Clinical and Pathophysiologic Rationale for Pharmacological Delirium Treatments

Intervention	Rationale
Antipsychotics	The neurotransmitter imbalance theory, including a deficiency of acetylcholine and an excess of dopamine (1,2) is one of the more popular theories of the pathophysiology underlying delirium. This theory provides the pathophysiologic basis for antipsychotic treatment of delirious patients.
Cholinesterase Inhibitors	The cholinergic deficiency hypothesis of delirium has been bolstered by clinical investigations demonstrating that anticholinergic medication usage is associated with delirium (3) and observations that other agents associated with delirium, such as anesthetic drugs and opiates, are associated with acetylcholine receptor inhibition (1). This theory suggests that cholinesterase inhibitors may effectively prevent and/or treat the symptoms of delirium.
Anesthetic Technique	It has been suggested that anesthetic technique may be of importance in the development of post-operative delirium. A significantly higher incidence of non-cardiac post-operative cognitive dysfunction has been reported with use of general versus local anesthesia (4,5). Therefore, it is not unreasonable to extrapolate to a hypothesis that anesthetic technique may influence the risk of post-operative delirium.
Peri-operative Analgesia	Poorly controlled pain has been identified as a risk factor for delirium, particularly in the post-operative setting (6,7). However, opioids, so commonly used for pain control, are associated with increased rates of delirium (8,9). Given this, several trials have been conducted for the prevention of post-operative delirium by providing more aggressive prophylactic pain control, or by using alternatives to opioid based analgesic strategies.
Dexmedetomidine Sedation of Mechanically Ventilated Patients	Sedative drugs with GABA-A (gamma-aminobutyric acid) receptor agonist properties such as benzodiazepines and propofol are routinely given to mechanically ventilated ICU patients to reduce pain and anxiety (10,11), however these agents are associated with an increased risk of delirium. Dexmedetomidine is a promising alternative to GABAergic agonist sedatives in mechanically ventilated ICU patients because it is a highly selective alpha-2 adrenergic receptor agonist with actions at the locus ceruleus and spinal cord (12), and thus may have a lower liability for ICU delirium compared to other sedatives in mechanically ventilated patients.
Melatonin	The relationship between sleep deprivation and delirium has been studied for many years and has been viewed as reciprocal. A potential link between them may be an alteration of melatonin production (13). Interestingly, delirium can be associated with either an increased (hypoactive subtype) or decreased (hyperactive subtype) level of melatonin (14). This data has led researchers to hypothesize that melatonin supplementation may reduce delirium.
Bright Light Therapy	Several studies which have demonstrated a possible link between delirium and circadian rhythm irregularities have also specifically identified an irregular melatonin

Intervention	Rationale
	circadian rhythm in associated delirium symptoms in ICU patients (15). Consequently, bright light therapy has gained attention as a method of maintain or restore natural circadian rhythms by assisting daytime awakening.
Ketamine	Ketamine, an antagonist of the N-methyl-D-aspartate (NMDA) receptor, is believed to have neuroprotective effects on the brain by mediating glutamate neurotoxic actions including decreased influx of intracellular sodium and calcium, and reduction of enzymatic actions which lead to neuronal death (16). Data suggests brain neurotoxic effects of delirium as evidenced by permanent atrophic brain changes following the resolution of delirium (17,18), changes associated with long term cognitive impairment (17,18). Therefore, it has been speculated that the neuroprotection provided by ketamine may diminish delirium.
Depth of Intra-operative Propofol Sedation	Sedation level in the ICU setting is an important risk factor for delirium (19). Moreover, the inconsistent findings of regional anesthetic techniques to reduce the prevalence of post-operative delirium compared to general anesthesia has been explained by observations that sedation levels consistent with general anesthesia are frequently observed during regional anesthesia (20). Given that IV propofol is commonly used to provide intraoperative sedation during spinal anesthesia and other regional anesthetics it is hypothesized that minimizing sedation depth with propofol (deep vs. light) during spinal anesthesia could decrease the occurrence of post-operative delirium (20).

References

1. Hshieh TT, Fong TG, Marcantonio ER, Inouye SK: Cholinergic deficiency hypothesis in delirium: a synthesis of current evidence. J Gerontol A Biol Sci Med Sci 2008; 63:764–772.

2. Trzepacz PT. Is there a final common neural pathway in delirium? Focus on acetylcholine and dopamine. Semin Clin Neuropsychiatry 2000; 5:132–148.

3. Han L, McCusker J, Cole M, Abrahamowicz M, Primeau F, Elie M: Use of medications with anticholinergic effect predicts clinical severity of delirium symptoms in older medical inpatients. Arch Intern Med 2001; 161:1099-1105.

4. Hole A, Terjesen T, Breivik H: Epidural versus general anaesthesia for total hip arthroplasty in elderly patients. Acta Anaesthesiol Scand 1980; 24:279-87.

