Why Ketamine?

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Objectives

- Be familiar with the pharmacology, dosing, and administration of Ketamine
- Understand the indications, contraindications, benefits, and side effects of Ketamine
- Know the various uses of Ketamine and its abuse potential

History

- Developed in early 1960s and FDA approved in 1970
- First used in soldiers in Vietnam War for warfare surgical procedures
- Classified as schedule III drug August 1999
- Outlawed in United Kingdom January 2006

History

- According to DEA, 80% seized is from Mexico
- Most commonly used in clubs at raves
- 2002 statistic, almost 3% of 12th grade students admitted to using ketamine in the last year

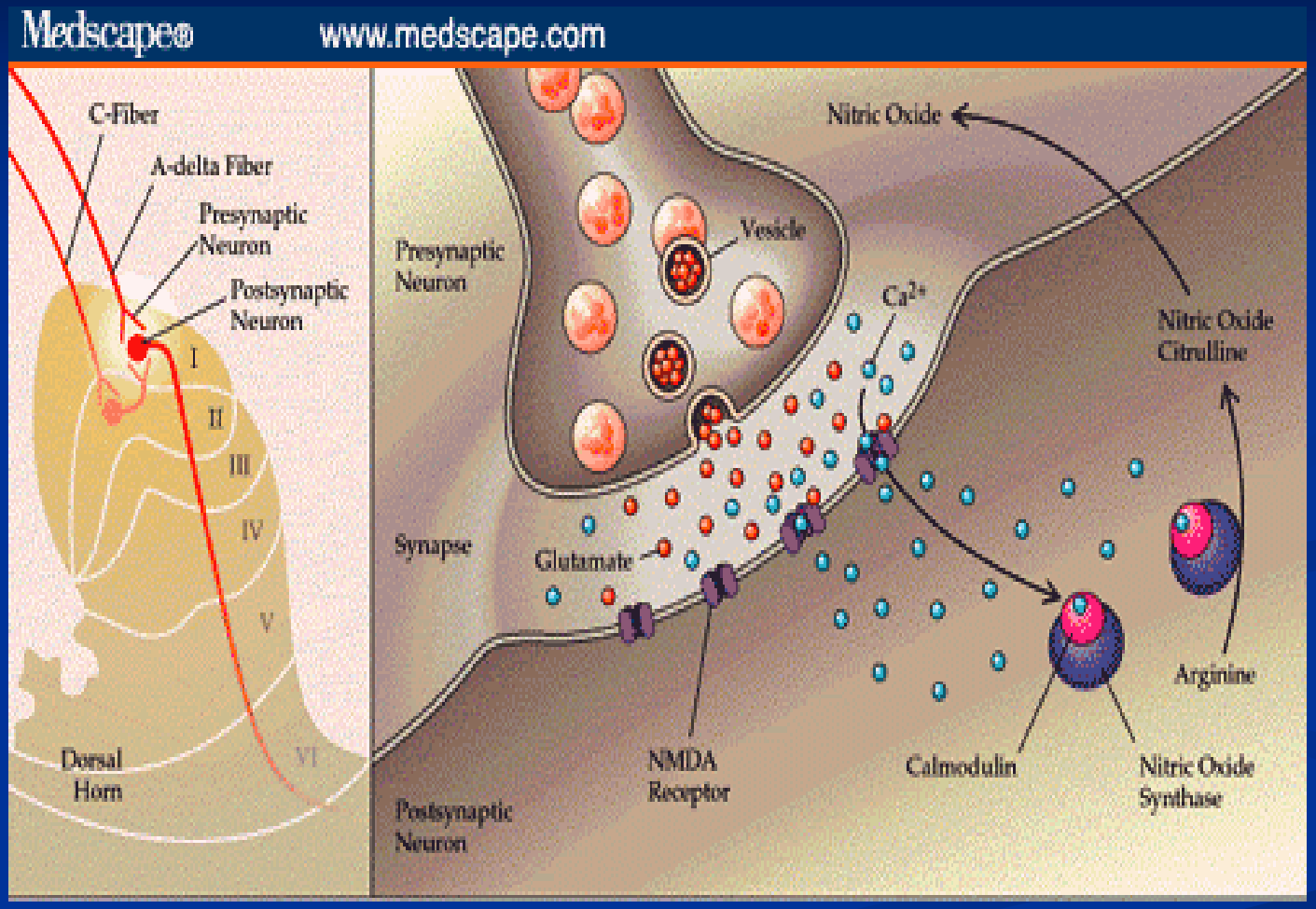
Rave?

