# IV Ketamine and Other Treatment Options

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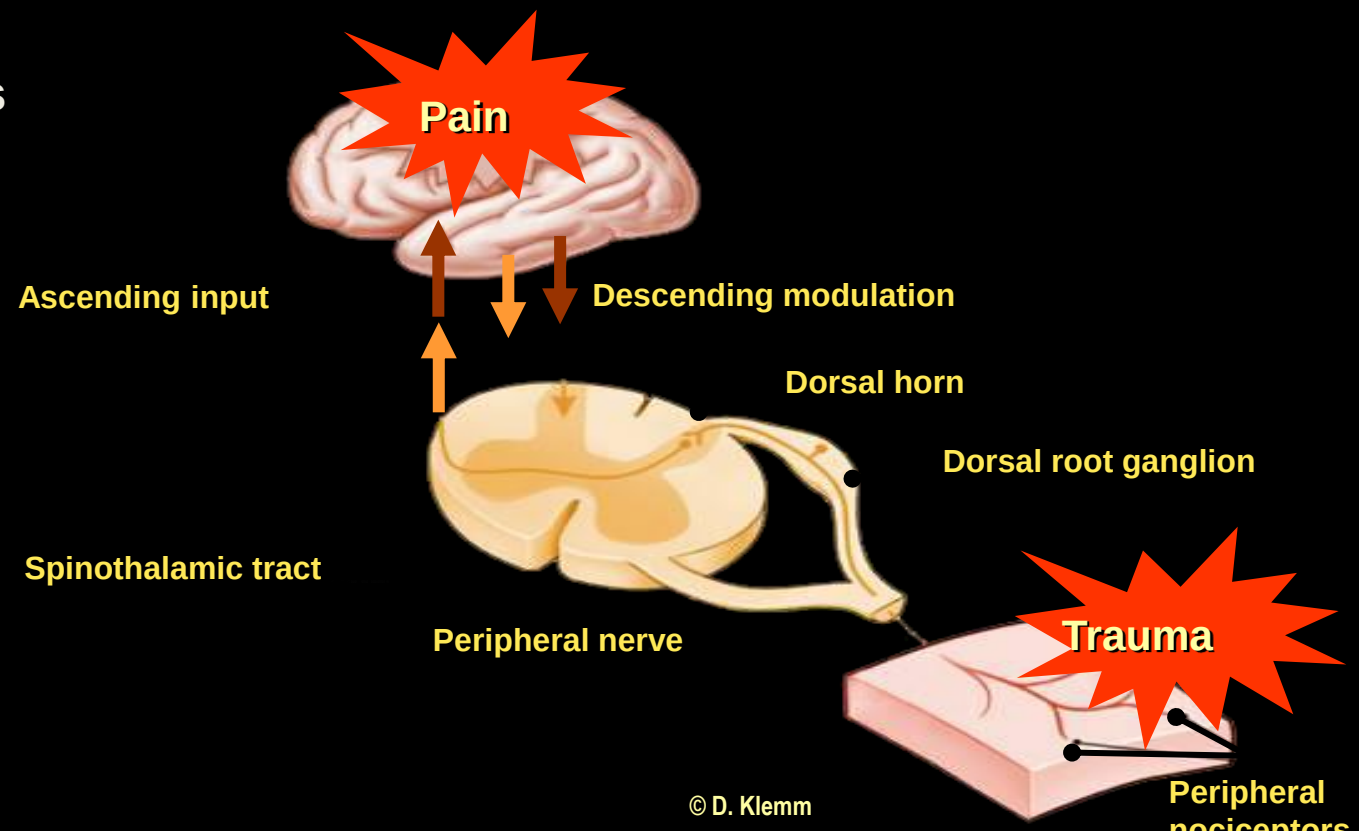
# Disclosure

- Nothing to disclose

# How Is Pain Defined?

- **Unpleasant sensory or emotional experience associated with actual or potential tissue damage[1]**
  - **Individual, subjective experience**
  - **Influenced by patient characteristics**
    - **Culture**
    - **Previous pain experience**
    - **Coping skills**
- **Pain classifications[1,2]**
  - **Duration**
    - **Acute vs chronic**
  - **Pathophysiology**
    - **Nociceptive vs neuropathic**





