

## Ketamine: Its Role in Acute Pain in the Opioid Tolerant

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### Objectives

- 1. Identify the role of NMDA receptor antagonists
- 2. Recognize how ketamine can be used safely and effectively in acute pain management

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### Off-Label Use

- Use outside FDA approved indication
- FDA allows off label prescribing
- Professional judgment safe and effective

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### Off-Label

- Pharma cannot promote off label use
- FDA does not restrict other parties from discussing or distributing written materials
- Can anyone request a label change?
- Extremely costly and time consuming

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### Opioid Tolerance

- Develops with repeated use of opioids
- Need to increase dose to maintain equipotent analgesic effects
- Expected physiologic occurrence
- Does not imply or cause addiction

Ballantyne, J. NEJM 2003; 349:1943-1963  
deLeon-Casasola, O. Clinical Anaesthesiology. 16(4):521-5, 2002 Dec.

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### Cellular Mechanisms of Tolerance

- Uncoupling of G-proteins from opioid receptors
- Down regulation of opioid receptors
- Activation of *N*-methyl-D-aspartate (NMDA) receptor

Gintzler, A. et al. *Molecular Neurobiology* 21(1-2):21-33, 2000.  
Smith, H.S., *Drugs for Pain*. 2003. pp. 153-155.  
Ballantyne, J., *NEJM*. 2003;349: 1943-53

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## Opioid Induced Hyperalgesia

- Abnormally intense or prolonged pain
- Likely up-regulation of compensatory pronociceptive pathways
- May aggravate pre-existing pain
- Does develop in humans

Angst M, Clark D. *Anesthesiology*. 2006; 104: 570-587.

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## Glutamate

- Major excitatory amino acid
- Interaction with receptors essential for CNS function
- Activates the NMDA receptor

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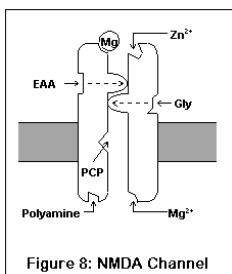
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## N-methyl-D-aspartate Receptor



- Glutamate receptor
- Involve ion channel
- Distinct binding sites
- Ketamine binds to PCP

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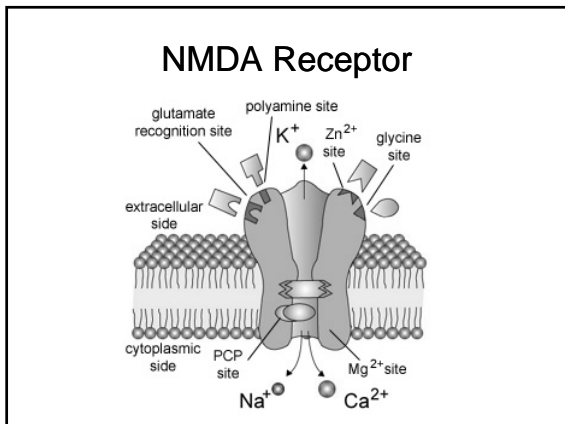
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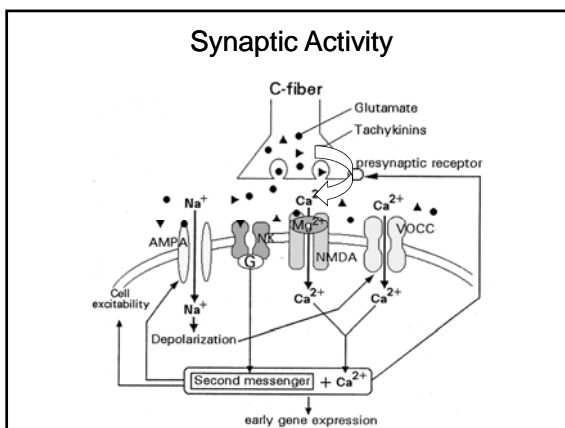
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### NMDA Receptor Antagonist

- Inhibit the normal function of the receptor
- Interrupts flow through ion channel
- Decreased transmission of nociceptive information

Santiago-Palma J, Smith H, Sang, C. *Drugs for Pain*. Haley & Belfus 2003: 241-53

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## NMDA Receptor Antagonists

