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Pharmacy & Therapeutics Update: Drug Information for Health Care Professionals

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In This Issue

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Sedation in Critically Ill Patients

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Many critically ill patients experience agitation and anxiety in the intensive care unit (ICU) setting. It has been reported that up to 70% of patients in an ICU experience at least 1 episode of agitation.[1] Patient distress is inherently multifactorial and can ultimately lead to increased complications and a longer ICU length of stay.[1-3] The goals of providing patient-directed ICU care include adequate sedation to enhance comfort and provide relief from anxiety and agitation.[2]

Prior to initiating sedation, it is important to conduct a thorough patient assessment. Potential factors for causing anxiety should be considered (Table 1) and any reversible sources of patient distress should be removed or treated.[1-3] Healthcare providers should assess for these confounding factors upon patient admission and continue to evaluate for withdrawal symptoms.[1,2]

Medication reconciliation and a thorough patient history are fundamental components of the initial evaluation of the patient.[1,2] A patient's home medications, or the lack thereof, may lead to significant adverse effects and/or drug interactions.[1,3] Anxiolytics, analgesics, antidepressants, antipsychotics, and other medications, including herbal products, can cause significant withdrawal or rebound of chronic disease symptoms if withheld for even short periods of time.[1,2] Furthermore, alcohol and elicit drugs may cause similar symptoms of agitation during the acute detoxification and withdrawal phases.[1,2] However, if it is not possible to attain a patient history on admission, it should be completed as soon as possible through patient or family interview.

Sedation treatment goals should be established by the healthcare team to guide drug dosing and to help avoid excessive sedation.[2]

Table 1. Factors Causing ICU Agitation and Anxiety[1-3]

Pain	Hypoxemia	Suctioning
Medications	Hypoglycemia	Room temperature
Mechanical ventilation	Hypotension	Delirium
Oral and nasal tubes	Underlying medical conditions	Sleep deprivation
Invasive interventions	Immobility	− Ambient light
Substance withdrawal	Turning/rolling	− Noise

Table 2. Riker Sedation-Agitation Scale (SAS)[1]

Score	Description	Definition
7	Dangerous agitation	Pulling endotracheal tube (ETT), trying to remove catheters, climbing over bedrail, striking at staff, thrashing from side-to-side
6	Very agitated	Does not calm despite frequent verbal reminding of limits, requires physical restraints, biting ETT
5	Agitated	Anxious or mildly agitated, attempting to sit up, calms to verbal instructions
4	Calm and cooperative	Calm, awakens easily, follows commands
3	Sedated	Difficult to arouse, awakens to verbal stimuli or gentle shaking but drifts off again, follows simple commands
2	Very sedated	Arouses to physical stimuli but does not communicate or follow commands, may move spontaneously
1	Unarousable	Minimal or no response to noxious stimuli, does not communicate or follow commands

The need for sedation varies between patients and fluctuates over time; thus, the level of sedation requires frequent reassessment.[1,2] For example, an individual sedation requirement may increase dramatically once the patient is switched to a more stressful form of mechanical ventilation. Higher levels of sedation and possibly neuromuscular blockade may then be needed to achieve adequate sedation for ventilator synchrony.[2] As the patient clinically improves, sedation requirements should be reassessed and decreased accordingly. A common sedation target is a calm patient who is easily aroused with maintenance of the normal sleep-wake cycle, except when deeper sedation is required as previously mentioned.[1]

Once treatment goals are established, patients should be evaluated using a clinically validated scale. A variety of scales have been developed, validated, and tested for inter-rater variability.[1-4] A gold standard ICU sedation scale has not been established, but the Riker Sedation-Agitation Scale (SAS) was the first sedation scale proven to be reliable and valid in critically ill patients (Table 2).[1,3] At MUSC, the SAS is most commonly used with a target score of 4. The Ramsay Sedation Scale, Motor Activity Assessment Scale (MAAS), and Richmond Agitation-Sedation Scale (RASS) are examples of other validated scales that may be used.[1-4]

Sedation evaluation using a validated scale is essential to patient treatment. Patient distress causes metabolic changes that result in tissue ischemia, fluid and electrolyte disturbances, and decreased wound healing.[3] Failure to achieve adequate sedation allows many patients to recall frightening or unpleasant ICU memories that contribute to symptoms of post-traumatic stress disorder (PTSD).[1,3] In contrast, unnecessarily prolonged and excessive sedation has been shown to increase ICU length of stay and a number of complications.[1,2] Patient evaluation should include an assessment of the following: level of consciousness, ability to arouse, cognition, pain, and agitation.[2]

It is important to combine the sedation scale assessment with clinical judgment and experience. Not all anxious patients will exhibit normal signs of anxiety and agitation; instead, some patients may be fearful and withdrawn.[1] Objective sedation assessment is recommended for deeply sedated patients, such as those treated with therapeutic neuromuscular blockade or a pentobarbital-induced coma.[1,2]

Heart rate variability, lower-esophageal contractility, and electroencephalogram signals processed by algorithms such as the bispectral index (BIS) are commonly used to evaluate sedation in critically ill patients due to the lack of specificity and sensitivity of vital sign assessment.[1,2] Subjective and objective assessment allow the titration of sedatives to goal while avoiding inadequate and excessive sedation.

