Extending the Use of Ketamine

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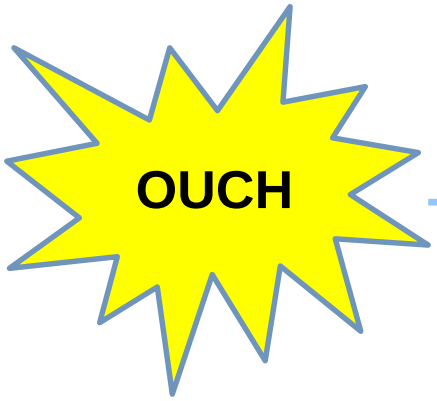
Clinical implications of pain

- Adverse health effects
  - Physical and emotional stress
  - Increased sympathetic outflow
  - Weight gain
  - Depression
  - Anxiety
  - Sleep disorders
  - Impaired cognitive function
  - Decreased activity
- Decreases quality of life
- Slows recovery or rehabilitation

Poor control of postoperative pain is associated with a delay in ambulation and rehabilitation, longer hospital stays, decreased patient satisfaction scores, and higher rates of medical complications like deep vein thrombosis (Maganizer & McLaughlin, 2003; Chelley et al, 2001).



Primary afferents

Almost all excite interneuron by releasing glutamate to NMDA-like receptors

DORSAL HORN

- **10 layers called lamina**
- **Majority of nociception fibers terminate in RL I & II**
- **RL II + RL III = SG**

Synapse on **SPINOTHALAMIC TRACT** → true for fast and slow pain responses

Supraspinal Structures

- **Thalamus** – interpretation
- **Amygdala** – combines nociception with other afferent input
- **Basal ganglia** – encode intensity of stimulus
- **Cortex**

