Richmond Agitation-Sedation Scale (RASS)
Ely EW, JAMA 2003:289(22):2983

- +4 = Combative, violent
- +3 = Very agitated, pulls at catheters
- +2 = Agitated, fights the ventilator
- +1 = Restless
- 0 = Alert and calm
- -1 = Drowsy, >10 sec. eye open to voice
- -2 = Light sedation, <10 sec. eye open to voice
- -3 = Moderate sedation, movement to voice
- -4 = Deep sedation, movement to touch
- -5 = Unarousable, no response to touch
"Daily Interruption of Sedative Infusions..."

- n=128, intubated, morphine plus either midazolam or propofol

- Daily interruption group:
  - shorter vent duration (4.9 vs. 7.3 day, p=0.004)
  - shorter ICU LOS (6.4 vs. 9.9 day, p = 0.02)
Do I Really Have to Wake Them Up?

• 336 mechanically ventilated ICU patients prospectively randomized to getting a SAT or not before their SBT

• SAT+SBT group did better than SBT group
  – more ventilator free days (28 day study period, 14.7 vs. 11.6, p=0.02)
  – shorter ICU LOS (9.1 vs. 12.9 days, p=0.01)
  – lower 1 year mortality (HR 0.68, 95% CI 0.5 to 0.92, p=0.01)
But ... That’s Not What The Talk Is Supposed To Be About ...

• My “easy to sedate” patients should be titrated to the minimum dose necessary, and have a daily wake-up. Got it.

• What about my difficult to sedate patients?
Case: The ASF Won’t Sit Still

• 58 year old male who remains intubated in the ICU with upper airway edema immediately after a multilevel anterior cervical spine fusion who is sedated with a propofol infusion

• He is alternating between hypotension and agitation with propofol titration.

• What’s wrong?
Case: The TKR Just Kicked Me

- 52 year old male POD #1 from a left total knee replacement, who is hypertensive, tachycardic, agitated, and delirious. He just kicked the RN with his left leg.
- Low dose fentanyl does nothing. High dose fentanyl causes transient hypoxia and unresponsiveness.
- What is wrong?
How to "Sedate" in the ICU

- Identify goals:
  - Analgesia
  - Anxiolysis
  - Amnesia
  - Hypnosis
  - Paralysis
- Choose a drug and titrate to effect
- Anticipate side effects
"Analgesia"

Sources of Pain in the ICU

- Surgical incisions
- Tissue injury from malignancy, infection, ischemia
- Indwelling catheters and monitors
- Discomfort from lying in bed in one position for hours or days
Opioids

• The mainstay of analgesic therapy
• Do NOT reliably produce amnesia, anxiolysis, or hypnosis
• Lots of side effects (itching, nausea, constipation, urine retention, myoclonus, respiratory depression)
• Very little direct organ toxicity
Opioid Side Effects Are A Spectrum

• By varying the opioid dose you can move between:
  – Screaming in pain
  – Awake and comfortable
  – Nauseous, itching, “woozy”
  – Somnolent
  – Dead (from respiratory depression)
• You can move up and down the spectrum with any pure opioid agonist
  – Or antagonist
• Changing the pain intensity has the same effect as changing the opioid dose
  – Epidural infusion clogs --> Incisional pain --> IV fentanyl --> Comfort
    --> Epidural unclogged --> Respiratory Arrest
Opioids: How to Reduce Side Effects

- If the patient is comfortable, decrease the dose
- Change opioids
  - Fentanyl and Dilaudid may be better than morphine
- Add non-opioid adjuncts to reduce opioid dose needed
  - NSAIDS, acetaminophen, neuropathic pain treatments, regional anesthesia, dexmedetomidine, ketamine, etc.
- Reduce the source of pain
  - Tracheostomy, for example
IV Opioid Choices

- Morphine
  - Familiar
  - Multiple problems
    - histamine release
    - active metabolite accumulates in renal failure
    - ? more confusion in elderly
- Hydromorphone (Dilaudid)
  - Roughly the same onset and duration as morphine
- Fentanyl
  - Faster onset
  - Terminal elimination is similar to morphine
Short Acting Opioids: Remifentanil