The keys to managing anxiety are listed in Table 3.[1] Sedation should be started only after providing sufficient analgesia to control pain.[1,2] Patients that require frequent reloading and/or particularly high infusion rates should be reassessed for pain control and delirium.[1,2,5] Opioid analgesics provide some sedation, but they do not reduce awareness or have an amnestic effect.[1] Therefore,

the majority of patients will require sedative therapy to control anxiety and limit the amount of unpleasant memories.

Sedation should be provided intermittently or on an as needed basis.[1,2] Continuous sedation has been associated with longer periods of sedation and ICU length of stay.[1] However, a scheduled daily interruption of sedation (DIS), or "sedation vacation," should be provided in situations requiring continuous sedation for optimal patient treatment in order to avoid excessive and prolonged effects.[2] Sedatives should also be used judiciously and only to the extent required to achieve the established sedation goal.[1] Federal regulations have established that sedation is neither intended to be a method of restraint nor to be "used as a means of coercion, discipline, convenience, or retaliation by staff."[6] Furthermore, excessive sedation has been shown to be an independent risk factor for delirium, which increases the incidence of PTSD and long-term mortality.[2] Fortu-

Table 3. ICU Anxiety Management[1,2]

Patient assessment
- Identify potential causes of anxiety
- Remove or treat reversible sources
- Complete patient history/medication reconciliation

Monitoring
- Define treatment goals
- Assess pain and sedation
- Identify delirium

Management
- Frequently reorient the patient
- Maintain patient comfort and optimize the environment
- Select medications based on patient characteristics, need for rapid onset/offset of action, duration of therapy, and prior response
- Provide analgesia, then sedation
- Titrate medications to goal with the lowest effective dose
- Provide daily "sedation vacations" (if possible)
- Treat delirium and remove precipitating factors

De-escalation of therapy

Table 4. Pharmacology of Sedative-hypnotics[1,2,5,7]

Drug	Onset/ Duration	Unique Adverse Effects	Dosing		Comments	Daily Cost
			Intermittent	Continuous		
Lorazepam	5-20 min/ 6-8 hr	Acidosis and renal failure at high doses due to the solvents	0.02-0.06 mg/kg every 2-6 hr (start at 50% if patient > 65 years)	0.01-0.1 mg/kg/hr	Longer half-life,	$$
Midazolam	2-5 min/ 1-4 hr	N/A	0.02-0.08 mg/kg every 0.5-2 hr	0.04-0.2 mg/kg/hr	Active metabolite (renal elimination)	$$$
Diazepam	2-5 min/ >12 hr	Phlebitis	0.03-0.1 mg/kg every 0.5-6 hr	N/A	Active metabolite	$
Propofol	30-50 sec/ 3-10 min	Elevated triglycerides, pancreatitis, propofol infusion syndrome, zinc depletion	N/A	5-150 mcg/kg/min (>40 mcg/kg/min requires MD approval)	Contains egg & soy products	$$$$
Dexmedetomidine	2-15 min/ 6 min	Dystonia	N/A	0.5-1 mcg/kg over 10 min, then 0.2-0.7 mcg/kg/hr up to 24 hr	Not FDA-approved for use >24 hr, some analgesic properties	$$$$$
Haloperidol	3-20 min/ 6-24 hr	QT interval prolongation, extrapyramidal symptoms	0.03-0.15 mg/kg every 0.5-6 hr	0.04-0.15 mg/kg/hr	Active metabolite	$$

nately, analgesia and sedation act synergistically and allow for reduced dosing of both medications.[1,2]

Sedative-hypnotic agents should be selected based on patient and medication characteristics (ie, drug allergies, organ dysfunction, active metabolites), the need for rapid onset/offset of action, expected duration of therapy, and prior response.[1,2] A variety of these agents exist, such as benzodiazepines, propofol, and α_2-agonists.[1-3] The commonly used sedative-hypnotic agents at MUSC are listed in Table 4 along with some of their key characteristics.[1,2,7]

