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## Pharmacology in Critical Care: What are We Giving?

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 RUSH Rush is a not-for-profit health care, education and research enterprise comprising Rush University Medical Center, Rush University, Rush Oak Park Hospital and Rush Health.

## Conflict of Interest

I disclose affiliations with Aerogen and Sunovion Pharmaceuticals. Any use of brand names is not in any way meant to be an endorsement of a specific product, but to merely illustrate a point of emphasis.

## What we'll cover.

- **Analgesics**
- Sedatives/Reversal Agents
- Neuromuscular Blockade
- Vasoactive and Inotropic agents
- Drugs that induce methemoglobinemia
- Prophylaxis for deep vein thrombosis, stress ulcers, and delirium

**Caution:**  
**NO ALBUTEROL/NO IPRATROPIUM ZONE!**

## Analgesics

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- Drugs that are used to provide pain relief
- Subdivided into two groups: narcotic and non-narcotic medications
- Narcotics are derivatives of opium (morphine and codeine)
- Non-narcotics are useful in treating pain and inflammation (may also have antipyretic uses)

## Pain in the ICU

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- Pain is subjective. Difficult to measure objectively
- Increased attention has been given to pain control due to the physiological and psychological issues associated
- Often considered the fifth vital sign along with: blood pressure, heart rate, respiratory rate, and temperature

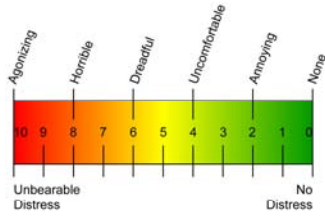
# Pain Scales



Wong-Baker FACES Pain Rating Scale



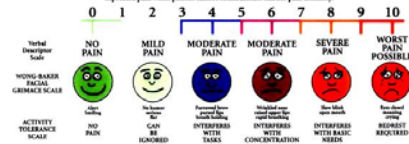
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Task \_\_\_\_\_  
Date \_\_\_\_\_ Start \_\_\_\_\_ End \_\_\_\_\_

## UNIVERSAL PAIN ASSESSMENT TOOL

This pain assessment tool is intended to help patient care providers assess pain according to individual patient needs. Explain and use 0-10 Scale for patient self-assessment. Use the faces or behavioral observations to interpret expressed pain when patient cannot communicate his/her pain intensity.



# Components of Pain



**Two Components:**

*The sensation of pain.*  
Mediated by the central nervous system receiving input from peripheral pain receptors.

*Suffering.* The negative, personal response to the painful stimuli.

## Narcotic Analgesics

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- Used to treat moderate to severe pain
- Act by binding to opioid receptors in the brain and spinal cord
- Most narcotics are metabolized by the liver, and ultimately excreted in the urine
- Produce a euphoric effect on mood, making them popular drugs for abuse
- People can develop a rapid tolerance and withdrawal is very painful and unpleasant

## Narcotics

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- **Morphine:**
  - Peak Effect (IV): 30 minutes
  - Duration is 3 to 7 hours
  - May cause histamine release and hypotension
  - May cause significant respiratory suppression and/or apnea!!
  - Decrease in GI motility

## Narcotics

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- **Fentanyl:**
  - Peak Effect (IV): 4 minutes (onset is almost immediate)
  - Duration 30-60 minutes
  - May cause respiratory depression, drowsiness, and sedation
  - Unlike morphine, fentanyl has minimum cardiovascular depressive effects
  - No issues with histamine release
  - Rare issues with bradycardia and chest wall rigidity when given rapidly in large doses

## Narcotics

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- **Hydromorphone (Dilaudid®):**
  - Peak Effect (IV): 20 minutes
  - Duration: Up to 4-5 hours
  - Acceptable alternative to morphine (semisynthetic opioid)
  - Minimal hemodynamic effects and does not cause histamine release
  - Side effects such as pruritus (itching), sedation, nausea/vomiting less than with morphine

## Strong Non-narcotics

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- **Ketamine:**
  - Peak Effect (IV): 30-60 seconds
  - Elimination Half-Life: 2-3 hrs (duration can be unpredictable)
  - Not usually used alone, but can be a useful addition in difficult to control pain
  - Bolus doses may increase BP, HR, and cardiac output. Also, may promote bronchodilation
  - Caution in patients with  $\uparrow$ ICP. Also vivid hallucinations may occur

