a double-blind feasibility trial comparing haloperidol, ziprasidone, and placebo in patients with delirium or at high risk of delirium (n = 101), found no difference in the median number of days alive without delirium or coma, and no differences in ventilator-free days, length of stay, or mortality rate. Results supporting the efficacy of atypical antipsychotics are certainly inconsistent, and larger trials, such as the in-progress MIND-USA study,[13] are needed to ascertain the effect of these drugs on delirium-related outcomes. Furthermore, although none of these trials showed a significant increase in adverse drug events, their numbers of participants were relatively small compared with those of large cohort studies that have associated antipsychotic use with harm.[14,15] Given the high prevalence of delirium in the ICU, caution is required when assessing the risk of using antipsychotics in this vulnerable population.

Benzodiazepines are frequently administered to ICU patients for sedation and to treat agitation, yet these drugs have been shown to be deliriogenic in certain patient populations.[16,17] This effect is problematic, given the increased propensity for delirium among critically ill patients; alternatives to benzodiazepines are therefore desired to provide appropriate sedation without conferring additional risk. With regard to sedation of critically ill patients with delirium unrelated to benzodiazepine or alcohol withdrawal, the guidelines on pain, agitation, and delirium recommend using dexmedetomidine instead of benzodiazepines.[6] Two RCTs have compared benzodiazepines and dexmedetomidine for sedation.[18,19] The MENDS RCT[18] compared dexmedetomidine and lorazepam (n = 106) and demonstrated that dexmedetomidine-treated patients spent more days alive, without delirium or coma, than those who received lorazepam. The prevalence of delirium was high in both groups, and there was no statistical difference in rate of delirium between the 2 groups. The SEDCOM RCT[19] compared dexmedetomidine and midazolam (n = 366) and demonstrated a lower prevalence of delirium in the dexmedetomidine-treated patients. Although both of these trials included high percentages of patients with delirium, neither was designed to specifically treat delirium, and not all patients had delirium at enrolment. In addition, the use of dexmedetomidine may have allowed patients to be less sedated, affecting the inattention measure of the confusion assessment method for the ICU. It can thus be posited that these studies were more likely to measure level of sedation than degree of delirium. In another study, a small, open-label pilot trial of 20 patients in whom extubation was not possible because of delirious agitation, dexmedetomidine shortened the median time to extubation and the ICU length of stay relative to haloperidol.[20] About one-third of patients were confirmed to have delirium at enrolment, and only half experienced delirium at any point during the study. As such, there is insufficient information to confirm the role of dexmedetomidine in treating ICU delirium. In my opinion, these studies suggest a role for dexmedetomidine in the *prevention* of delirium, particularly as it offers an alternative to benzodiazepines, but it is not possible to state its role in the *treatment* of delirium at this time. Studies enrolling patients with confirmed delirium are required, and important factors such as sedation level must be well controlled to appropriately investigate this possibility.

Taken together, the current evidence fails to support the position that any single drug intervention favourably alters delirium outcomes in critically ill patients. Given the heterogeneity of the ICU population and the likely complex pathophysiology of the syndrome of delirium, it is unlikely we will find a magic bullet anytime soon. Until the pathophysiology of delirium is elucidated, prevention will remain our best approach.