- Ultra-short acting opioid
  - Rapid organ independent metabolism by plasma esterases
- Usual dose:
  - Light sedation = 0.01-0.05 mcg/kg/min IV
  - General anesthesia = 0.1 - 0.2 mcg/kg/min IV
- May be useful in neuro patients (especially with Propofol)
- Can precipitate SEVERE pain if the infusion suddenly stops
Opioid Tips:
Long Acting Agents ... A Few Choices

• Extended release morphine, oxycodone, oxymorphone
  – Can't crush for FT
    • Impossible to give to an intubated patient
• Methadone
  – Cheap, available PO and IV
  – Takes 2+ days for dose change to take effect
  – QT prolongation, especially at high doses
• Fentanyl patch
  – Doesn't rely on IV or PO route
  – 12h++ onset and offset, fever causes increased absorption
"Sedation"

• There are many components besides analgesia, including:
  – anxiolysis
  – amnesia
  – hypnosis
  – anti-psychosis or anti-delirium
  – paralysis
• Need to identify what your goals are in order to choose the proper therapy
Benzodiazepines

- Excellent anxiolysis, amnesia, hypnosis
- Minimal hemodynamic effects
- Anticonvulsant (useful for seizures or alcohol withdrawal)
- Relatively little respiratory depression when used alone, but very synergistic with opioids
- Little analgesia
- Cause delirium
  - Lorazepam was an independent risk factor for transition to delirium in ICU patients (OR 1.2, 95% CI 1.2-1.4), while fentanyl, morphine, and propofol were not (Pandharipande P et al. Anes 2006, 104:21-26)
Benzodiazepines Are Bad!

- Should not be used in ICU patients at risk for delirium
  - Which is basically everyone
- Benzodiazepines can be reserved for patients with poor cardiac function or those at risk of alcohol or sedative withdrawal seizures
Propofol vs. Lorazepam

- Adult medical ICU patients expected to be intubated for >48 hours
- Randomized to lorazepam bolus or propofol infusion
- Daily interruption of sedatives in both groups
- Propofol group did better:
  - Fewer ventilator days (median 5.8 vs. 8.4, p = 0.04)
  - A strong trend toward greater ventilator-free survival (18.5 vs. 10.2 days, p = 0.06)
Case: Propofol Works Great, but....... 

- 48 year old morbidly obese male intubated for altered mental status and high ICP after SAH.
- Sedated well on propofol 90 mcg/kg/min (based on actual body weight)
- Triglyceride level 482 mg/dL.
Propofol - Hypertriglyceridemia

- Incidence estimates vary: up to 3-10% (Kang TM Ann Pharmacother 2002;36:1453-6)
- Risk factors likely include prolonged infusion ( > 80 mcg/kg/min for > 24 hrs)
- SCCM Clinical Practice Guidelines for the Sustained Use of Sedatives and Analgesics in the Critically Ill Adult - 2002
  - "Triglyceride concentrations should be monitored after two days of propofol infusion." Jacobi J et al. CCM 2002;30(1):119-41
Propofol Infusion Syndrome

• Severe metabolic acidosis
  – Progressing to hyperkalemia, rhabdomyolysis, hypotension, bradycardia, and death

• Risk factors are suspected to include
  – Prolonged infusion (>48 hrs) of higher doses (> 80 mcg/kg/min)
  – Steroid use
  – Catecholamine use
  – Brain Injury
  – Sepsis or other Systemic Inflammatory Response Syndrome
  – Pediatric patients
Propofol Infusion Syndrome: Practical Advice

• Prevention
  – Minimize the dose administered (<80 mcg/kg/min), especially with prolonged infusion (>48 hours), through addition of supplemental agents
  – If acidosis develops
    • Discontinue propofol
    • Follow laboratory parameters (arterial blood gas, creatinine kinase, electrolytes, triglycerides)

• Treatment
  – Supportive care
  – (Possibly) hemodialysis/hemofiltration
Dexmedetomidine

- Selective alpha-2 agonist (IV infusion)
- Sedation, anxiolysis, analgesia, sympatholysis
- Not reliably amnestic
- Still arousable for neuro exam
- Not a major respiratory depressant
  - Can be used on extubated patients
Dexmedetomidine vs. Lorazepam
(Pandharipande PP et al. JAMA 2007)

