ICU PAIN, ANXIETY, AGITATION, DELIRIUM: IN SEARCH OF THE HOLY GRAIL

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INTRODUCTION

Pain, anxiety, agitation, and delirium occur in 15-60% of elderly hospitalized patients. The prevalence of anxiety and delirium in the mechanically ventilated ICU patients ranges from 7-80%, with the highest rates seen in those aged 65 years or older.1-4 Despite the availability of a few quickly administered bedside tests, the multifactorial causes of anxiety and delirium, many of which are preventable, are underrecognized by many caregivers (Table 1). Anxiety and delirium are associated with significant hospital morbidity and post-discharge morbidity and mortality (Figure 1). Definitions of key terms for the purposes of this article include the following:

- **Agitation - an excessive motor activity associated with internal tension. This motor activity is usually nonpurposeful but may be irrationally purposeful and counterproductive.**
- **Anxiety - a sustained state of apprehension with accompanying autonomic arousal in response to a real or perceived threat.**
- **Delirium - an acute, potentially reversible impairment of consciousness and cognitive function that fluctuates in severity. Manifestations include apprehension, agitation, cognitive distortion, abnormal thought processes, hallucinations, and impairment of short-term memory, arousal and attention.**
- **Psychosis - active hallucination; however, in the literature, there are misnomers such as ICU psychosis, toxic confusional state, critical illness encephalopathy, and septic encephalopathy.**
- **Subsyndromal delirium - the presence of some, but not all, of the criteria for delirium.**
- **Stupor - a sustained state of spontaneous unarousability interruptible only by vigorous, direct external stimulation.**
- **Coma - a state of unarousability and unresponsiveness to all stimuli.**

Given the range of manifestations, the continuum/spectrum of acute brain dysfunction is shown in Figure 2.

To assess the presence of delirium, one may use various bedside tools, such as the Confusion Assessment Method (CAM-ICU), which Ely et al.7 modified from the Diagnostic and Statistical Manual of Mental Disorders (DSM-IIIR).8 This is shown in Figure 3.

ICU STUDIES AND ASSESSMENT TOOLS

A recent study by Peterson et al. of 614 consecucive medical ICU patients, who were monitored for delirium over one year, reported that hypoactive delirium occurred in 44% and mixed delirium in 55% of the patients while hyperacdve delirium was found in about 2%.[9] A majority of the patients with hypoactive delirium were 65 years of age and older.

The Richmond Agitation-Sedacion Scale (RASS) can be used to assess and monitor sedation (Table 2).

Several studies have shown that ICU agitation may cause an inability to exrubace in a timely manner and increases the incidence of premature exrubation and central line removal. Self-inflicted

Causes are multiple and with complex interaction.
Pain: acute surgical, endotracheal tube, chronic, neuropathic
Anxiety: despondency (feeling of helplessness and lack of control)
Discomfort: position, patient-mechanical ventilation dyssynchrony
Drug withdrawal: alcohol, recreational drugs
Physiology: shock and hypoperiusion, sepsis, fever, cytokines
Encephalopathy: uremia, hepatic failure, hypoglycemia, hypoxia, hypercarbia
Drug induced delirium: lidocaine, steroids, meperidine, PCN, atropine
Excess use of: benzodiazepines, morphine
Sleep deprivation: reduced total sleep,_ stage 3/4, _ REM
ICU environment: noise, alarms, conversation
Age and pre-existing neuro: cognitive impairment

Table 1. Multifactorial causes of pain, anxiety and delirium.