Benzodiazepines

Benzodiazepines have both sedative and hypnotic effects that beneficially produce anterograde, but not retrograde, amnesia.[1] Additionally, benzodiazepines can suppress the patient's anticipatory pain response; thus, providing a synergistic opioid-sparing effect.[1]

Diazepam may be used for acute agitation and in rare instances for long-term sedation, but it is generally avoided due to the long half-life of its active metabolite.[1,7] Lorazepam and midazolam are the most commonly used benzodiazepines for ICU sedation.[1,2]

Midazolam has a rapid onset and short duration of action, which makes it preferable for treating acutely agitated patients.[1,2] However, midazolam accumulates and causes prolonged sedation in obese patients, as well as patients with hypoalbuminemia, renal failure, or liver failure.[1,2] Additionally, midazolam has significant drug interactions due to its metabolism via cytochrome P450 isoenzyme 3A4 and has unpredictable effects reported with infusions longer than 48-72 hours.[1,2] Because of these reasons, midazolam is only recommended for short-term (less than 48 hours) sedation.[1,2]

Lorazepam is metabolized via glucuronidation; therefore, has fewer potential drug interactions than midazolam.[1] In patients with renal or hepatic insufficiency, lorazepam is preferred over midazolam.[1,8] Lorazepam is also recommended for patients requiring prolonged sedation; however, it is not ideal for the treatment of acute agitation due to a slower onset of action.[1,2] Lorazepam is particularly difficult to titrate due to its elimination half-life (12-15 hours).[1] Loading doses should be given by intravenous push to supplement a scheduled dosing regimen.[1,5] A continuous infusion should be started only after the patient fails at least 3 scheduled doses of lorazepam.[5] Caution is warranted since prolonged high-rate infusions have resulted in serious complications.[1,2,8] Propylene glycol (PG) is used as a solvent in various lorazepam formulations due to its poor solubility.[1,2,8] PG has been associated with causing reversible acute tubular necrosis, osmol gap lactic acidosis, and hyperosmolarity in patients receiving lorazepam at doses exceeding 18 mg/hr for greater than four weeks or 25 mg/hr for hours to days.[1,2,8] Therefore, intermittent or continuous infusions up to 10 mg/hr are recommended.

Propofol (Diprivan®)

Propofol is a general anesthetic agent with favorable sedative, hypnotic, anticonvulsant, antiemetic, and intracranial pressure (ICP)-lowering properties.[1,7] However, like the benzodiazepines, propofol lacks any analgesic properties.[1,7] Propofol has a rapid onset of action due to its ability to cross the blood brain barrier within minutes and short duration of activity.[1,2,7] Consequently, propofol is preferred in patients that require rapid awakening for neurological assessments.[1]

Although propofol appears to be an ideal sedative, it is more costly than benzodiazepines and has many potential complications. Propofol is manufactured as a phospholipid emulsion, which provides 1.1 kcal/mL of fat. This must be considered in the patient's nutritional assessment.[1,7] Due to the phospholipid vehicle, long-term or high-dose propofol infusions may cause hypertriglyceridemia and/or pancreatitis.[1,7] Additionally, the phospholipid emulsion requires a dedicated intravenous line due to drug compatibility issues.[1,7] Propofol is contraindicated in patients with egg or soy allergies.[1,7] Dose-dependent hypotension, bradycardia and lactic acidosis may occur, as well as propofol infusion syndrome.[1,2,7] Propofol infusion syndrome is associated with rhabdomyolysis, metabolic acidosis, hepatomegaly, renal failure, and car-

diac failure with high-dose infusions (>5 mg/kg/hr).[2,5,9] Due to the various potential complications with long-term therapy, the Society of Critical Care Medicine recommends limiting propofol infusions to less than 48 hours.[1,2]

Dexmedetomidine (Precedex®)

Dexmedetomidine is a selective α_2-adrenergic receptor agonist with sedative, analgesic, anxiolytic, and sympatholytic properties.[2,7] Dexmedetomidine is a relatively new option for ICU sedation but remains restricted to specific indications due to its limited data, potential safety concerns, and significantly higher acquisition cost.[2,5,9] The MUSC Critical Care Committee recently updated the guidelines for dexmedetomidine use and has finalized a pre-printed order form.[5] Currently, it is only FDA-indicated for the sedation of initially intubated and mechanically ventilated patients for up to 24 hours.[2,10] Dexmedetomidine has a short half-life and almost immediate onset, making it a second-line agent to propofol in patients requiring frequent neurological assessments.[2,9,10] Dexmedetomidine would be beneficial to allow for cooperative sedation in patients who cannot tolerate propofol (eg, propofol infusion syndrome, hypertriglyceridemia) or are obese with a redistribution phenomenon of propofol.[2]