History

- The Scientist by John Lilly
- Journeys into the Bright World by Marcia Moore and Howard Alltounian
- The Essential Psychedelic Guide by D.M. Turner

Pharmacology

- Dissociative anesthetic and analgesic that binds the phencyclidine (PCP) site
- Noncompetitively blocks the excitatory NMDA-glutamate receptor, a calcium channel in the transmission of pain signals via dorsal horn
- NMDA receptor plays a role in opioid tolerance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C-Fiber
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Presynaptic Neuron
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I
II
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Vesicle
Nitric Oxide
Ca2+
Nitric Oxide Citrulline
Synapse
Glutamate
Arginine
NMDA Receptor
Calmodulin
Nitric Oxide Synthase
Postsynaptic Neuron

Pharmacology

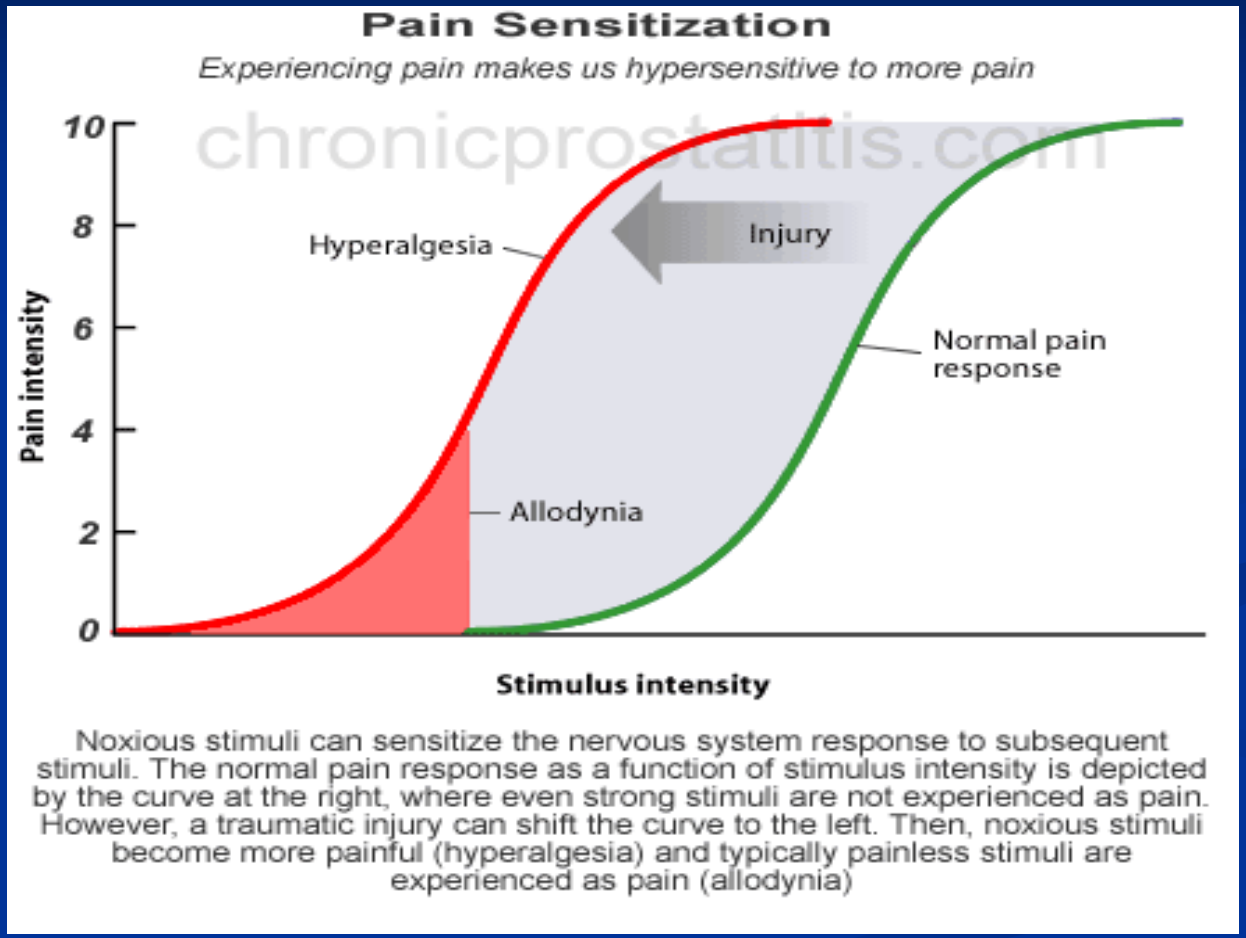
- Also interacts with other calcium and sodium channels, dopamine receptors, cholinergic transmission, noradrenergic and serotoninergic reuptake, mu/delta/kappa opioid receptors, monoaminergic and muscarinic receptors, and possibly GABA receptors