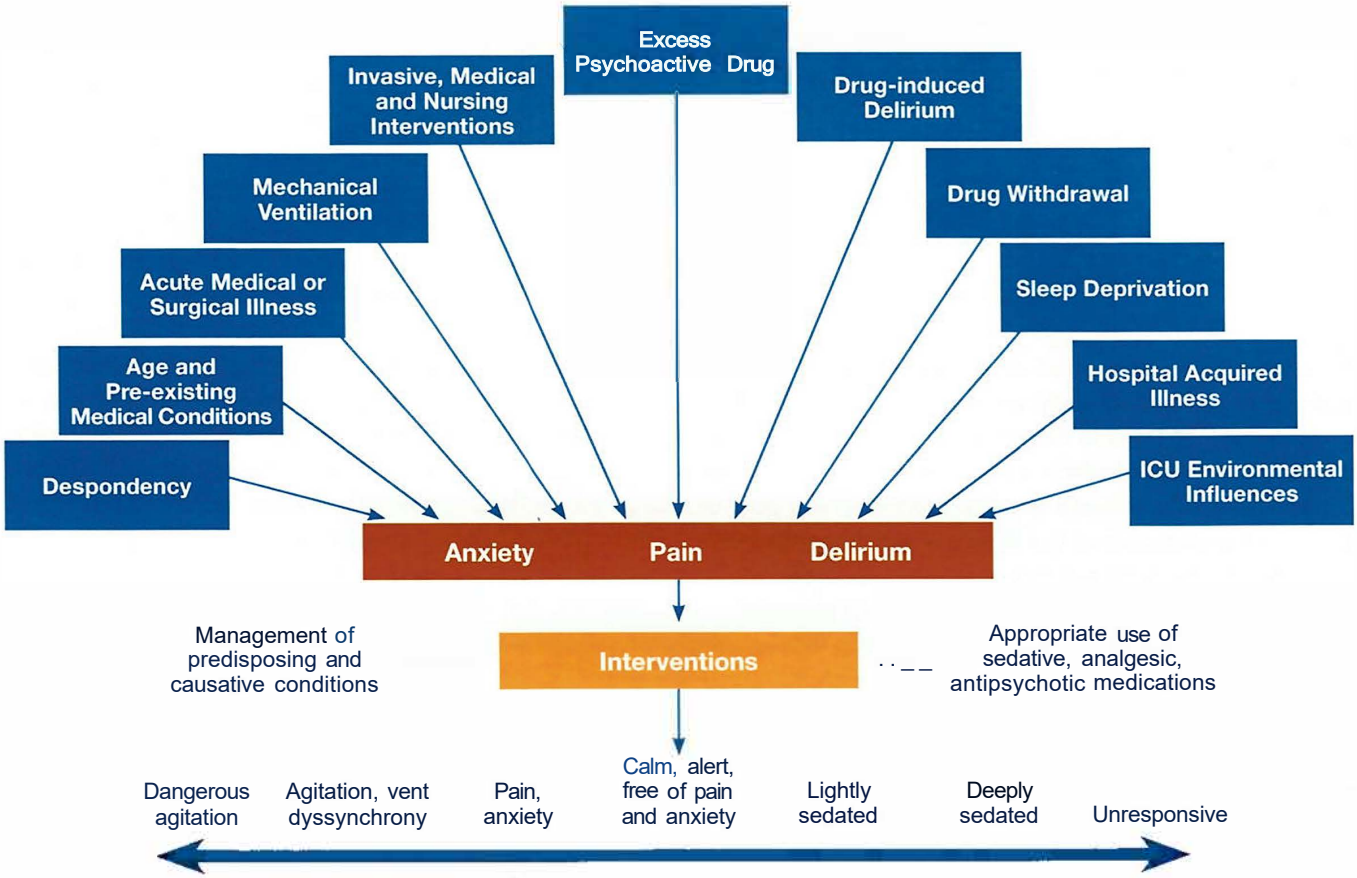

Figure 1. Overview of the factors related to development and management of anxiety, pain and delirium, resulting in a spectrum of comfort/discomfort sensations ranging from dangerous agitation to unresponsiveness. Adapted from Sessler et al.5

Figure 2. Proposed continuum of acute brain dysfunction in the ICU. Adapted from Miller and Ely.6

injury and harm to caregivers are also significant issues. All of these events increase the potential for nosocomial pneumonia and extended ICU and/or in-hospital stays, resulting in less than satisfactory pacient recovery and an overall increase in coses.

Ely et al. followed 275 mechanically ventilated, medical ICU patients prospectively for six months from the cime of hospital discharge. They noted a threefold increase in rhe risk of death by six months, even after adjustment for age, severity of illness, comorbid conditions, coma, and the use of sedatives and analgesics (Figure 4).10

Jackson et al. found chat in-hospital delirium increased the likelihood of dementia as much as threefold up to three years from the time of hospital discharge.11 Additionally, the duration of mechanical ventilation and nosocomial pneumonia increased. A significant increase in long-term cognitive impairment was reported in some of the delirious ICU patients months after hospical discharge.

APPROACHES TO MANAGEMENT

Management of pain, anxiety, and delirium requires multimodal approaches. Based on the Sedation Guidelines published by the Society of Critical Care Medicine in 2002,[12] the Methodist DeBakey Heare Center's Cardiovascular ICU developed a sedation protocol. It is monitored by using RASS to titrate drug dosing. (Several large institutions are using a combination of RASS and CAM-ICU evaluations in their protocols.)