Dexmedetomidine lacks the respiratory depressant effects seen with other sedative-hypnotic agents; therefore, may decrease mechanical ventilation time.[2,9,10] However, there are also disadvantages of its use. Dexmedetomidine may cause bradycardia and hypertension after initial bolus injections due to vasoconstrictive effects.[2,10] Hypotension potentially occurs with continuous infusions as vasoconstriction shifts to vasodilation as a result of central sympatholysis.[2,10] Dexmedetomidine should be used cautiously in patients with low ventricular ejection fraction (≤ 30 %) or heart block due to the potential for severe bradycardia and cardiac arrhythmias.[2,10] Of note, dystonic reactions have also been reported with dexmedetomidine use.[2]

Multiple patient factors can cause anxiety, as well as influence the duration and intensity of effects of sedative-hypnotics (Table 1).[1,2] Parent drug and active metabolites can lead to adverse or prolonged sedation effects in patients with at least one of these confounding factors. Elderly patients and those with renal or hepatic dysfunction may require an initial dosage reduction depending on the choice of sedative-hypnotic agent.[1,2] Consequently, sedatives must be individually dosed and titrated from recommended starting doses to optimize patient sedation.[1,2] Managing patient sedation by following a structured approach with sedation protocols facilitates sedative dosing.

Sedation protocols that incorporate a validated scale are the key to sedation management as they have been shown to decrease the amount of adverse effects, time of mechanical ventilation, duration of ICU and hospital length of stay, incidence of ICU-related medical complications, and hospitalization costs.[2] An effective sedation protocol provides titration strategies for specific sedation targets, offers guidance for daily interruption of sedation, outlines a step-wise approach to transitioning from intermittent to continuous therapy, and ensures that reversible causes of agitation and anxiety are identified and treated.[1,2] The MUSC sedation protocol is adapted from the Society of Critical Care Medicine guidelines, and is available on the Clinicians Orders Forms page under Critical Care or at: http://www.musc.edu/cce/ORDFRMS/CriticalCare/indexcriticalcare.htm.[1,5]

Patients treated with sedative-hypnotics for longer than 1 week may develop physiological dependence, which can cause withdrawal symptoms if these agents are rapidly discontinued (Table 5).[1,2,9] Withdrawal has been shown to lead to further complications and increased sedation requirements.[1,2] Therefore, detailed

Table 5. Signs and Symptoms of Sedative Withdrawal[2]

Dysphoria	Increased sensitivity to light and sound
Tremor	Paresthesias
Headache	Muscle cramps
Nausea	Myoclonus
Diaphoresis	Sleep disturbances
Fatigue	Delirium
Anxiety	Seizures
Agitation	

plans should be made to gradually taper these medications and possibly transition to oral therapy, especially in high-risk patients with a history of alcohol or substance dependence.[1,2]

The majority of critically ill patients receive sedation during their ICU stay. With proper patient assessment, therapeutic monitoring, medication selection and titration, and de-escalation of drug therapy, clinicians can adequately treat patient anxiety and agitation in the critical care environment while avoiding excessive or prolonged sedation that leads to deleterious outcomes. (*References available upon request.)*

Did You Know…

Revisions to the South Carolina Medicaid Preferred Drug List

In 2004, the South Carolina Department of Health and Human Services established a Preferred Drug List (PDL), which serves as a component of the prior authorization (PA) program for Medicaid. Products listed on the PDL do not require PA; however, any drug product not listed does require PA. The South Carolina Medicaid P&T Committee meets quarterly to determine any additions or deletions to the PDL. Notification of changes are sent to providers as a Medicaid Bulletin the month following the meetings. The PDL was amended in September to include platelet inhibitors as a therapeutic class. Other revisions have also been made to existing therapeutic drug classes (Tables 6 and 7). Additional information and a complete list of the Medicaid preferred drug list is available at:
http://www.dhhs.state.sc.us/Internet/pdf/Pharmacy%20PDL%20Sept%202008.pdf.

Effective with dates of service November 12, 2008, PA will be required in order for patients to receive newly designated non-preferred products within the therapeutic classes listed in Table 7. Pharmacists should be aware that until final implementation on November 12, soft edits will be displayed indicating the change in listing. Pharmacists are encouraged to make prescribers and patients aware when a soft edit appears between now and implementation.