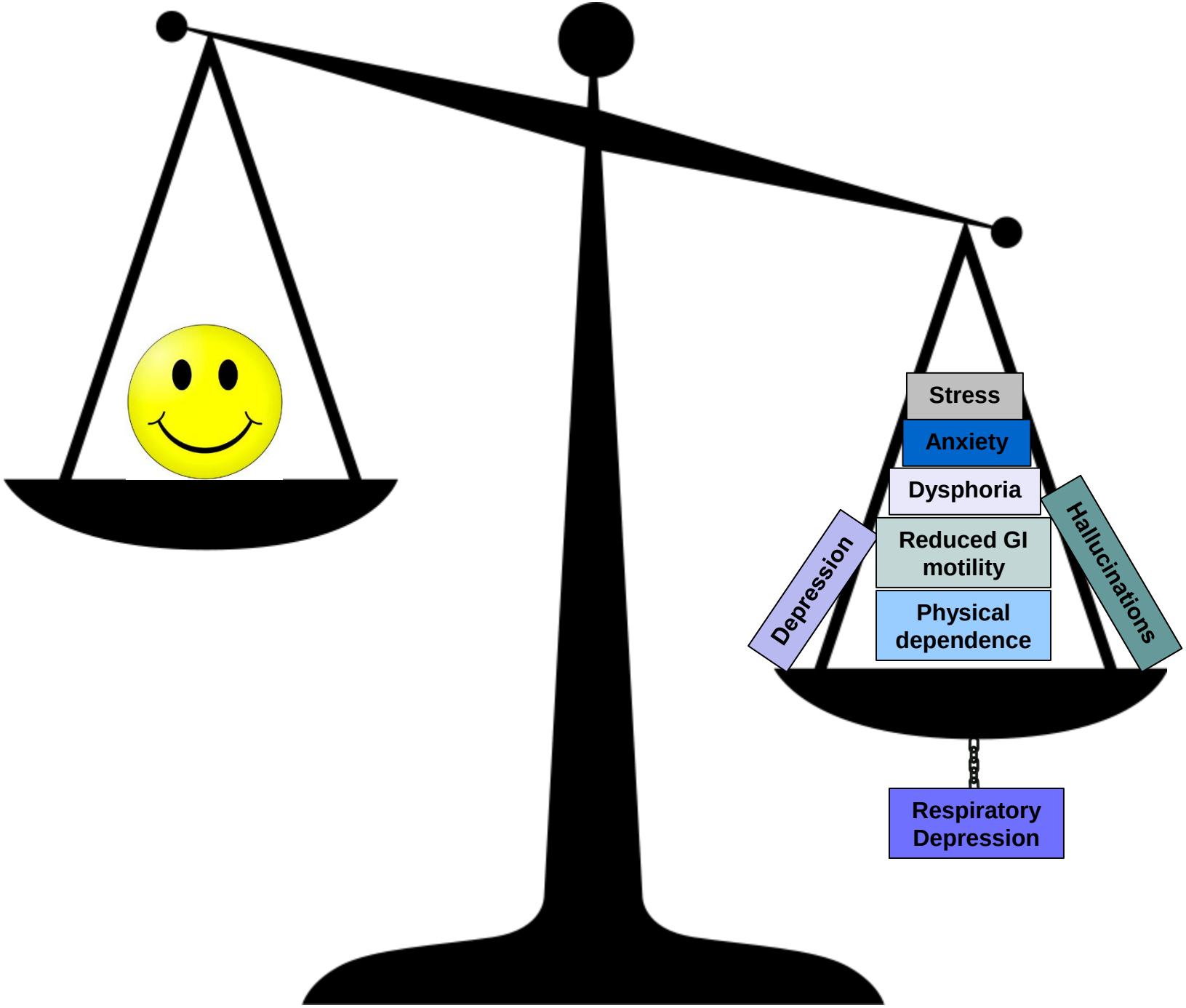
Pain

- Nociceptive vs neuropathic pain
  - Nociceptive – activity in neural pathways in response to stimuli
  - Neuropathic – caused by lesion or dysfunction in nervous system
- Mixed type pain – caused by a combination of primary injury and secondary effects (tissue damage and/or inflammation)
- Acute vs chronic pain
  - Varying patient populations
- Common treatment: OPIOIDs

Opioids

- Agonize the opioid receptor
  - Inhibitory G protein-linked receptors
  - 4 primary subtypes:

Receptor Subtype		Positive	Negative
Delta	D1, D2	• Analgesia • Antidepressant	• Physical dependence • Respiratory depression
Kappa	K1, K2, K3	• Analgesia • Neuroprotection	• Dysphoria • Hallucinogen • Stress
Mu	M1, m2, m3	• Analgesia • Vasodilation	• Physical dependence • Respiratory depression • Reduced GI motility
Nociceptin	NOP		• Anxiety • Depression • Tolerance to mu agonists


Stress
Anxiety
Dysphoria
Depression
Reduced GI motility
Hallucinations
Physical dependence
Respiratory Depression

Current use of opioids

- CDC reports that enough opioid analgesics were prescribed in 2018 to medicate every American adult around the clock for a month
- Both use and abuse lead to development of tolerance
  - Require larger dose for diminishing effect
  - Clinical implications
    - Continuing to treat only with opioid analgesics causes:
      1. An increase in frequency/severity of unwanted effects
      2. Inadequate pain relief due to tolerance

Challenges

- Increasing incidence of opioid use
  - Aging population – more osteoarthritis
    - Analgesia need can be for medical therapy or for pain control following surgical procedure
- Obesity – sequelae of problems
- Patient expectations
- Financial considerations
  - Push to early discharge

Challenges

- 77% of all patients undergoing major orthopedic surgery report moderate to severe pain (Warfield & Kahn, 1995)
- 25% of patients report undesired effects resulting from the administration of opioids (Lachiewicz, 2013)
- **The fear of pain is a barrier to patients seeking surgical interventions** (Ranawat & Ranawat, 2007)

Utopia Anesthesia: Providing perfect care in a dream world

- Is this anesthetic possible?