## Strong Non-narcotics

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- **Dexmedetomidine (Precedex™):**
  - Peak Effect (IV): 1-2 minutes
  - Elimination Half-Life: 2-3 hours
  - Relatively new (approved for use in U.S. in 1999)
  - Both sedative and analgesic properties
  - Used as a continuous infusion. Provides sedation without the significant respiratory depression
  - Patients often appear calm, capable of being aroused, and without pain. May tolerate mechanical ventilation better

## Routes of Administration

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- Oral
- Sublingual and buccal (between the teeth and the mucous membranes of the cheek)
- Rectal
- Subcutaneous
- Intramuscular
- Intravenous
- Transdermal
- Epidural
- Patient-controlled analgesia (PCA)
- Inhalation

## Narcotic Inhalation

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- Occasional administration by inhalation
- May be effective at decreasing the sensation of dyspnea in patients with advanced respiratory failure
- Not well studied
- Some reports show promise in terminally ill patients



## Reversals: *A friend when you need 'em*

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- **Naloxone (Narcan®):**
  - Notes: Onset of action for IV is 1-3 minutes vs. 10-15 minutes for IM
  - Rebound sedation may occur
  - May cause acute withdrawal if used in patients with chronic narcotic use

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## What is sedation?

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- *Defined:* The production of a restful state of mind, particularly by the use of drugs that have a calming effect, relieving anxiety and tension
- *Upside:* Relieve pain (or perception of pain), decrease agitation, reduce patient-ventilator asynchrony, decrease O<sub>2</sub> consumption, facilitate patient care
- *Downside:* May prolong mechanical ventilation and increase cost

## Sedation

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- Pain control alone may allow patients to be comfortable enough to require no sedation.
- Goals for sedation have changed somewhat and may vary:
  - Obtundation may be the goal early
  - Current trends are sleepy but arousable patients
  - Sedatives are very frequently used with analgesics

## Benzodiazepines

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- Two common sedation drugs in ICU:
  1. Midazolam (Versed®)
  2. Lorazepam (Ativan®)
  - Both drugs are lipophilic (having an affinity for fat or lipids; lipid soluble)
  - Midazolam has a more rapid onset of action than lorazepam
  - Lorazepam is longer acting

## Benzodiazepines

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- **Lorazepam (Ativan®):**
  - Onset: 5-15 minutes
  - Duration: 6-8 hours
  - Less lipophilic, because of this it has a slower onset of action
  - Compared to midazolam, it has been shown to provide a higher rate of adequate sedation and was more cost-effective
  - May be the preferred benzo in patients with renal failure

## Benzodiazepines

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- **Midazolam (Versed®):**
  - Onset: 2-5 minutes
  - Peak Effect: 5-30 minutes (30-120 minutes duration)
  - Fast onset, short duration
  - May accumulate in the setting of renal failure
  - Generally not preferred in patients with renal failure

## Reversals: A friend indeed!

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- **Flumazenil (Romazicon®):** Reverses benzodiazepines
- Rebound sedation may occur
- If used in patients with chronic benzodiazepine use, may cause acute withdrawal
- May precipitate seizures unresponsive to benzodiazepines (may see some hesitation to use because of this)

## Propofol (Diprivan®)

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- Onset: 30 seconds
- Duration: 3-10 minutes (dose and rate dependent)
- Commonly used ICU sedative
- Respiratory and cardiovascular depression
- Some use as an antiepileptic for refractory seizures
- Formulated in lipid emulsion, monitor triglycerides

## What say you?

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Q. You are planning to extubate your patient. Just prior to extubation, the nurse gives a large dose of lorazepam (Ativan®) for anxiety. Are you concerned? Why/why not?

## Were you sedated?

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Q. What agent is used to reverse the effects of benzodiazepines?



A. Flumazenil (Romazicon®)

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## Neuromuscular Blocking Agents

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- Intubation
- Surgery
- Reduce O<sub>2</sub> Consumption
- Facilitate procedures and studies
- Reduce ICP's in intubated patients with uncontrolled intracranial pressures

## NMBAs

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### – ***Depolarizing agents***

Mode of Action: Depolarizing agents mimic acetylcholine but stay at the neuromuscular junction for a longer period of time. Initially, depolarizing agents stimulate the muscles, causing transient twitching (fasciculations). As it sits in the junction, it prolongs depolarization. The muscles are paralyzed because they cannot repolarize.