- **= DIRTY DRUG**

Pharmacology

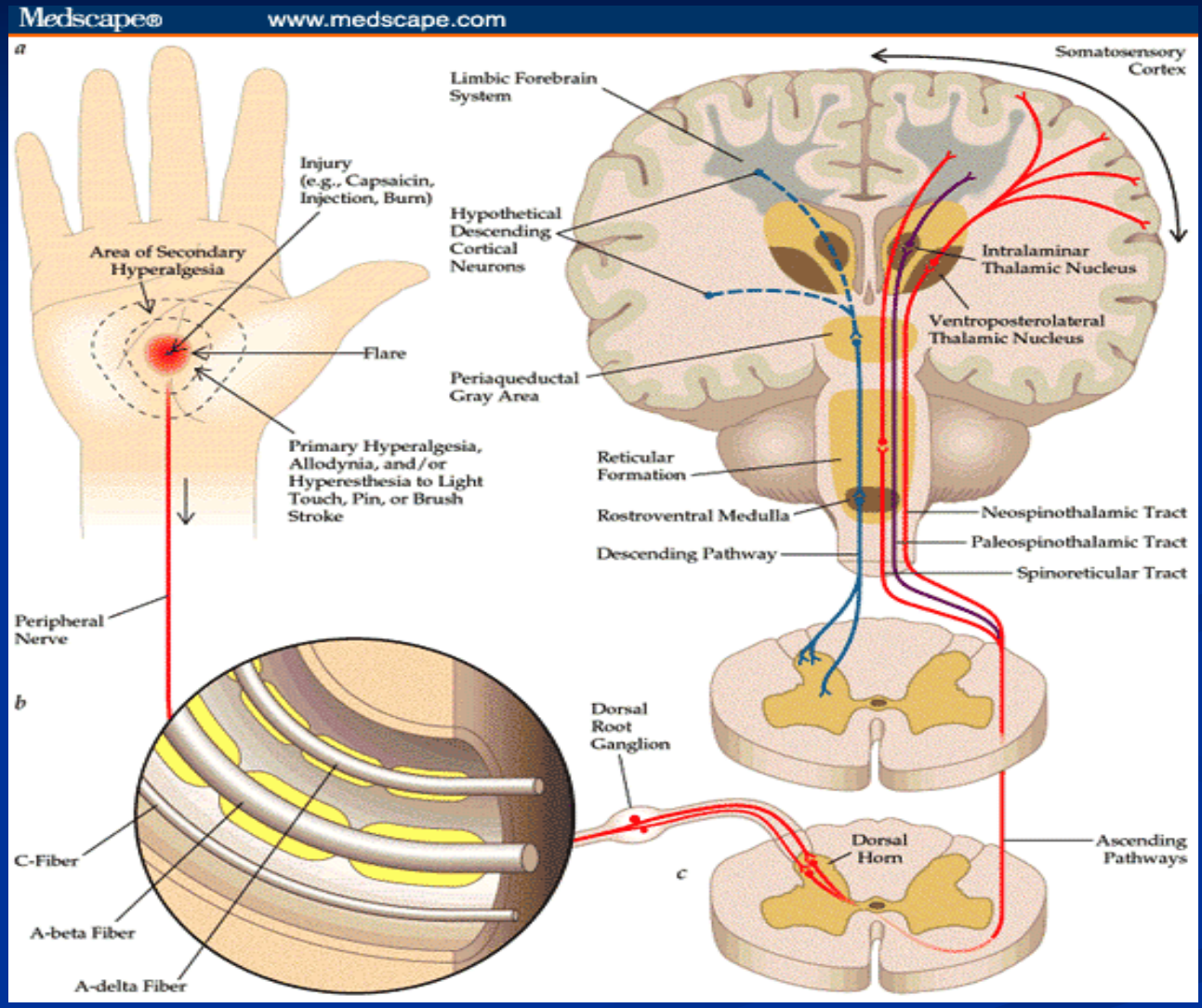
- **Central sensitization:** persistent noxious stimuli lead to progressively higher pain intensity via NMDA receptor hyperexcitation