Non-opioid pain management

- A means of providing analgesia without resorting to opioid administration alone

A preemptive multimodal pathway featuring peripheral nerve block improves perioperative outcomes after major orthopedic surgery (Hebl, et al, 2008)

• Decreased opioid requirement	(p = 0.04)
• Decreased PONV on Day 1	(p = 0.002)
• Decreased length of stay	(p < 0.001)
• Increased range of motion	(p = 0.008)
• Decrease post op urinary retention	(p < 0.001)
• Decreased formation of post-op ileus	(p = 0.01)

- Components include pharmacotherapy and regional anesthesia techniques

Pharmacotherapy

- Non-steroidal anti-inflammatories
- Acetaminophen
- Gabapentinoids
- **Ketamine**
- Glucocorticoids
- Antidepressants
- Anxiolytics

Ketamine

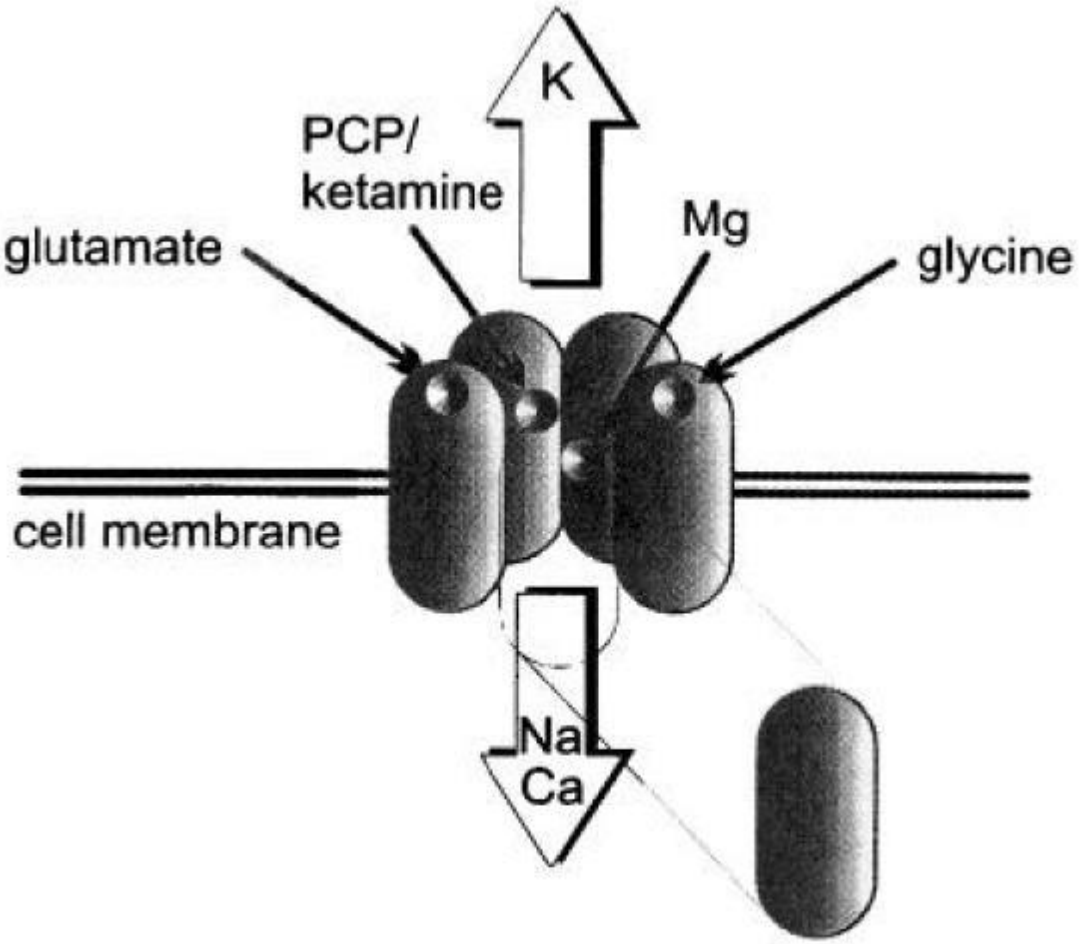
- Phencyclidine derivative
- Binds to **N-methyl d-aspartate receptor** (NMDA)
- Non-competitive receptor **antagonist of glutamate** (neurotransmitter)
- Effect: **dissociative anesthesia**