The pharmacological approach includes four major classes of drugs: narcotics, benzodiazepines, antipsychotics, and miscellaneous. The principle of drug therapy is the appropriate use of medication from each class while avoiding overmedicacion. Because the etiology is multifactorial, it is important to appreciate chat there is no perfect drug for this situation. A summary of the various pharmacological options is listed in Table 3.

Narcotics are frequently prescribed co paciencs for pain control in the ICU setcing. Intravenous (IV) fencanyl

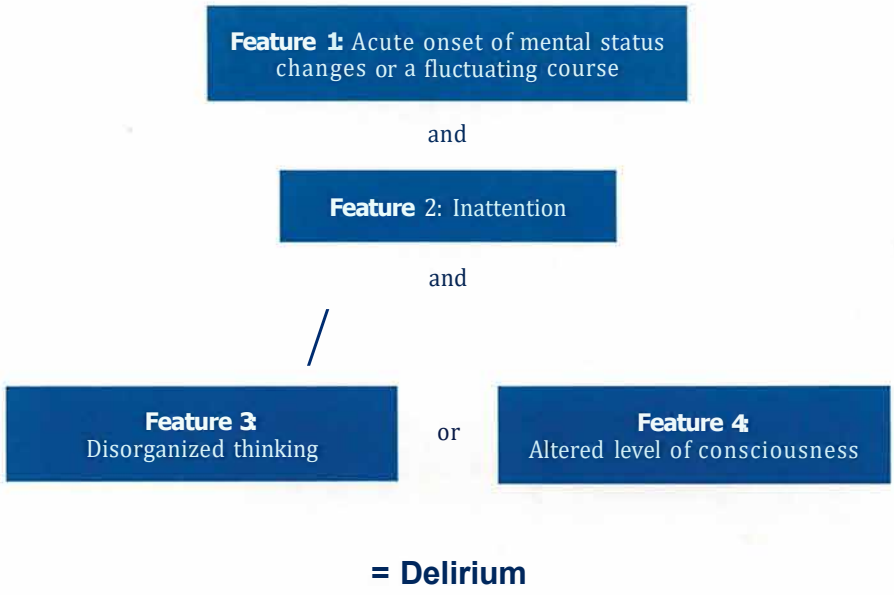

Figure 3. Diagnosis of delirium with the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU). Adapted from Miller and Ely.6

Richmond Agitation-Sedation Scale (RASS)		
Score	**Term**	**Description**
+4	Combative	Overtly combative or violent; immediate danger to staff
+3	Very agitated	Pulls on or removes tube(s} or catheter(s) or has aggressive behavior toward staff
+2	Agitated	Frequent nonpurposeful movement or patient-ventilator dyssynchrony
+1	Restless	Anxious or apprehensive but movements are not aggressive or vigorous
0	Alert and calm	
-1	Drowsy	Not fully alert, but has sustained (>10s) awakening, with eye contact, to voice
-2	Light Sedation	Briefly {<10s} awakens with eye contact to voice
-3	Moderate Sedation	Any movement (but no eye contact) to voice
-4	Deep Sedation	No response to voice, but any movement to physical stimulation
-5	Unarousable	**No** response to voice or physical stimulation

Table 2. Richmond Agitation-Sedation Scale (RASS).

controlled with a patienc-concrolled analgesia administration may be implemented for spontaneously breathing patients. A continuous infusion of IV fentanyl is preferred in hemodynamically unstable patients, provided the patients are intubated and ventilated. Meperidine (Demerol) is usually avoided due co its adverse side effects such as seizure, dysphoria, etc. Hydromorphone is preferred for chronic pain patients because of its long half-life. It is important co appreciate that excess morphine can suppress REM cycles and reduce stage 3 and 4 non-REM sleep. Prolonged use or excess dosage of morphine may lead co ICU delirium and psychosis.

The benzodiazepine class drugs, namely midazolam and lorazepam, are good anxiolytics and are especially useful for alcohol withdrawal. However, Pandharipande et al. showed chat even after excluding observations for coma, lorazepam was an independent risk factor for daily transition to delirium. This incremental risk was high at low doses and reached a plateau at approximately 20 mg per day.13 When administered intravenously, an antipsychotic drug such as haloperidol has unique pharmokinecic properties that counteract this effect. Even at a high dose, IV haloperidol (as opposed to the oral or intramuscular route) may maintain hemodynamic scabilicy and does nor suppress respirations. Atypical antipsychocics such as olanzapine, ziprasidone, risperidone and quetiapine have antidelirium effects wich fewer side effects than haloperidol but do not have IV formulation.