- **Wind up phenomenon:** repeated transmission of nociceptive stimuli resulting in summation of the stimuli with co-release of excitatory amino acid and slow lasting potentials leading to hyper-responsive spinal neurons and decreased opioid responsiveness


Pain Sensitization
Experiencing pain makes us hypersensitive to more pain
chronicprostatitis.com
10
8
6
4
2
0
Pain intensity
Hyperalgesia
Injury
Normal pain response
Allodynia
Stimulus intensity
Noxious stimuli can sensitize the nervous system response to subsequent stimuli. The normal pain response as a function of stimulus intensity is depicted by the curve at the right, where even strong stimuli are not experienced as pain. However, a traumatic injury can shift the curve to the left. Then, noxious stimuli become more painful (hyperalgesia) and typically painless stimuli are experienced as pain (allodynia)

Pharmacology

- **Hyperalgesia:** an exaggerate pain response to mildly noxious stimuli
- **Secondary hyperalgesia:** perception of pain outside the area initially injured
- **Allodynia:** pain elicited by non-noxious stimuli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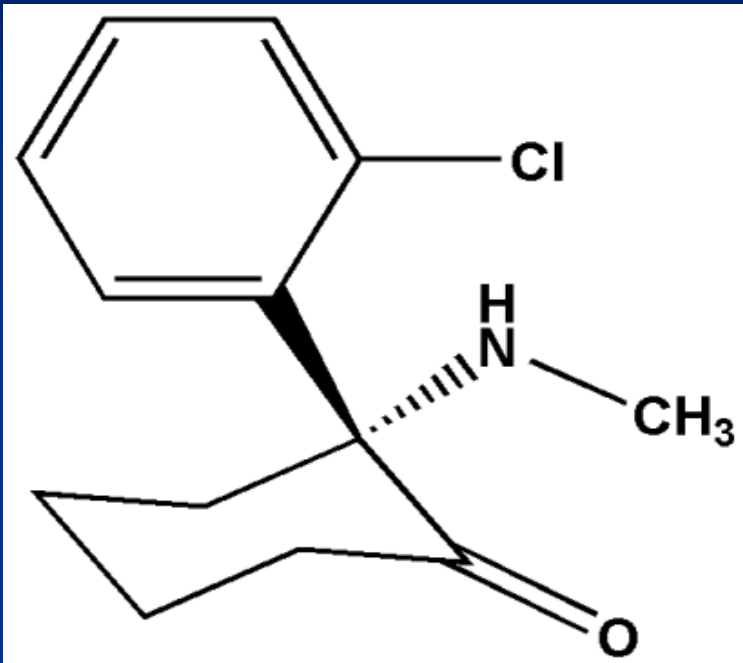
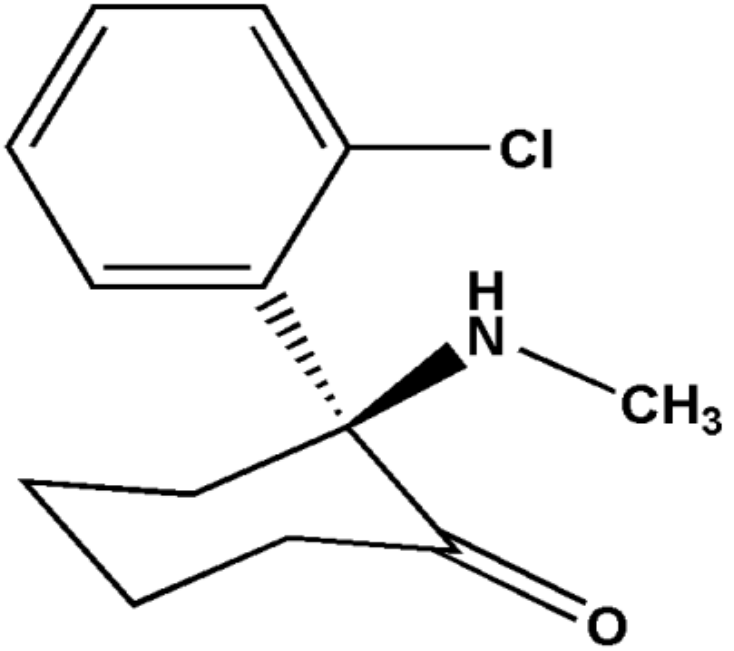
a
Injury
(e.g., Capsaicin,
Injection, Burn)
Area of Secondary
Hyperalgesia
Flare
Primary Hyperalgesia,
Allodynia, and/or
Hyperesthesia to Light
Touch, Pin, or Brush
Stroke
Peripheral
Nerve
b
C-Fiber
A-beta Fiber
A-delta Fiber
Limbic Forebrain
System
Hypothetical
Descending
Cortical
Neurons
Periaqueductal
Gray Area
Reticular
Formation
Rostroventral Medulla
Descending Pathway
Somatosensory
Cortex
Intralaminar
Thalamic Nucleus
Ventroposterolateral
Thalamic Nucleus
Neospinothalamic Tract
Paleospinothalamic Tract
Spinoreticular Tract
Dorsal
Root
Ganglion
c
Dorsal
Horn
Ascending
Pathways