Ketamine

Method of action

- Does not depress the RAS → weak action only at the $GABA_A$ receptor
- **Instead, dissociates the thalamus from the limbic system**
  - Limbic system responsible for behaviors governed by emotions, such as rage, fear, anger, affection, etc
- Some brain neurons are inhibited, some are excited

Method of action: NMDA Receptor



Method of action: Other receptors

- Antagonizes some muscarinic receptors
  - Anticholinergic symptoms → can be + or -
    - Bronchodilation
    - Emergence delirium
  - These effects can be attenuated by anticholinesterase drugs
- Interacts with voltage gated Na+ channels to produce mild local anesthetic effects
- Can act as an agonist of mu opioid receptors

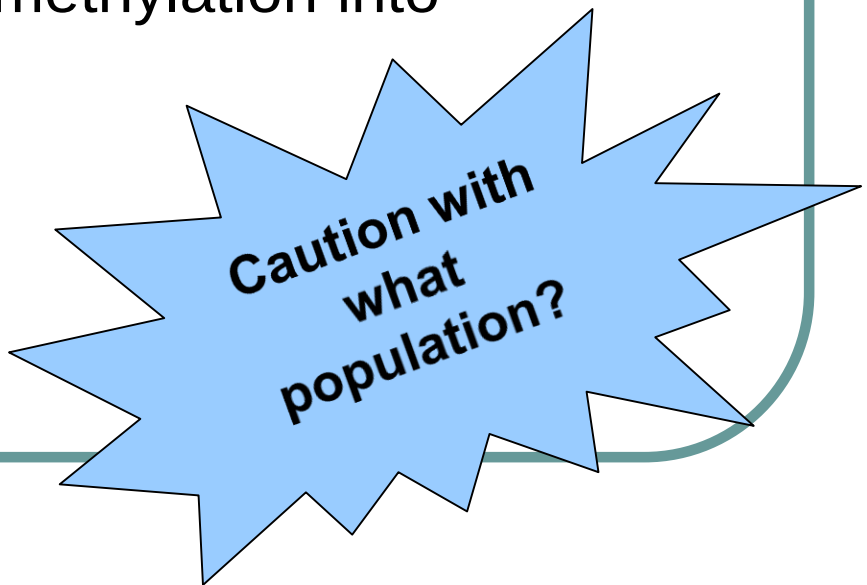
Ketamine

Pharmacokinetics overview

- Rapid brain uptake and rapid redistribution
  - Duration of induction dose = 10-15min
- More lipid soluble and less protein bound than sodium thiopental **(GOLD STANDARD)**
  - Peak concentration within 1 minute
  - More free drug reaches brain

Pharmacokinetics

- VD = 3L/kg → **widely distributed**
- Context sensitive half time
  - < 15 min for cases < 2 hrs
  - < 30 min for cases > 2 hrs
- Elimination half life = 2-3 hrs
- Clearance moderately high – 1L/min
- Metabolism in liver via N-demethylation into **norketamine**
  - Active, major metabolite
  - Has 25% activity of ketamine
- Glucoronidine conjugates excreted in urine



Dosages

- $Induction_{IV}$: 1-2mg/kg
- $Induction_{IM}$: 3-5mg/kg → “dart”
- 10-20mg IV bolus in combination with midazolam (1-2mg) for sedation or as an adjunct to MAC anesthesia or a “spotty” regional
- **KETOFOL** – mixture of ketamine or propofol for MAC anesthesia

Ketamine

Pharmacodynamics: CNS

- Produces dissociative state – “cataleptic state”
  - Recipient will appear conscious by will be unable to process or respond to stimuli, even noxious
  - Eyes may be open → nystagmic stare common
  - Purposeful and non-purposeful movement noted, independent of surgical stimulation
  - Noncommunicative, even though patient may appear awake
- Salivation and lacrimation
  - May be attenuated with anticholinergic drugs such as glycopyrrolate