- 103 adult medical and surgical ICU patients requiring mechanical ventilation for >24 hrs prospectively randomized to:
  - Lorazepam 1 mg/hr IV titrated between 0-10 (no boluses allowed)
  - Dexmedetomidine 0.15 mcg/kg/hr titrated between 0-1.5
- All patients received fentanyl boluses or infusion if necessary
- Continued until extubation or until FDA mandated endpoint of 120 hours
- Dexmedetomidine group did better
  - More delirium and coma free days (7.0 vs. 3.0, p=0.01)
  - Trend toward lower 28 day mortality (17% vs. 27%, p=0.18)
- Dexmedetomidine group received significantly more fentanyl (575 vs. 150 mcg/24h, p=0.006)
- No difference in cortisol or ACTH levels 2 days after discontinuation
Dexmedetomidine vs. Midazolam  
(Riker RR et al. JAMA 2009)

- PDBRCT 375 intubated med/surg ICU patients expected to require ventilation for at least 3 more days
- Dex 0.2 - 1.4 mcg/kg/hr vs Midaz 0.02 - 0.1 mg/kg/hr until extubation or 30 days
- Excluded (among other things) hypotension defined as SBP < 90 despite 2 vasopressors
- Also
  - Study drug boluses prn
  - Open-label midazolam 0.01-0.05 mg/kg iv q10-15min prn agitation
  - Fentanyl 0.5-1 mcg/kg iv q15mr prn pain
  - Haloperidol 1-5 mg iv q10-20min prn delirium
Dex vs. Midazolam

- Dex group did better
  - Less delirium (54% vs. 76.6%, p<0.001)
  - Shorter time to extubation (3.7 vs. 5.6 days, p=0.01)
- No difference
  - ICU LOS (5.9 vs. 7.6 days, p=0.24)
  - 30 day mortality (22.5% vs 25.4%, p=0.60)
- Dex had more bradycardia (42.2% vs. 18.9%, p<0.001)
Dex vs. Midazolam

- Mean doses: dex 0.83 mg/kg/hr, midaz 0.056 mg/kg/hr
- Average duration of study drug: 3.5 days for dex, 4.1 days for midaz
- 1/244 dex patients had adrenal insufficiency (0/122 in midaz group)
Hospital Drug Acquisition Costs

Drug only ... does not include preparation, etc.
All costs are for 24 hours for a 70 kg patient

• Propofol 75 mcg/kg/min = $100
• Dexmedetomodine 1 mcg/kg/hr = $500
  – MICU patients needed 1 mcg/kg/hr (Venn RM et al. ICM 2003)
  – CABG patients on a 0-0.7 mcg/kg/hr dex protocol only reduced their Propofol dose from 20 to 5 mcg/kg/min
• Midazolam 2 mg/hr = $10
• Fentanyl 50 mcg/hr = $7
• Remifentanil 0.10 mcg/kg/min = $100
Case: The Last Resort

• 25 year old male with active polysubstance abuse who suffered a gun shot wound to the liver. A tenuous repair of hepatic vasculature has left him at extreme risk for massive bleeding.

• On POD #1, delirious and combative, he rips out all of his IVs and runs off down the hallway.
Ketamine: A Unique Sedative

- Phencyclidine derivative (like PCP)
- NMDA receptor antagonist
- Dissociative hypnotic, amnestic
- Analgesic
  - The only potent analgesic without much respiratory depression
  - One of the few non-opioid analgesics that can be given IV
- Classically used for brief procedures (such as dressing changes) on unintubated patients
  - Or IM injections of combative patients without IV access
- Little to no tolerance
Ketamine: Problems

- Increases BP and HR via sympathetic stimulation
  - Actually a direct negative inotrope
- May increase in ICP, also because of sympathetic stimulation
  - But no increase in ICP in patients who are sedated and fully mechanically ventilated (Himmelseher S Anes Analg 2005)
- Causes unpleasant dreams and hallucinations
  - Consider benzo use if dose is > 5 mcg/kg/min IV
- Increases bronchodilation by sympathetic stimulation
  - But also increases secretions
- Maintains airway tone, but not necessarily airway reflexes
Ketamine: Last Resort Sedative