- ketamine
- dextromethorphan
- amantidine/memantine
- magnesium

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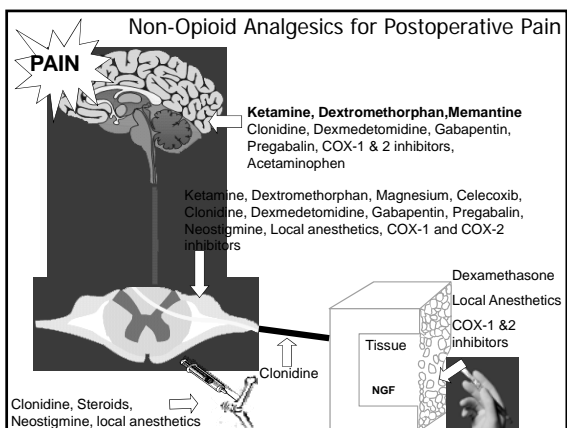
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## Dextromethorphan

- Most readily available NMDA receptor antagonist
- Antitussive approved in 1958
- Reduced pain intensity<sup>1,2</sup>
- Reduced analgesic requirements<sup>1,2</sup>

Weinbroum A. et al. *Anaesthesia* 2001; 56 (7): 616-22<sup>1</sup>  
Weinbroum A. *Anaesthesia & Analgesia* 2002 94(6): 1547-52<sup>2</sup>

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## Dextromethorphan

- Less psychotomimetic effects<sup>1</sup>
- Anti-hyperalgesic effect<sup>2</sup>
- Safe to be an adjuvant<sup>3</sup>
- Study results inconsistent<sup>3</sup>
- Didn't recommend for post op pain<sup>3</sup>

<sup>1</sup>LePage, KT et al. Neuropharm. 2005; 49: 1-16.

<sup>2</sup>Duedahl, T. et al Pain 2005; 113 (3): 360-368.

<sup>3</sup>Duedahl, T. et al Acta Anaesth Scand. 2006; 50 (1): 1-13

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## Amantadine

- Low affinity NMDA channel blocker
- Anti-viral, Parkinson's
- Did not reduce pain scores in TAH pts.<sup>1</sup>
- Reduced IV PCA morphine consumption<sup>2</sup>
- Lower VAS scores around wound<sup>2</sup>

Gottschalk et al. Anesth & Analg. 2001; 93:192-6.<sup>1</sup>  
 Snijdelaar D. et al. Anesth 2004; 100 (1): 134-141.<sup>2</sup>

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## Magnesium

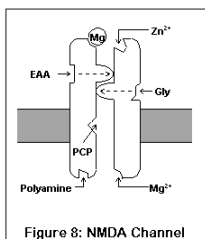


Figure 8: NMDA Channel

- Magnesium blocks ion channel
- Reduced opioid consumption<sup>1</sup>
- Intrathecal-prolonged analgesia<sup>2</sup>

Ozcan, P et al. J Cardiothoracic & Vascular Anesthesia.2007; 21(6): 827-31<sup>1</sup>  
 Buvanendran, A et al. Anesth & Analg 2002; 95(3): 661-6<sup>2</sup>

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### Ketamine

- Dissociative anesthetic, Schedule III
- Used in human and veterinary medicine
- Analgesic mechanisms centrally and peripherally<sup>1</sup>
- Reversal of opioid tolerance involve interaction between NMDA, nitric oxide pathway &  $\mu$ -opioid receptors<sup>2</sup>

Kohrs R, Durieux ME. *Anesth Analg*. 1998; 87:1186-93  
Mao J et al. *Pain* 1995; 62: 259-274

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### Ketamine

- FDA label
  - General anesthesia; Adjunct
  - Procedural sedation
- Crosses placenta
- WHO-compatible with breastfeeding
- Thompson-can't rule out infant risk
- Metabolized by liver- half life 2.5hr.
- Pharyngeal & laryngeal tone maintained

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### Levels of Evidence

- Level I- systematic review of randomized controlled trials-meta analysis
- Level II- one or more well designed randomized controlled trials
- Level III-non randomized or cohort or case controlled analytical studies (multi-center)
- Level IV-opinions of respected authorities based on clinical experience, descriptive studies, or expert committies

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### Ketamine

- Reduces morphine requirements<sup>1</sup>
- Adverse effects mild or absent<sup>1</sup>
- Reduced post op nausea and vomiting<sup>1</sup>
- Reduced post op pain in opioid tolerant spinal fusion patient<sup>2</sup>

Bell, R.F. et al. *Acta Anaesthesiol Scand.* 2005; 49:1405-1428 (Cochrane review)<sup>1</sup>  
Urban, M. et al. *HSSJ* (2008) 4: 62-65. Published online: 12/19/2007. Hospital for Special Surgery.<sup>2</sup>

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### Ketamine

- Attenuated tolerance<sup>1</sup>
- Reduced opioid consumption<sup>1</sup>
- Prevent central sensitization<sup>2</sup>
- Reduces wind up<sup>2</sup>