References

1. Inouye SK, Westendorp RG, Saczynski JS. Delirium in elderly people. *Lancet*. 2014;383(9920):911-22.
2. Ely EW, Shintani A, Truman B, Speroff T, Gordon SM, Harrell FE Jr, et al. Delirium as a predictor of mortality in mechanically ventilated patients in the intensive care unit. *JAM*A. 2004;291(14):1753-62.
3. Girard TD, Jackson JC, 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(7):1513-20.
4. van den Boogaard M, Schoonhoven L, Evers AW, van der Hoeven JG, van Achterberg T, Pickkers P. Delirium in critically ill patients: impact on long-term health-related quality of life and cognitive functioning. *Crit Care Med.* 2012;40(1):112-8.
5. Gunther ML, Morandi A, Ely EW. Pathophysiology of delirium in the intensive care unit. *Crit Care Clin.* 2008;24(1):45-65, viii.
6. Barr J, Fraser GL, Puntillo K, Ely EW, Gélinas C, Dasta JF, 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;41(1):263-306.
7. van Eijk MM, Roes KC, Honing ML, Kuiper MA, Karakus A, van der Jagt M, et al. Effect of rivastigmine as an adjunct to usual care with haloperidol on duration of delirium and mortality in critically ill patients: a multicentre, double-blind, placebo-controlled randomised trial. *Lancet.* 2010;376(9755):1829-37.
8. Burry LD, Williamson DR, Perreault MM, Rose L, Cook DJ, Ferguson ND, et al. Analgesic, sedative, antipsychotic, and neuromuscular blocker use in Canadian intensive care units: a prospective, multicentre, observational study. *Can J Anaesth.* 2014;61(7):619-30.
9. Mac Sweeney R, Barber V, Page V, Ely EW, Perkins GD, Young JD, et al. A national survey of the management of delirium in UK intensive care units. *QJM*. 2010;103(4):243-51.
10. 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(7):515-23.
11. 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, multicenter, randomized, double-blind, placebo-controlled pilot study. *Crit Care Med*. 2010;38(2):419-27.
12. Girard TD, Pandharipande PP, Carson SS, Schmidt GA, Wright PE, Canonico 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(2):428-37.
13. The Modifying the Impact of ICU-Associated Neurological Dysfunction-USA (MIND-USA) study [trial registration]. Bethesda (MD): National Institutes of Health; 2010 Sep 28, updated 2014 Jun 19 [cited 2015 Sep 8]. Available from: https://clinicaltrials.gov/ct2/show/NCT01211522

14. Gill SS, Bronskill SE, Normand SL, Anderson GM, Sykora K, Lam K, et al. Antipsychotic drug use and mortality in older adults with dementia. *Ann Intern Med.* 2007;146(11):775-86.
15. Wang PS, Schneeweiss S, Avorn J, Fischer MA, Mogun H, Solomon DH, et al. Risk of death in elderly users of conventional vs. atypical antipsychotic medications. *N Engl J Med.* 2005;353(22):2335-41.
16. Pandharipande P, Cotton BA, Shintani A, Thompson J, Pun BT, Morris JA Jr, et al. Prevalence and risk factors for development of delirium in surgical and trauma intensive care unit patients. *J Trauma*. 2008;65(1):34-41.
17. Pandharipande P, Shintani A, Peterson J, Pun BT, Wilkinson GR, Dittus RS, et al. Lorazepam is an independent risk factor for transitioning to delirium in intensive care unit patients. *Anesthesiology*. 2006;104(1):21-6.
18. Pandharipande PP, Pun BT, Herr DL, Maze M, Girard TD, Miller RR, et al. Effect of sedation with dexmedetomidine vs lorazepam on acute brain dysfunction in mechanically ventilated patients: the MENDS randomized controlled trial. *JAMA.* 2007;298(22):2644-53.
19. Riker RR, Shehabi Y, Bokesch PM, Ceraso D, Wisemandle W, Koura F, et al. Dexmedetomidine vs midazolam for sedation of critically ill patients: a randomized trial. *JAMA.* 2009;301(5):489-99.
20. Reade MC, O'Sullivan K, Bates S, Goldsmith D, Ainslie WR, Bellomo R. Dexmedetomidine vs. haloperidol in delirious, agitated, intubated patients: a randomised open-label trial. *Crit Care*. 2009;13(3):R75.

Lisa D Burry, BScPharm, PharmD, FCCP, FDM
Pharmacy
Mount Sinai Hospital
Toronto, Ontario

Competing interests: None declared.