1. Spacek A. *Biomed Pharmacother.* 2006;60:329-335.
2. Stillman M. *Cleve Clin J Med.* 2006;73:726-739.

# Common Causes of Pain

- Low back pain and arthritis account for half of all musculoskeletal disease diagnoses[1]

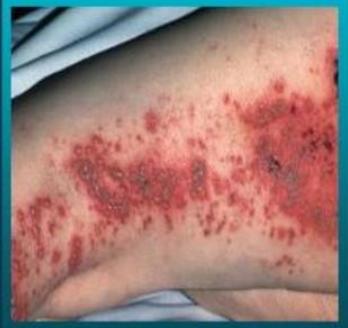
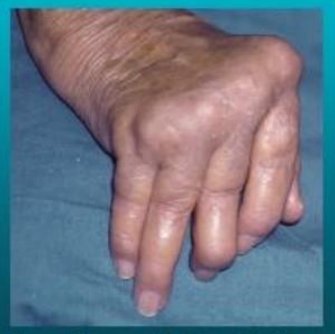
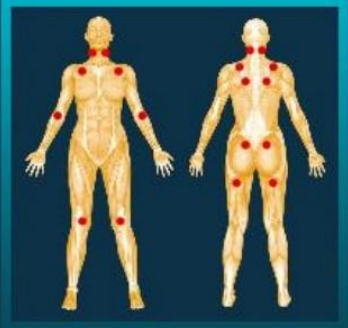
- Low back pain is most commonly reported type of pain[2]
  - Leading cause of disability among Americans <45 years of age[2,3]
  - >26 million adults experience frequent back pain2
  - ~15% of Americans experience back pain lasting >2 weeks[1]

- Arthritis and chronic joint problems affect ~70 million individuals[1]
  - ~18 million affected by osteoarthritis
  - ~2 million suffer from rheumatoid arthritis


1. Emons MF. *Manag Care.* 2003;12(8 suppl):2-7.
2. Pain facts and figures. American Pain Foundation Web site. http://www.painfoundation.org/print.asp?file=Newsroom/PainFacts.htm. Accessed September 12, 2007.
3. Pai S et al. Orthop Clin North Am. 2004;35:1-5

# Types of Pain

## Pain is the most common reason for physician visits[2]

| Nociceptive Pain | Neuropathic Pain | Inflammatory Pain | Central Pain Amplification |
|---|---|---|---|
|  |  |  |  |
| (eg, burns, cuts) | (eg, herpes zoster, pDPN) | (eg, rheumatoid arthritis, psoriatic arthritis) | (eg, FM) |
| Painful Stimuli | Neuronal Damage | Inflammation | Abnormal Pain Processing by CNS |

pDPN=painful diabetic peripheral neuropathy.