Two miscellaneous drugs include propofol and dexmedecomidine (Precedex®). Propofol, an anesthetic agent, has the advantage of quick onset and rapid offset but can cause myocardial depression and hypotension. Precedex produces mild to moderate analgesia, sedation and hypnosis without respiratory suppression. It offers the unique property of promoting che sleep-wake cycle and increased REM sleep, an effect not observed with any of the other drugs. The side effect of drug-withdrawal does not occur with Precedex, and it is more specific for delirium secondary to substance abuse. The FDA has not approved any drug to prevent delirium at rhis rime.

The nonpharmacological approach is preventive in nature, the goal being co make rhe ICU environment more pleasant. This includes reducing noise, minimizing undue stimuli, promoting the sleep/wake cycle, and providing appropriate audio-visual aids, physical therapy and regular reorientation

	Sedation		Analgesia			Miscellaneous		Antipsychotics
	Lorazepam (Ativan®)	Midazolam (Versed®)	Morphine	Fentanyl	Hydromorphone (Dilaudid®)	Propofol	Dexmedetomidine (Precedex®)	Haloperidol (Haldol®)
Indication	DOC: Long- term sedation Anti-anxiety Antiemetic ETOH withdrawal	Sedative/Hypnotic Short-term sedation or intermittent doses	Preferred agent in ICU	Preferred in: -Hemodynamic instability (↓BP) -Rapid onset in acute critically ill -Histamine release w/ MSO4-MSO4 - allergy	Semisynthetic opioid use in severe long-term pain	-Sedative/Hypnotic –short-term use ≤72 hrs -Frequent neuro assessments-Anticipate quick extubation -↑ Intracranial pressure (ICP) *NO Analgesia*	Sedative Analgesic Amnestic * Approved by FDA for 24 hr use only*	DOC for ICU delirium no sedative effects Antiemetic
Dose Intermittent	0.02 – 0.06 mg/kg IV q 2-6 hr (1-4 mg)	0.02 – 0.08 mg/kg IV q 0.5-2 hr (1-6 mg)	0.01 – 0.15 mg/kg IV q 1-2 hr (1-10 mg)	0.35 – 1.5 mcg/kg IV q 0.5-1 hr(25-100 mcg)	10 – 30 mcg/kg IV q 1-2 hr (1-2 mg)	5-50 mcg/kg/min (titrate by 5-10 mcg q10min) Max dose: 75 mcg/kg/min	LD: 1 mcg/kg IV over 20 minutes MD: 0.2-0.7 mcg/ kg/hr IV	2-5 mg IV q 4-6 hrs
Infusion	0.01 – 0.1 mg/kg hr (1 – 7 mg/hr)	0.04 – 0.2 mg/kg/hr (3 – 14 mg/hr)	0.07 – 0.5 mg/kg/hr (5 – 35 mg/hr)	0.7 – 10 mcg/kg/hr (50 – 700 mcg/hr)	7 – 15 mcg/kg /hr (0.5 – 1 mg/hr)			
Dose adjustment	Use caution with multiple dosing in patients with renal impairment	Use caution with multiple dosing in patients with renal impairment	CrCl 10-50 ml/min: 75% normal dose CrCl <10: 50% normal dose	CrCl 10-50 ml/min: 75% normal dose CrCl <10: 50% normal dose	Consider adjustments in hepatic insufficiency		Consider adjustments in renal/ hepatic insufficiency	
Onset	2-5 min	2-5 min	5-10 min	1-2 min	15-30 min	1-2 min	Up to 30 minutes	3-20 min
$T_{1/2}$	8-15 hrs	3-11 hrs	2-4 hrs	2-4 hrs Prolonged infusion:↑ t1/2 9-16 hrs	1-3 hrs	1.5-12.4 hrs	2-5 min	18-54 hrs
PK	Metabolized by glucuronidation	Metabolized by oxidation	-Longest duration of action -Metabolized by glucuronidation -Caution in renal/ hepatic dysfunction	-Rapid onset -Shorter duration of action -Metabolized by oxidation	-Metabolized by glucuronidation -May accumulate in hepatic failure	Metabolized by oxidation	Metabolized by glucuronidation and CYP450 enzymes	Metabolized by oxidation
Metabolites	None	Active	Active	None Parent drug accumulated w/ prolonged use	None	None	None	Active
AE	-Solvent-related acidosis/death (propylene glycol >10mg/hr) -Renal failure w/ high prolonged dose -Respiratory depression	-Renal insufficiency/ failure -Apnea -↓ Respiratory rate Hiccups	-Histamine release (pruritis) -Hypotension - Urinary retention -Respiratory depression	-Rigidity w/ high dose -Respiratory depression -hypotension	-Potent respiratory depression -Hypotension	-Cardiac depression (doses > 80 mcg) -Lactic acidosis (doses >66 mcg) -↑ TG (get baseline & periodic TG) -Pancreatitis (moderate doses for long time) -Hypotension (26%) -↓ Heart rate (1-3%) -Pain @ injection site -Respiratory acidosis (High doses) -Green urine	-Hypotension (30%), avoid loading dose -↓ HR (~ 10bpm), caution in bradycardia	-QTc prolongation -Torsades de pointes -Neuroleptic malignant syndrome -↓ Sz threshold -Extra-pyramidal syndrome -Leukopenia -many drug interactions
Respiratory Suppression	Y	Y	Y	Y	Y	Y	N	N
Promotes sleep wake cycle	N	N	N	N	N	N	Y	N
Assessment scale	RASS, BIS if on paralytics	RASS, BIS if on paralytics	Visual Analog Numeric Scale	Visual Analog Numeric Scale	Visual Analog Numeric Scale	RASS	RASS	CAM-ICU