Pharmacology

- Mostly a racemic mixture of two stereoisomers: R(-) and S(+)
- S enantiomer is 4 times more potent than R enantiomer and twice as potent as mixture
- S(+) produces longer hypnosis, greater BP and HR, less locomotor activity, shorter recovery time



(S)-Ketamine



(R)-Ketamine

Pharmacology

- **Metabolism:** 80% first pass hepatic metabolism
- **Metabolite:** norketamine is 1/3 as potent as parenteral form as anesthetic but equipotent as an analgesic
- **Bioavailability:** ranges from 93% IM to 16% PO
- **Excretion:** in the urine primarily

Pharmacology

- **Onset of action:**
  IV=30sec, IM=3-5min, SC=15-30min, PO=30min
- **Duration of action:**
  IV=5-10min, IM=12min-2hr, PO=4-6hr
- **Half life:** 3 hours
- **Steady state:** 12-15 min

Pharmacology

- No adjustment needed for renal impairment, and insufficient data for liver impairment
- Binding is less in elderly, so dose reduction would be reasonable
- Avoid in pregnancy and breastfeeding, no data

Pharmacology

- **Adverse drug reactions:** clonidine, anticholinergics, benzodiazepines, barbiturates, risperidone, opioids, anesthetics, alcohol
- Generic ketamine 50mg/ml in 10ml vial ($17.70) vs. Ketalar ($33)
- 100ml of 50mg/5ml solution for IV: 2x10ml ketamine vials (50mg/ml) + 80ml purified water

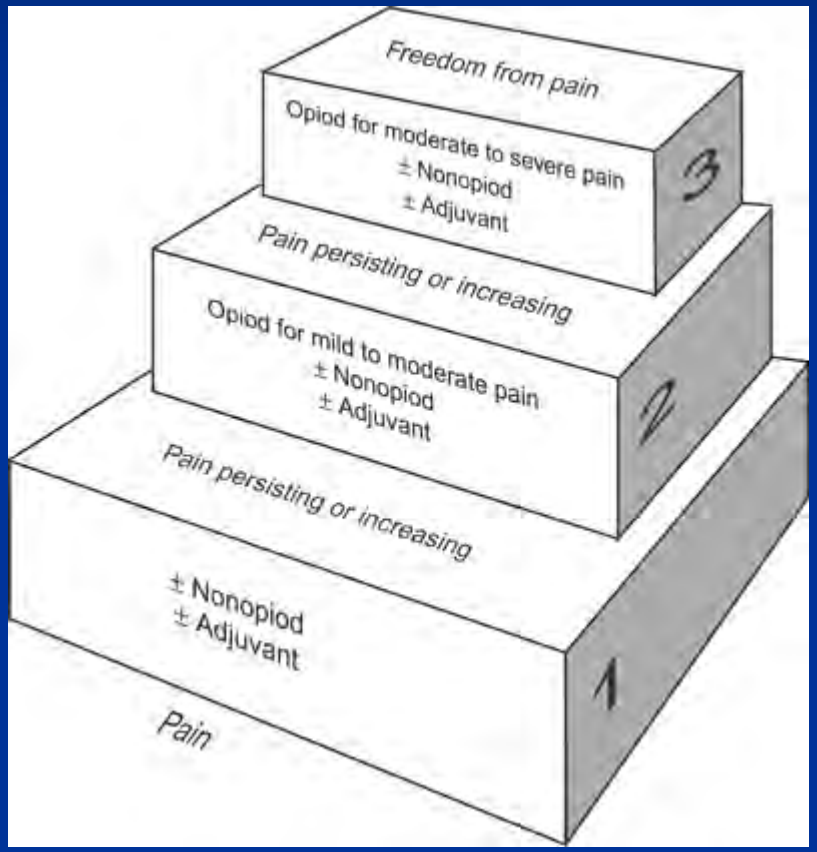
Indications

- Induction and maintenance anesthesia
- Pain unresponsive to standard treatment
- Failure of opioid rotation
- Severe neuropathic pain
- Opioid tolerance based on rapid escalation
- Bronchospasm in asthma and COPD
- Depression in bipolar disorder
- Minor procedures
- Migraine headaches