Ketamine

Pharmacodynamics: CNS

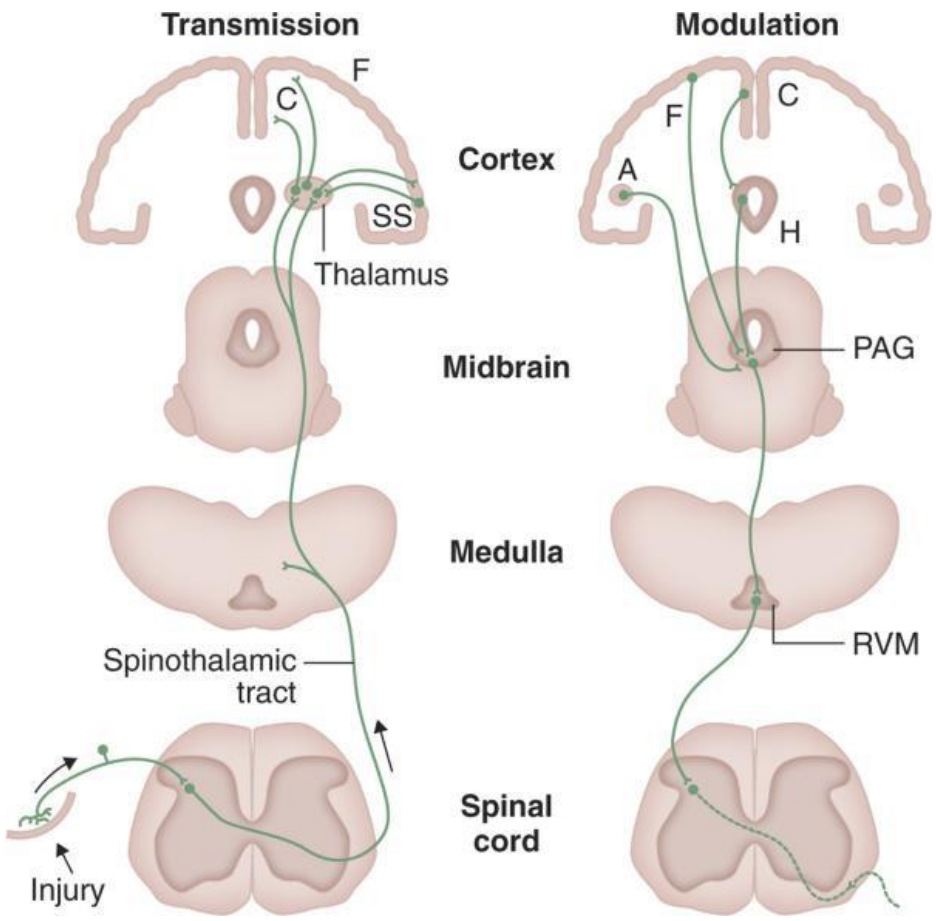
- ↑ **CBF, ICP, and CMRO2**
  - Avoid in increased ICP
- Emergence reactions
  - Causes unpleasant hallucinations, vivid dreams, and delirium
    - Reason it is not used more widely
  - Observed least often in pediatrics (younger) and patients that receive benzodiazepines
  - Usually associated with larger doses - **> 2mg/kg**
- ↑ **IOP (do not use with narrow angle glaucoma)**
- Cerebral reactivity to CO2 and autoregulation are maintained
- “Brain protection” is being researched – possible

Ketamine

Pharmacodynamics: CNS/analgesia

- **Significant effects even at sub-anesthetic doses, like 0.5mg/kg**
- Outlasts dissociative state
- Can occupy opioid receptors in brain and spinal cord → this is controversial
- **Blocks glutamate at spinal cord**
  - Antagonism of glutamate at the NMDA receptor
  - This is the major mechanism for transmission of pain impulses → pain happens but brain doesn't process it