5. Rasmussen LS, Johnson T, Kuipers HM, Kristensen D, Siersma VD, Vila P, Jolles J, Papaioannou A, Abildstrom H, Silverstein JH, Bonal JA, Raeder J, Nielsen IK, Korttila K, Munoz L, Dodds C, Hanning CD, Moller JT; ISPOCD2(International Study of Postoperative Cognitive Dysfunction) Investigators: Does anaesthesia cause postoperative cognitive dysfunction? A randomised study of regional versus general anaesthesia in 438 elderly patients. Acta Anaesthesiol Scand 2003; 47(3):260-6.

6. Lynch EP, Lazor MA, Gellis JE, Orav J, Goldman L, Marcantonio ER. The impact of postoperative pain on the development of postoperative delirium. Anesth Analg 1998; 86:781-785.

7. Vaurio LE, Sands LP, Wang Y, Mullen EA, Leung JM: Postoperative delirium: the importance of pain and pain management. Anesth Analg 2006; 102:1267-1273.

8. Dubois MJ, Bergeron N, Dumont M, Dial S, Skrobik Y: Delirium in an intensive care unit: a study of risk factors. Intensive Care Med 2001; 27:1297-1304.

9. Ersek M, Cherrier MM, Overman SS, Irving GA: The cognitive effects of opioids. Pain Manag Nurs 2004; 5:75-93.

10. Pandharipande P, Shintani A, Peterson J, Pun BT, Wilkinson GR, Dittus RS, Bernard GR, Ely EW: Lorazepam is an independent risk factor for transitioning to delirium in intensive care unit patients. Anesthesiology 2006; 104:21-26.

11. Riker RR, Fraser GL: Adverse events associated with sedatives, analgesics, and other drugs that provide patient comfort in the intensive care unit. Pharmacotherapy 2005; 25:8S-18S.

12. Gerlach AT, Dasta JF: Dexmedetomidine: an updated review. Ann Pharmacother 2007; 41:245-252.

13. Figueroa-Ramos MI, Arroyo-Novoa CM, Lee KA, Padilla G, Puntillo KA: Sleep and delirium in ICU patients: a review of mechanisms and manifestations. Intensive Care Med 2009; 35:781-795.

14. Balan S, Leibovitz A, Zila SO, Ruth M, Chana W, Yassica B, Rahel B, Richard G, Neumann E, Blagman B, Habot B: The relation between the clinical subtypes of delirium and the urinary level of 6-SMT. J Neuropsychiatry Clin Neurosci 2003; 15:363-366.

15. Weinhouse GL, Schwab RJ, Watson PL, Patil N, Vaccaro B, Pandharipande P, Ely EW: Bench-to-bedside review: delirium in ICU patients - importance of sleep deprivation. Crit Care 2009; 13:234.

16. Proescholdt M, Heimann A, Kempski O: Neuroprotection of S(+) ketamine isomer in global forebrain ischemia. Brain Res 2001; 904:245-251.

17. Morandi A, Rogers BP, Gunther ML, Merkle K, Pandharipande P, Girard TD, Jackson JC, Thompson J, Shintani AK, Geevarghese S, Miller RR 3rd, Canonico A, Cannistraci CJ, Gore JC, Ely EW, Hopkins RO; VISIONS Investigation, VISualizing Icu SurvivOrs Neuroradiological Sequelae: The relationship between delirium duration, white matter integrity, and cognitive impairment in intensive care unit survivors as determined by diffusion tensor imaging: the VISIONS prospective cohort magnetic resonance imaging study*. Crit Care Med 2012; 40:2182-2189.

18. Gunther ML, Morandi A, Krauskopf E, Pandharipande P, Girard TD, Jackson JC, Thompson J, Shintani AK, Geevarghese S, Miller RR 3rd, Canonico A, Merkle K, Cannistraci CJ, Rogers BP, Gatenby JC, Heckers S, Gore JC, Hopkins RO, Ely EW; VISIONS Investigation, VISualizing Icu SurvivOrs Neuroradiological Sequelae: The association between brain volumes, delirium duration, and cognitive outcomes in intensive care unit survivors: the VISIONS cohort magnetic resonance imaging study*. Crit Care Med 2012; 40:2022-2032.

19. Pandharipande P, Shintani A, Peterson J, Pun BT, Wilkinson GR, Dittus RS, Bernard GR, Ely EW: Lorazepam is an independent risk factor for transitioning to delirium in intensive care unit patients. Anesthesiology 2006; 104:21-26.

20. Sieber FE, Zakriya KJ, Gottschalk A, Blute MR, Lee HB, Rosenberg PB, Mears SC: Sedation depth during spinal anesthesia and the development of postoperative delirium in elderly patients undergoing hip fracture repair. Mayo Clin Proc 2010; 85:18-26.