Contraindications

- Increased blood pressure
- Increased intracranial pressure
- Acute intermittent porphyria (induces ALA syn)
- Current or history of psychiatric disorder, seizures, glaucoma, heart failure, ischemic heart disease, CVA, severe hepatic impairment, severe neurologic impairment

WHO Ladder



← Is there a place for Ketamine?

Pros

- Can be given PO, IV, IM, SL, SC, PR, intranasal, transdermal, topical, and epidural, intrathecal
- Can be applied directly to the skin as an aerosol spray to wounds
- Can be used as an oral rinse for mucositis

Pros

- Opioid sparing effect leads to reduced opioid requirement and opioid associated side effects
- May prevent opioid tolerance and reduce central sensitization and hyperalgesia
- May have anti-inflammatory effects

Pros

- Excellent analgesia with limited respiratory depression
- Patient can remain awake and breathe unassisted but not aware
- Used in ICU for prolonged status epilepticus

Pros

- Recent use in treatment of alcoholism, heroin addiction, and depression
- Rapid onset and minimal side effects at subanesthetic doses
- Small dose ketamine has been shown useful and safe as additive to standard opioid therapy in 54% of studies (A&A 2004)

Cons

- There are not sufficient DBRCT studies showing efficacy as an analgesic, but numerous case reports and small trials
- Concern for withdraw and associated hyperalgesia and allodynia upon sudden cessation
- Significant number of clinical trials 45% demonstrated no benefit to adding ketamine to opioids explained by the nature of the procedure, degree of post-op pain, and method of administration

Cons

- Should require informed consent
- Requires close monitoring
- Irritation to SC site
- Crosses the blood brain barrier
- Bitter taste
- Concern for side effects

Cons

- Studies have shown no benefit when added to opioid PCA after major abdominal surgery
- Ineffective in intrathecal route, peripheral regional use, local anesthesia, intra-articular, nerve block, and would infiltration
- Preemptive and postoperative benefits have been difficult to determine with conflicting results and many different kinds of surgeries

HOLIDAYS

Pain

- Post spinal cord injury chronic pain
- Sickle cell vaso-occlusive pain
- Chronic post surgical pain
- Major surgery with high opioid requirement

Pain

- Pre and post incisional
- Chronic regional pain syndrome I
- Fracture reductions
- Calciphylaxis

Pain

- Incident pain from movement
- Opioid refractory pain
- Neuropathic pain: post-herpetic neuralgia, trigeminal neuralgia, spinal cord injury, phantom limb pain, limb ischemia, fibromyalgia, multiple sclerosis, Guillain-Barre syndrome
- Chronic abdominal pain such as pancreatitis and angina

Pain

- Chronic neck, back, and leg pain
- Migraine headaches
- Cancer related pain in children and adults
- Painful dressing changes such as burns

How much do we give?

Let's look at the evidence . . .

Trials and Case Series

Fine JPSM 1999 (2 case reports):

- Ketamine bolus 0.1-0.2mg/kg IV or 0.5mg/kg SC or IM
- After 15 minutes if no relief double dose
- Continue to reassess and increase dose until pain relief or undesirable side effects occur
- Convert to constant IV infusion
- Decrease opioid by 50% every 6-12 hours as tolerated
- Rebolus and increase infusion as needed

Trials and Case Series

Mercadante JPSM 2000 (DBRCT):

- On 3 separate days, 2 days apart, 10 patients given slow bolus of either 0.25mg/kg vs. 0.50mg/kg vs. normal saline
- Ketamine, but not saline, significantly reduced pain in almost all patients at both doses

Berger AJHPC 2000 (small trial):

- IV K-F-M 2mg/ml - 5ug/ml - 0.1mg/ml at rate range of 2-12ml/hr
- All 9 patients showed improvement

Trials and Case Series

Reeves A&A 2001 (DBRCT):