- For continuous sedation in the ICU
  - 1 - 10 mcg/kg/min IV has been studied in post-op patients for pain relief (typically keep dose < 5 for awake patients)
  - Up to 20 - 30 mcg/kg/min IV used at UCSF for "impossible to sedate" intubated patients to avoid paralysis
- Low dose oral (<50 mg po TID) and IV (< 5 mcg/kg/min) ketamine is used outside the ICU by many centers
- Oral ketamine also used on outpatients by Pain Clinics
Polysubstance Abuse

- Alcohol / Benzodiazepines
  - Withdrawal is difficult to manage with a high morbidity / mortality
  - Watch for seizures, don’t use only neuroleptics, etc.
- Opioids
  - Titrate opioid dose up to effect
  - Withdrawal is relatively benign
- Amphetamine / Cocaine
  - Main problem is fatigue
  - Withdrawal is relatively benign
- Marijuana
  - Consider oral marinol
  - Withdrawal is relatively benign
Haloperidol

- Anti-psychotic
- Not FDA approved for IV administration or ICU sedation
- Relatively little respiratory depression compared with alternative sedatives
- Useful for management of agitation due to delirium
Haloperidol: Side Effects

- Extrapyramidal effects
- QT prolongation leading to torsades-de pointes
  - Seen at total doses as low as 20-35 mg (no reports of torsades at < 2 mg)
  - Regular ECGs to assess for QT prolongation (printed on order form)
- Reduced seizure threshold
  - Increased mortality when used for alcohol withdrawal
  - Relative risk of mortality with neuroleptic treatment compared with sedative-hypnotic treatment of 6.6 (95% confidence interval, 1.2-34.7)
  Mayo-Smith MF, Arch Int Med 2004
- Neuroleptic Malignant Syndrome
  - Fever, rigidity, cognitive changes, tachypnea, tachycardia, diaphoresis, leukocytosis, elevated CK
  - Supportive care, discontinue inciting agent
  - Dopamine agonists (bromocriptine, amantadine, levodopa/carbidopa)
  - Dantrolene
"Atypical" Antipsychotics: Abilify, Zyprexa, etc.

- Don't prolong the QT interval
  - A controversial area: difficulty to measure accurately
- May have fewer side effects
- Many are not available IV (PO / SL / IM only)
- Beware drug interactions. For Abilify, for example
  - 2D6 inhibitors like Prozac or Paxil, and 3A4 inhibitors like itraconazole and erythromycin inhibit metabolism: reduce dose by half
  - 3A4 inducers like carbamazepine enhance metabolism: double dose
- Still cause NMS
What About Paralytics?

- They are NOT sedatives
  - No analgesia
  - No amnesia
  - No anxiolysis

- They don’t belong in a “how to sedate” talk
  - Morally no different than putting your hands over your eyes and saying “see, now the patient doesn’t look agitated any more”
Take Home Messages

• Define your goals (analgesia, anxiolysis, hypnosis, amnesia, antipsychosis) and choose your drugs appropriately
• Titrate to effect (daily wake ups)
• Watch for side effects specific to that drug, and proactively treat
• Don’t use benzodiazepines unless you absolutely have to.
Reprints / Questions

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Is a Daily Wake-up the Magical Cure?
de Wit M et al. Crit Care 2008:12:R70

- RCT of Daily Interruption vs. Sedation Algorithm
  - Daily Interruption group did NOT use the algorithm
- Mechanically ventilated medical ICU patients
  - excluded neurocognitive dysfunction, paralytic use, or tracheostomy
  - did NOT exclude alcohol withdrawal
- Daily Interruption did worse (stopped at n=74 by DSMB)
  - longer duration of mechanical ventilation (6.7 vs. 3.9 days, p = 0.0003)
  - longer ICU LOS (15 vs. 8 days, p < 0.0001)
  - longer hospital LOS (23 vs. 12 days p = 0.01)
  - trend toward lower 28 day ventilator free survival (16.1 vs. 23.1 days, p = 0.0004 but NS with the preset alpha of 0.001 for the interim analysis)