Pain transmission



- 1st neuron begins in periphery and ends in SC
- Synapses with a second neuron that then travels to the brain

Pain transmission

Central sensitization

- Process by which neurons have a greater response to a stimulus
- **The threshold for depolarization of 2nd order neuron is decreased, making it more likely to reach AP**
- The perceptive field of the 2nd order neuron is widened
- Response of the dorsal horn (2nd order neuron) is increased → known as "**windup**"
  - Result is hyperalgesia – pain perception increased to the same noxious stimuli
- **Glutamate is the primary neurotransmitter involved**

Ketamine

Pharmacodynamics: Cardiovascular

- Stimulates SNS and inhibits the reuptake of norepinephrine, resulting in:
  - ↑ BP, HR, and CO (by approximately 20%)
  - ↑ PAP
  - ↑ myocardial oxygen consumption
    - Avoid in patients with severe CAD, CHF, uncontrolled HTN, and arterial aneurysms
- Great agent for hypovolemic patients
- CV stimulatory effects can be attenuated with benzodiazepines

Ketamine

Pharmacodynamics: Cardiovascular

- Possesses myocardial depressant effects
  - Usually masked by SNS stimulation
  - In a patient who is maximally sympathetically stimulated (like a trauma patient or severe CHF), they may show signs of myocardial depression (like hypotension) after administration

Ketamine

Pharmacodynamics: Respiratory

- K has **minimal effect on respiratory system**
  - Apnea possible with large doses or rapid administration
  - Unlike other hypnotics, K has no effect on ventilatory response to CO_2 and causes minimal change in minute ventilation
- **Potent bronchodilator** – similar in efficacy to VAs
- Maintains upper airway reflexes
- Good agent to use when you desire that the patient remain spontaneously ventilating → MAC or with an **awake FOI**

Ketamine

Pharmacodynamics: Miscellaneous

- Associated with moderate incidence of:
  - PONV
  - Psychotic emergence reaction – 10-15%
    - Severely limits popularity
    - Worse in young adult males
- No pain on injection
- **Not a trigger for MH**

Negative effects are not typically observed unless the total dose exceeds 1mg/kg IV

Ketamine

Traditional uses

- Induction of:
  - Patients with hemodynamic shock
  - Patients with asthmatic disease
- Sedation of:
  - Uncooperative patients → IM dart
  - ICU patients
- Supplementation of incomplete regional or local anesthesia
- Short, painful procedures → dressing changes in burn patients

Newer uses

- Preemptive analgesia and to assist with postoperative pain control
  - 0.25-0.5mg/kg
  - Not as concerned with CNS reactions with lower dosage
- Opioid tolerance

Opioid Free Anesthesia: Ketamine

- Induction: 0.3 - 0.5 mg/kg
- Maintenance: 2 - 10 mcg/kg/min
  - 0.1 - 0.6 mg/kg/hr
- PACU: 0.1 - 0.3 mg/kg/5 minutes
- *This infusion can be used in conjunction with a combination of other infusions and medications*

Drug interactions

- **Potentiates NDMBs**
- Theophylline and ketamine when administered concomitantly can predispose a patient to seizures
- **SNS antagonists unmask the myocardial depressant effect of ketamine**
- Lithium may prolong duration

Multimodal analgesia protocol for TKA

Preoperative	Intraoperative	PACU	Floor
• Oxycodone 10-20mg PO	• Decadron 8mg IV	• Acetaminophen 1000mg IV	• Ketorolac 15mg IV Q6h X 4 doses only
• Celecoxib 400mg PO	• Ketamine 0.25mg/kg IVP	• If not dosed with EXPAREL, start INC infusion	• Acetaminophen 1000mg IV TID
• Gabapentin 600mg PO	• Ketamine infusion 4mcg/kg/min		• Celecoxib 200mg PO BID
			• Gabapentin 300mg PO BID
			• Hydromorphone PCIA
			• Oxycodone 5-10mg PO Q4h for breakthrough pain
			• Oxycodone 10-20mg PO BID X 4 doses only

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