- 71 patients either received morphine 1mg/ml or morphine 1mg/ml + ketamine 1mg/ml via PCA
- Post-op, there was no difference except worse cognitive testing in the MK group

Jackson JPSM 2001 (unblinded trial):

- 39 patients received 3-5 day ketamine infusion at 100mg/24h for 3 days or increased to 300mg/24h for 3 days or increased to 500mg/24h for 3 days
- Overall response rate of 67%

Trials and Case Series

Kannan JPSM 2002 (small trial) :

- 0.5mg/kg three times daily PO as adjuvant
- 7/9 patients showed improvement

Mitchell Pain 2002 (DBRCT):

- 35 patients received either Opioids + ketamine infusion (0.6mg/kg) vs. opioids + placebo over 4 hours
- OK group (16/28) showed statistically significant difference in pain improvement

Trials and Case Series

Fitzgibbon JPM 2005 (retrospective audit):

- Ketamine was effective in 11/16 patients with range of use from 1-120 days
- Starting dose of 40-90mg/24h increased by 50-100mg/24h every 24 hours with stable dose of 50-768mg/24h

Lossignol SCC 2005 (small trial):

- 12 patients received a test dose of 5mg and if tolerated were given starting dose of 1.5mg/kg/24h
- Final doses ranged from 195-1000mg/24h with duration of treatment ranging from 7-350 days
- Pain control remained acceptable in 11/12 patients

Trials and Case Series

Polizzotto JPSM 2006 (case series):

- Calciphylaxis patients received doses ranging from boluses of SC ketamine 50mg for dressing changes and continuous infusions of 300-500mg/24hr

Finkel JP 2007 (small trial):

- 8/11 children on adjuvant ketamine infusion had opioid sparing effects, improvement of pain, and more family interaction
- Doses ranged from 0.1-1mg/kg/hr and duration ranged from 1-75 days

Trials and Case Series

Mercadante CJP 2009 (2 case reports):

- Opioid switching from morphine to methadone and burst ketamine in incident pain
- 2 day infusion of ketamine 100mg/d then stopped, continued on methadone, and D/C

Schwartzman Pain 2009 (DBRCT):

- 19 CRPS patients infused with saline with or without ketamine (50mg/h) 4 hours/day for 5 days on, 2 days off, 5 days on
- Ketamine group had statistically significant reduction in many pain parameters

Trials and Case Series

Zempsky CJP 2010 (retrospective case review):

- 5 children received ketamine infusion for Sickle Cell pain (4 with opioids and 1 in place of)
- 2 patients has significant pain control and 1 patient had significant opioid reduction
- Dose ranged from 0.06-0.2 mg/kg/h and duration ranged from 19-90 hours

Amr Pain Physician 2010 (DBRCT):

- 40 patients randomized to ketamine + gabapentin and placebo + gabapentin
- Ketamine dose 80mg IV over 5hours daily for 7 days
- KG group showed significant improvement over PG group during infusion and 2 weeks after

Trials and Case Series

Irwin JPM 2010 (case series):

- 2 cases of anxiety and depression treated with ketamine
- 0.5mg/kg PO single dose

PORTRAITS

Dosing

- Initial test dose given to assess tolerability and efficacy
- Some give prophylactic concurrent benzodiazepine or antipsychotic
- Often mixed with other drugs such as opioids
- Opioid dose should be reduced by 25-50% with parenteral ketamine
- Conversion: after few days CSCI=PO, after weeks to months 25-50%CSCI=PO

Dosing

PO:

- 10-25mg TID-QID and prn, increase by 10-25mg increments up to 200mg QID
- Or weight based 0.25-0.5mg/kg TID
- Give smaller more frequent doses if side effects occur
- Direct from vial or diluted mixed in tasty liquid

Dosing

SL:

- 10-25mg, do not swallow for 2 minutes
- Use higher concentrations to minimize volume

SC:

- 10-25mg prn
- Increase in increments of 25-33%

IV:

- 0.5-1mg/kg
- Give over 1-2 minutes preceded by benzodiazepine

Dosing

CSCI:

- Dilute in large volume to avoid site irritation
- 1-2.5mg/kg/24h
- Increase by 50-100mg/24h, max dose 3.6g/24h
- Some use loading dose 0.5mg/kg over 30 min, followed by continuous 2mg/h
- Some just start with 100mg/24h, “burst”
- Increase to 300mg/24h, then 500mg/24h and stop 3 days after last increment

Dosing

CIVI:

- 50-200microgram/kg/h and titrate
- Single burst 600micrograms/kg up to 6mg/4h
- Increase next dose by 30% if no response
- Repeat daily for up to 5 days
- Various titration techniques reported
- Some start with 0.1mg/kg and double Q15min
- Others start at 10mg/h and titrate up from there


Ketamine
So good,
the horses want it back

Side Effects

euphoria, dysphasia, blunted affect, psychomotor retardation, vivid dreams, nightmares, impaired attention, memory problems, impaired judgment, illusions, hallucinations, altered body image, delirium, dizziness, diplopia, blurred vision, nystagmus, altered hearing, hypertension, tachycardia, hypersalivation, nausea, vomiting, erythema, pain at injection site, fatigue, increased muscle tone, increased pulmonary artery pressure

Side Effects

slurred speech, confusion, disorientation, hypotension, bradycardia, respiratory depression, apnea, malignant hyperthermia, agitation, coma, seizure, laryngospasm, bronchorrhea, arrhythmia, increased intracranial pressure, morbilliform rash, anorexia, anaphylaxis, out-of-body experience, sedation, euphoria, sense of calm and serenity, increased energy, open and closed eye visuals, meaningful spiritual experiences, ataxia

Side Effects

- For analgesic doses, impaired attention, memory, and judgment
- Occur less with subanesthetic dose given PO or CSCI and seem to be dose related
- Can be controlled with concurrent benzodiazepine or haloperidol

Side Effects

- Can be reduced by slowing dose titration and providing medications for side effects
- Occur more often in the elderly, in women, and patients with anxiety disorders
- Chronic use leads to cognitive impairment

Urinary Side Effects

Urinary Toxicity

- Frequency, urgency, dysuria, hematuria
- Suprapubic pain, “K-pains” and “Ketamine Cramps” usually with greater than 1gm/day
- Interstitial cystitis, detrusor overactivity, decreased bladder capacity
- Vesico-ureteric reflux, hydronephrosis, papillary necrosis, renal impairment, renal failure

Urinary Toxicity

- Urinalysis negative for bacteria or sterile pyuria
- 20-30% of frequent users of high quantities report bladder symptoms
- Appears to be a temporal link where severity of damage is determined by chronicity of abuse

Urinary Toxicity

- **Cystoscopy:** epithelial inflammation, ulceration, petechial hemorrhage, neovascularization, contact bleeding
- **Histology:** denuded bladder epithelium, eosinophilic infiltration
- **Urography:** shrunken bladder, decreased bladder compliance, detrusor overactivity, papillary necrosis, hydronephrosis

Urinary Toxicity

- Withdrawal of ketamine results in some degree of resolution of symptoms depending on severity

- **Other treatments:** NSAIDs, steroids, anticholinergics, cystodistension, intravesical instillation of hyaluranic acid, oral pentosan polysulfphate, and tyrosine

Nicknames

K
Super K
Vitamin K
Special K
Mean green
Rockmesc
Ket
Kitties
K2
Jet
Super acid
Green
Cat valium
KitKat

Combinations

Strawberry: ketamine + ephedrine + selegiline

Sitting Duck: ketamine + ecstasy

CK1: ketamine + cocaine

Ketamine Abuse

Abuse

- Similar to PCP but with less violent, confused behavior when coming off
- Severe impairment of working, episodic, and semantic memory
- Increased schizotypal and dissociative symptoms
- "K hole": at the brink of being fully sedated, out-of-body or near-death experience
- Desired depersonalization and derealization

Abuse

- Mortality is low
- Consequences are related to dangerous behaviors and accidents
- Used as a date rape drug
- Long term adverse effects: flashbacks, attentional dysfunction, memory impairment, tolerance, high dependency potential

Abuse

- Rapid onset and duration means quick recovery
- Only 4% of dose recovered in urine
- Not included in standard urine toxicology screens
- Blood levels: therapeutic use: 0.5-5mg/L, arrest for impairment: 1-2mg/L, fatal overdose: 3-20mg/L

Abuse

- Powder can be insufflated, injected or oral
- Injection bypasses liver metabolism providing more efficient, smoother high up to 2 hours
- Oral route requires more drug but longer trip without dissociative state
- Onset for injection: 1-5min, snorted: 5-15min, oral: 5-30min

What have we learned?

- A little History and A LOT of Pharmacology
- About Use and Abuse of this mystic drug
- Recent Supportive Evidence in Palliation
- Dosing and Administration and Side Effects
- **Who is ready to give some Ketamine ???**

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