1. Woolf C. *Ann Intern Med*. 2004;140(6):441-451.
2. Abbott FV, Fraser MI. *J Psychiatry Neurosci*. 1998;23(1):13-34.

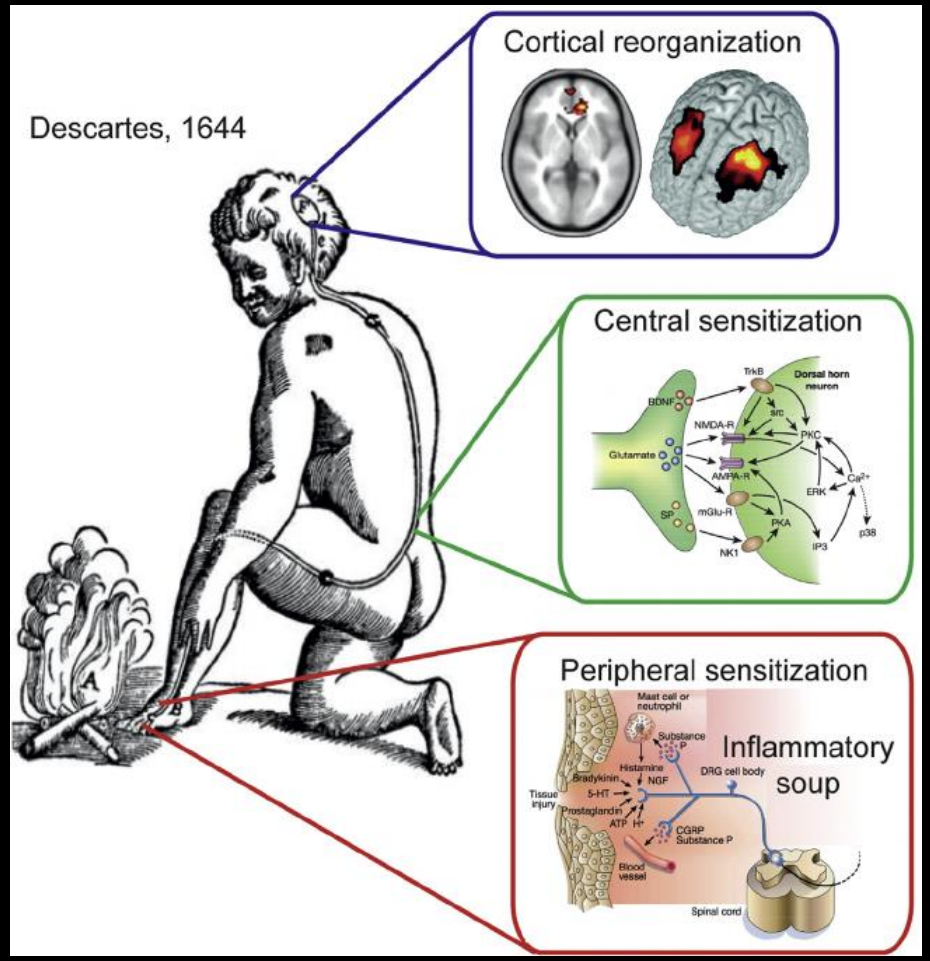
# Interventional Pain Options

- Epidural Steroid Injections (about 25 locations)
- Transforaminal Epidural Steroid Injections (theoretically over 50 locations)
- Facet Medial Branch Block (approximately 60 locations)
- Radiofrequency Ablation (well over 100 locations)
- Joint Blocks (multiple area)
- Nerve Blocks (multiple areas besides TFESI)
- Ganglion Blocks (multiple)
- Intrathecal Pumps
- Spinal Cord Stimulators
- Percutaneous Disc Decompression

# What is Central Sensitization

- Central Sensitization:
  - Increased responsiveness of nociceptive neurons to their normal input, and/or recruitment of a response to normally subthreshold inputs.
- “Wind-Up”:
  - Nervous system stays up-regulated and in a persistent state of high reactivity.
- Central vs. Peripheral
- Organic vs. Inorganic

# What is Central Sensitization




Descartes' Concept of Sensation Illustrates the Pain System and Its Reorganization Based on Modern Rodent Model Physiology and Human Brain Imaging Studies

(A) A stimulus is transmitted to a specific brain region where perception takes place.

(B) System undergoes reorganization following an injury that gives rise to a persistent or chronic pain state.

(C) End-organ injury gives rise to changes locally, collectively described as peripheral sensitization (adapted from Julius and Basbaum, 2001).

(D) Spinal cord circuitry undergoes a large number of changes, resulting in central sensitization (adapted from Scholz and Woolf, 2002), which includes enhanced glutamatergic signaling, changes in second-order messenger processes, and activation of microglia. At the level of the brain, human neuroimaging studies indicate anatomical and functional reorganization.

http://dx.doi.org/10.1016/j.neuron.2015.06.005

# What is Central Sensitization

- Many features of central sensitization resemble those that are responsible for memory.1
- Central sensitization is produced not only by increases in excitability but also by a reduction in inhibitory transmission due to reduced synthesis or action of inhibitory transmitters and to a loss of inhibitory interneurons, which may produce a persistent enhancement of pain sensitivity.2
- It has been suggested that central neuronal sensitization plays an important role in postoperative pain.3

1. Ji RR, Kohno T, Moore KA, Woolf CJ: Central sensitization and LTP: Do pain and memory share similar mechanisms? Trends Neurosci 2003; 26:696–705Ji, RR Kohno, T Moore, KA Woolf, CJ

2. Scholz J, Broom DC, Youn DH, Mills, CD, Kohno T, Suter MR, Moore KA, Decosterd I, Coggeshall RE, Woolf CJ: Blocking caspase activity prevents transsynaptic neuronal apoptosis and the loss of inhibition in lamina II of the dorsal horn after peripheral nerve injury. J Neurosci 2005; 25:7317–23Scholz, J Broom, DC Youn, DH Mills, CD Kohno, T Suter, MR Moore, KA Decosterd, I Coggeshall, RE Woolf, CJ