Table 3. A summary of various pharmacological options. Source: Dipiro J, Talbert RL, et al. Pharmacotherapy: A Pathophysiologic Approach. Stamford (CT): Appleton & Lange; 1999:1014-26. Sources: Jacobi et al. Critical Care Medicine 2002;30:119-141 MICROMEDEX® Healthcare Series, Thomson MICROMEDEX, Greenwood Village, Colorado (Edition expires 9/2004). Created by Elisa M. Chi, Pharm.D., 2006.

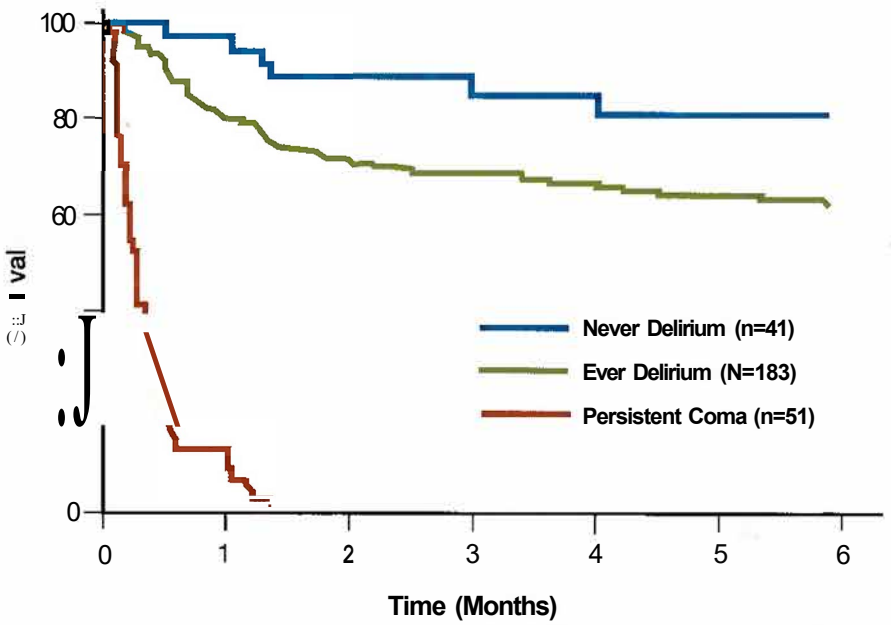

Figure 4 Kaplan-Meier analysis of delirium in the intensive care unit and six-month survival.

of time/place/date/person. Some use of audio-visual entertainment has also been successful.

CONCLUSION

Pain, anxiety, agitation, and delirium are frequently seen in patients in the intensive care setting and can lead to severe and long-lasting consequences. The etiology is mulri-factorial, with no single drug as a panacea. Hence, the search for che Holy Grail continues. There are several preventive measures to adopt, and early recognition with mulri-modaliry management is necessary.

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RECOMMENDED READING

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