Kisson, I. et al. *Anesth Analg.* 2000; 91:1483-1488.<sup>1</sup>  
Woolf, C.J, Thompson, SWN. *Pain.* 1991; 44: 293-299.<sup>2</sup>

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### Ketamine

- Low dose useful and safe in 54% studies
- Consider as additive in post op opioid tolerant
- Best used as continuous infusion
- Adding to PCA morphine not useful
- No reduction in opioid side effects
- Low dose not associated with CNS side effects

Subramaniam, K. et al. *Anesth Analg.* 2004; 99: 482-495

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### Ketamine as Multimodal Agent

- In RCT, perioperative ketamine use:
  - Reduces opioid dose by 30%
  - Reduces chronic post surgical pain syndromes<sup>1</sup>
- Dose:
  - 0.1 - 0.5 mg/ kg bolus ± 0.1- 0.5 mg/kg/hr infusion
- Side effects:
  - < 10% of patients had complaints of psycho-cognitive effects<sup>2</sup>

<sup>1</sup>Lavand'homme P et al: *Anesthesiology* 2005; 103: 813-20.  
<sup>2</sup>Visser E et al: *Biomedicine & Pharmacology* 2006; 60: 341

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### Ketamine in Chronic Pain Management

- Not enough evidence to advocate routine use of ketamine in chronic pain
- Lack of enough good quality studies
- Reasonable third line option
- Severe acute on chronic episodes of neuropathic pain use continuous infusions

Hocking G, Cousins, M. *Anesth Analg*. 2003; 97: 1730-1739

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### Ketamine Routes of Administration

- Oral
- Nasal
- Rectal
- Topical
- Epidural, Intrathecal
- Intramuscular
- Intravenous

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### Intranasal Ketamine

- Phase III trials
- Placebo controlled phase II trials
- Moderate – Severe post op pain
- Breakthrough pain
- 10-50mg doses
- No changes in vital signs or O<sub>2</sub> saturation

<http://www.javelinpharmaceuticals.com/pmi150.html>. Accessed 3/21/2009.

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### Considerations

- No dose adjustment for renal failure
- Insufficient data to direct use in liver failure
- Contraindicated in acute porphyria
- No good data for dosing in elderly
- Lack of safety data in pregnancy and breastfeeding
- No data for pts with resp. disease, OSA or cardiac disease

Visser, E et al. *Biomedicine & Pharmacology* 2006; 60: 341-8

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### Considerations

- Ketamine is opioid sparing
- May need to administer a benzodiazepine
- Use controlled administration device
- Administer boluses over 60 seconds

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### Precautions

- Psychosis and schizophrenia
- Post Traumatic Stress Disorder
- Neurological issues (Cranial)- Recent head injury, increased ICP

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### Dosing

- General anesthesia; Adjunct: induction
  - 1 to 4.5mg/kg IV single dose
  - 1-2mg/kg IV infusion at 0.5mg/kg/min
- GA; Adjunct: maintenance
  - 0.1 to 0.5mg/min IV infusion, repeat as needed
  - 0.01 to 0.03mg/kg/min continuous IV infusion
- Procedural sedation:
  - 1-2mg/kg IV over 1-2min, then 0.25-0.5mg/kg q5-10min as needed

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### Sub-anesthetic Ketamine Dosing

- Only to be ordered by those familiar with ketamine
- Literature favors intra-op initiation
  - 0.25-0.5mg/kg single bolus
  - 1 to 6 mcg/kg/min infusion (may continue for a few days)<sup>1</sup>

Carroll, I et al. *Reg Anesth & Pain Medicine*, 2004; 29(6): 576-591

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### Monitoring

- Pre and post bolus pain score, HR, BP, sedation scale
- At least same as opioid monitoring
- Monitor for adverse effects
- Notify physician if psychomimetic effects intolerable

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### Documentation

- Initiation of therapy
- Boluses and rate changes
- Document any side effects

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### Discontinuation of ketamine

- No formal weaning necessary
- Can just stop infusion
- If patient experiencing adverse CNS effects, may continue for several hours

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### Conclusion

- Subanesthetic ketamine safe & effective
- Protocols and dosing vary
- Use will most likely increase
- We have had no adverse events

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### Case Study

- 33 y.o. Iraq war veteran; s/p fall
- Mult. Fractures all four extremities
- Vertebral fx's- back surg. 6 days pre-call
- B/L wrist fusions day of pain consult
- External fixator- R tib/fib fx
- MSContin 30mg q6hr, hydromorphone pca

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### Questions



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