3. Woolf CJ, Chong MS: Preemptive analgesia-treating postoperative pain by preventing the establishment of central sensitization. Anesth Analg 1993; 77: 362–79Woolf, CJ Chong, MS

# What Causes Central Sensitization

- Potential mechanisms implicated in central sensitization:
  - NMDA receptor activation1
  - Altered gene expression in dorsal horn neurons1
  - Decreased inhibition2
  - Microglial activation3
  - Thalamic and somatosensory cortex changes4


1. Mannion RJ, Woolf CJ: Clin J Pain.2000;16(3):S151-S153.
2. Ossipov MH, et al. Ann NY Acad Sci.2000;909:12-24.
3. Wieseler-Frank J, et al. Neurosignals.2005;14:166-174.
4. Guilbaud G, et al. Exp Brain Res.1992;92:227-245.

# Types of Central Sensitization

- Anxiety
- Chronic Pain (In general)
- CRPS/RSD
- Depression
- Fibromyalgia
- Headaches
- Opioid Induced Hyperalgesia
- Phantom Limb Pain
- PTSD

# Treatments for Central Sensitization and CRPS

- Therapy Based:
  - Physical therapy
  - Mirror box therapy
  - Graded motor imagery
  - Tactile discrimination training
  - Sensory discrimination training
- Neuropsych Based:
  - EEG Biofeedback
  - Cognitive Behavioral Therapy
  - Relaxation Techniques
  - Hypnosis

# Treatments for Central Sensitization and CRPS

- Medications:
  - Alpha- or beta-adrenergic-blocking compounds
  - Anti-inflammatories (corticosteroids, COX-inhibitors)
  - Bisphosphonates
  - Botox
  - Calcium-regulating drugs
  - GABA analogs
  - Ketamine
  - Local Anesthetics
  - Opioids
  - SNRIs
  - Vasodilators

# Treatments for Central Sensitization and CRPS

- Interventional:
  - Epidural Blockade
  - Intravenous immunoglobulin
  - Intravenous regional sympathetic block
  - Ketamine Infusion
  - Selective sympathetic ganglion nerve blocks
  - Spinal cord stimulators