### – ***Nondepolarizing agents***

Mode of Action: Neuromuscular blocking agents act competitively with acetylcholine. Most NMBA's are nondepolarizing, which means that they work by binding to the acetylcholine receptors on the muscle side of the junction. With these receptors blocked, acetylcholine cannot transmit the nerve impulse, so the muscle cannot depolarize and contract.

## Depolarizing Agent

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- **Succinylcholine:**

- Very short duration of action. 4-6 minutes with single administration (I.V.)
- Quick onset of action: Complete muscular relaxation within 30-60 seconds
- There are no reversal agents
- Complications: May cause an efflux of potassium from muscle cells, causing serum potassium to increase. Severe hyperkalemia may cause arrhythmias and cardiac arrest
- Malignant hyperthermia (potentially fatal hypermetabolic state of skeletal muscle)
- **Does not relieve pain or produce sedation!**

## Nondepolarizing Agents

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- **Cisatracurium (Nimbex®)**

- Intermediate duration of action. 40-60 minutes
- Onset of action is 2-3 minutes
- Not eliminated by the liver or kidney, may be the best choice for patients with hepatic or renal failure
- Complications: May be a poor choice for patients with intracranial issues due to a breakdown product that causes neurostimulatory effects (e.g., severe head injury)
- **Does not relieve pain or produce sedation!**



## Nondepolarizing Agents

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- Rocuronium (Zemuron®)
  - Intermediate duration of action. 30-60 minutes
  - Onset of action is 1-2 minutes
- Vecuronium (Norcuron®)
  - Intermediate duration of action. 60-90 minutes
  - Onset of action is 2-4 minutes
- Pancuronium (Pavulon®)
  - Long duration of action. 120-180 minutes
  - Onset of action is 4-6 minutes

## Nondepolarizing Agents

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- Nondepolarizing agents can be reversed by cholinesterase inhibitors such as neostigmine, edrophonium, and pyridostigmine
- Have a tendency to release histamine from mast cells. Watch for bronchospasm, reflex tachycardia, and skin flushing
- **Do not relieve pain or produce sedation!**

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## Vasopressors and Inotropes

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- Defined:
  - *Vasopressors*: Drugs that cause contractions of the capillaries and arteries
  - *Inotropes*: Drugs affecting the strength of muscular contraction
- Vasopressors and inotropes are routinely used in the setting of cardiogenic shock

## Common Vasopressors and Inotropes

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- Dopamine (Inotropin)
- Dobutamine (Dobutrex®)
- Norepinephrine (Levophed®)
- Phenylephrine (Neo-Synephrine®)
- Vasopressin (Pitressin®)
- Epinephrine

## Dopamine (Inotropin)

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- Endogenous catecholamine that is a precursor to norepinephrine
- Doses between 5-20 µg/kg/min produce **chronotropic** and **inotropic** effects leading to an increase in cardiac output (**myocardial contractility** and **heart rate** are increased)
- The belief that low-dose dopamine selectively stimulates dopamine receptors causing vasodilation and increased blood flow to the kidneys has been nullified and considered antiquated
- Renal blood flow improvement is probably from increase in cardiac output
- **In sepsis, alternative to norepinephrine in highly selected patients (patients with low risk of tachyarrhythmias)**

## Dobutamine (Dobutrex®)

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- Inotropic Agent
- Indicated for the *short-term* inotropic support in patients with decompensated heart failure due to depressed contractility
- Chemically related to dopamine; however, it is not metabolized to norepinephrine nor does it stimulate dopamine receptors
- Dobutamine's pharmacologic actions are due to its effects of its racemic components
- The overall pharmacology of dobutamine is very complex, as it has both vasoconstrictive and vasodilatory effects

## Norepinephrine (Levophed®)

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- Catecholamine (like epinephrine)
- One of the principal neurotransmitters in the sympathetic nervous system
- Strong vasoconstrictor. Also increases both heart rate and contractility
- Used to treat acute hypotension resulting from conditions such as myocardial infarction, drug reactions, spinal anesthesia, and septicemia
- **First choice of vasopressor in sepsis**