Table 6. New PDL Class - Platelet Inhibitors

Preferred	Non-preferred
Aggrenox® Plavix®	Dipyridamole Ticlid® Ticlopidine

Prescribers are encouraged to write prescriptions for the "preferred" products rather than prescribing those that require PA. However, if a prescriber is concerned that the patient's clinical status necessitates a PA-required drug therapy, the prescriber should immediately initiate a PA request. A prospective, approved PA request will help to prevent rejection of prescription claims at the pharmacy due to the PA requirement.

All PA requests should be telephoned or submitted by fax to the First Health Clinical Call Center (866-247-118 or 866-247-1181, respectively) by the prescriber or the prescriber's designated office personnel. Questions about Medicare eligibility issues and Part D drug plans should be directed to 1-800-MEDICARE.

Table 7. Changes to Existing PDL Classes

Preferred	Non-preferred
Oral Quinolones	
	Factive® *(Removed from PDL)*
	Levaquin® *(Removed from PDL)*
Long Acting Opioids	
	Avinza® *(Removed from PDL)*
Nasal Steroids	
	Nasacort AQ® *(Removed from PDL)*
Sedative Hypnotics	
	Lunesta® *(Removed from PDL)*
Ophthalmic Prostaglandins	
Travatan Z® *(Added to PDL)*	
Hematopoietics	
	Epogen ® *(Removed from PDL)*
Benzoyl Peroxide/Clindamycin Combination Products	
Duac® *(Added to PDL)*	
Duac CS® *(Added to PDL)*	

FORMULARY UPDATE FOR JUNE & JULY 2008

The Pharmacy and Therapeutics Committee recently approved the actions listed below. The formulary effective was September 15, 2008.

Added: Cinacalcet (Sensipar®)
Cinacalcet is a type II calcimimetic agent approved for the treatment of secondary hyperparathyroidism in patients with end stage renal disease. Other treatment options for secondary hyperparathyroidism include vitamin D analogues and phosphate-binding agents. While both of these medications can lower parathyroid concentrations, they potentially exacerbate both hyperphosphatemia and hypercalcemia. Cinacalcet does not worsen or cause hyperphosphatemia or hypercalcemia; however, hypocalcemia may occur. Cinacalcet is recommended for treatment by the National Institute for Health and Clinical Excellence (NICE) in end-stage renal patients on dialysis refractory to prior treatment for secondary hyperparathyroidism and should be used as second-line therapy.
30-,60-, 90-mg tablets

Added with Restriction :
Regadenoson (Lexiscan®)
Regadenoson is indicated as a pharmacologic stress agent for radionuclide myocardial perfusion imaging (MPI) in patients unable to undergo adequate exercise stress. Regadenoson, an A_{2A} adenosine receptor agonist, produces coronary vasodilation and increases coronary blood flow. Regadenoson is administered as a rapid IV injection at a fixed dose, unlike its comparator, adenosine, which requires a weight based 6-minute infusion, while still producing images comparable to adenosine. Clinical trials demonstrate absence of AV block and bronchospasm suggesting that regadenoson might serve as an alternative stressor to adenosine in high-risk patients. Regadenoson will be restricted to patients that cannot tolerate or have failed testing with adenosine.
0.4 mg/5 mL prefilled syringe

Change in Restriction: Oral methotrexate (continuation of outpatient therapy) may now be ordered by attending physicians double-board certified in Psychiatry/Neurology or Psychiatry/Internal Medicine at the Institute of Psychiatry. This will alleviate the need for consultation to prescribe oral methotrexate by another service (ie, Rheumatology, Neurology). However, the outpatient physician who originally prescribed oral methotrexate for the patient must be documented and the pharmacy from where the medication was last filled must be contacted to verify the dose/regimen.

Policy C61 Update: Medication Administration
The time allowed for medication administration will be changed from 1 hour around the defined schedule to 30 minutes. This change is based on recommendations from the Centers of Medicare and Medicaid Services (CMS). For respiratory medications, the time allowed will remain at 60 minutes.

Line Extensions:

- Multivitamin (Nature's Bounty MultiDay®) [tablets]
- Baclofen [500 microgram/mL, 40-mL kit]
- Chlorhexadine [alcohol-free formulation]
- Recombinant coagulation factor VIIa (NovoSeven® RT) [1-, 2-, and 5-mg vials]
- Aluminum hydroxide (Amphogel®) [320-mg/30-mL unit-dose cups]
- Carbamazepine (Tegretol®) [200-mg/10-mL unit-dose cups]
- Oxytocin [30-units/500-mL (D5LR) infusion]

Deletions:

- Multivitamin (Hexavitamin®)
- ADEK chewable tablets
- Chlorhexadine (alcohol-based)
- Recombinant coagulation factor VIIa (NovoSeven®) [1.2- and 4.8-mg vials]

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