# Ketamine History

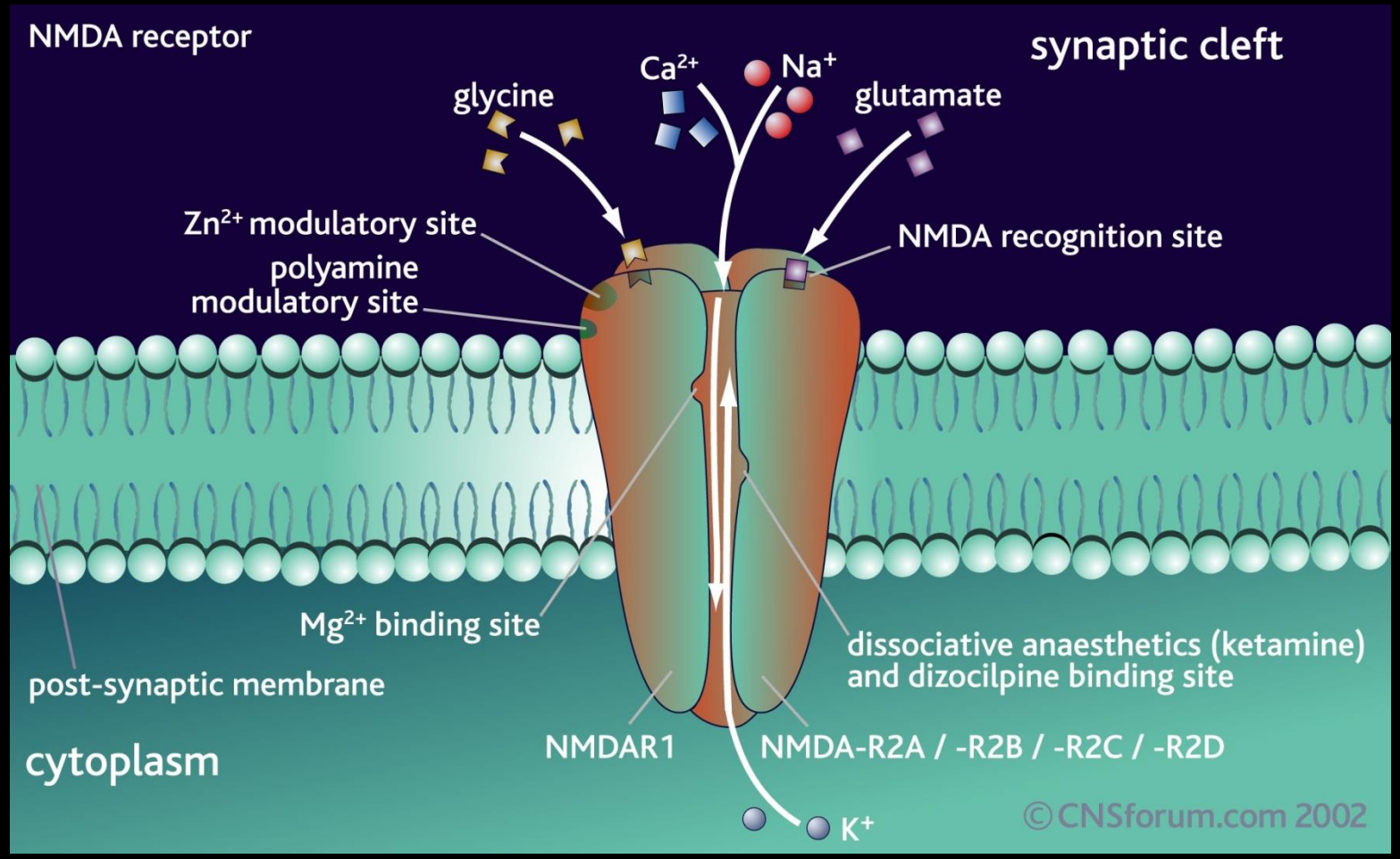
- Ketamine was first synthesized in 1962 by Calvin L. Stevens
- Ketamine was introduced to testing in human prisoners in 1964.1,2
- FDA approval in 1970
- Ketamine is a "core" medicine in the World Health Organization's Essential Drugs List, a list of minimum medical needs for a basic healthcare system.3

1. Morris, H; Wallach, J (July 2014). "From PCP to MXE: A comprehensive review of the non-medical use of dissociative drugs". Drug Testing and Analysis. 6 (7-8): 614–32