## Phenylephrine (Neo-Synephrine®)

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- Purely an alpha agonist
- Induces vasoconstriction in most vascular beds, causing an elevation in systolic and diastolic blood pressure
- Systemic blood pressure is effected by the overall increase in total peripheral resistance
- Does not increase heart rate and contractility
- **Not recommended in septic shock unless norepinephrine is associated with serious arrhythmias OR cardiac output is known  $\uparrow$  and BP is persistently low OR when other combined therapies have failed to achieve BP target**

## Vasopressin (Pitressin®)

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- Direct vasoconstrictor without inotropic/chronotropic effects
- Mostly recommended as a second-line vasopressor in addition to norepinephrine to increase blood pressure OR to reduce dose of norepinephrine
- High doses should be reserved for salvage therapy
  - Side effects (with  $\uparrow$  dose) include: coronary and mesenteric ischemia, skin necrosis. Potential for pulmonary vasoconstriction
- Low dose is not recommended as initial agent (alone) for treatment of hypotension secondary to sepsis

## Epinephrine

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- Potent beta-1 adrenergic receptor activity
- Moderate beta-2 and alpha-1 adrenergic receptor activity
- Increases blood pressure by increasing cardiac index and peripheral vascular tone
- Often used in septic shock as a second line agent after norepinephrine
- Potential side effects include dysrhythmias and decrease in splanchnic circulation

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## Drugs that induce methHB

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- Methemoglobin (metHb)
  - Some (small portion) of the Hb undergoes chemical changes and forms methemoglobin
  - This formation causes the Hb to be useless in oxygen carrying capacity
  - ↑metHb (methemoglobinemia) may be acquired or congenital
  - Possible causes of ↑ metHb:
    - Ingestion of nitroglycerin, topical anesthetics (Hurricane spray), ingestion of amyl nitrate
  - Normal Values: ~1%

## Drugs that induce methHB

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- Dapsone and topical anesthetic agents are most common causes
  - Dapsone: antibacterial
  - Anesthetic agents: benzocaine (Hurricane spray), lidocaine
- Nitric oxide: pulmonary vasodilator
- Nitroprusside: vasodilator/antihypertensive
- **Treatment:** Depends on situation → usually methylene blue

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## Prophylaxis for deep vein thrombosis, stress ulcers, and delirium

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- Pulmonary embolism (PE) believed to be responsible for 150,000 to 200,000 deaths/year in the United States!
- Two main approaches to prevent PE in medical patients:
  - Primary: **Medication** and physical methods (pneumatic compression)
  - Secondary: Screening patients at risk



## Preventing deep vein thrombosis

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- Heparin (low dose)
  - For thromboprophylaxis → SubQ unfractionated: 5000 units every 8-12 hours
  - Low-molecular weight heparins:
    - Enoxaparin (Lovenox<sup>®</sup>) 30 mg Q12
    - Dalteparin (Fragmin<sup>®</sup>) 5000 units Q day
- Fondaparinux (Arixtra<sup>®</sup>)
  - SubQ: Adults ≥50 kg: 2.5 mg once daily

## Prophylaxis for stress ulcers

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- Stress ulcers usually occur in the fundus and body of the stomach
- 1.5-8.5% of all ICU patients have GI bleeding
- May be up to 15% in patients that DO NOT receive prophylaxis for stress ulcers
- **Indications:** mechanically ventilated for more than 48 hours, coagulopathy, GI ulceration or bleeding within the past year, traumatic brain injury, traumatic spinal cord injury, severe burns, or two or more minor risk factors

## Stress ulcers

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- Histamine-2 receptor antagonists (H<sub>2</sub> blockers)
- Proton pump inhibitors (PPI)
- Antacids
  - All reduce overt GI bleeding in ICU patients compared to placebo or no prophylaxis
- Prophylactic agents that increase gastric pH (PPI, H<sub>2</sub> blockers, antacids) may increase the incidence of nosocomial pneumonia (compared to agents that do not alter gastric pH)
  - Sulcrafate does not alter gastric pH

## Prophylaxis for delirium

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- No large body of evidence to guide care
- In fact, currently evidence suggests medications **DO NOT** appear to be effective in preventing delirium
- With that said:
  - **Neuroleptic medications: *Haloperidol*** → may be useful in symptomatic relief, but not for prevention of delirium
  - **Benzodiazepines: *Lorazepam*** → May be useful in sedative/alcohol withdrawal or when neuroleptic drugs are contraindicated
  - **Cholinesterase inhibitors: *Rivastigmine*** → No real role in prevention or treatment of prevention