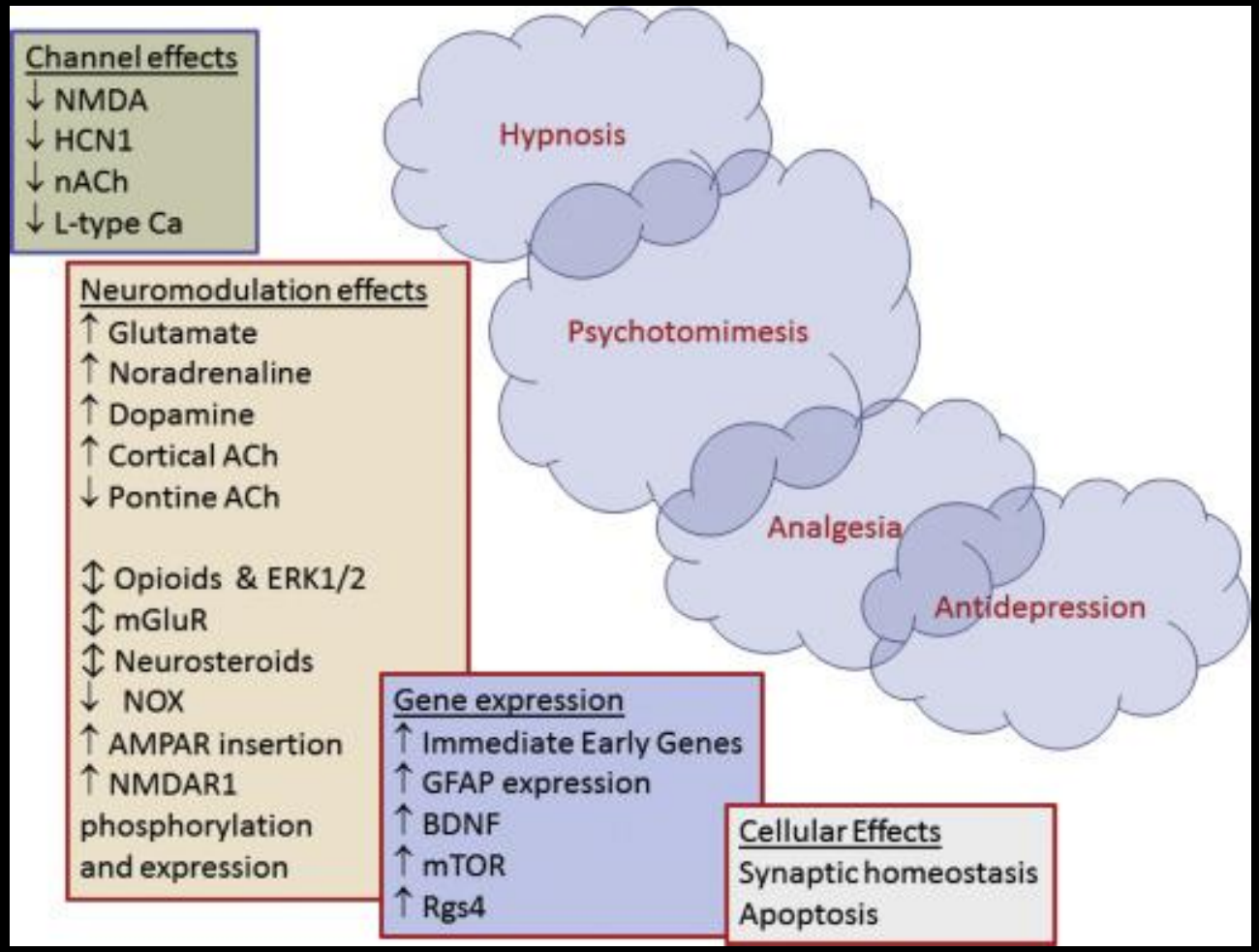
2. Domino, EF (September 2010). "Taming the ketamine tiger". Anesthesiology. 113 (3): 678–84.

3. WHO Model List of Essential Medicines (PDF) (18th ed.). World Health Organization. October 2013 [April 2013].

# NMDA Receptor



# Ketamine Mechanism of Action




Ketamine – More mechanisms of action than just NMDA blockade, Jamie Sleigh, Martyn Harvey, Logan Voss, Trends in Anaesthesia and Critical Care, Volume 4, Issue 2, Pages 76-81 (June 2014) DOI: 10.1016/j.tacc.2014.03.002

# Effects of Ketamine

- Preventing central sensitization in the dorsal horn neurons (interfere with pain transmission in spinal cord)
- Inhibits nitric oxide synthase
- CV - inhibits reuptake of catecholamines (NE) at nerve terminals, resulting in increase HR, BP, CO. It is thought ketamine attenuates baroreceptor function by affecting NMDA receptors in the nucleus tractus solitarius (central nervous system effect).
- Pulmonary - Stimulation of B2 adrenergic receptors -> results in bronchial smooth muscle relaxant (bronchodilation); increases salivary and tracheobronchial secretions (esp in kids). Does not lead to ventilatory depression
- Neurological - increases cerebral blood flow, metabolism and ICP. Seizure threshold unaltered
- Causes sensory and perceptual illusions, vivid dreams and “emergence reactions”

# Ketamine Perioperatively

- Bell et al. (2006) reviewed 37 RCT (over 2240 participants) - use of periop ketamine or placebo. Subanesthetic doses of ketamine (ranging from 10 mg - 270 mg) given at all different time periods.

- 27/37 trials found perioperative ketamine reduces rescue analgesic requirements or pain intensity or both.

- Ketamine in subanesthetic doses is effective in reducing morphine requirements in the first 24 hours after surgery.

Perioperative ketamine for acute postoperative pain. Bell RF, Dahl JB, Moore RA, Kalso E. Cochrane Database Syst Rev. 2006 Jan 25;(1):CD004603

# Ketamine Perioperatively

- Loftus et al. (2010) found intraoperative ketamine reduces opioid consumption (morphine) in the 48 hour postoperative period in opioid-dependent patients with chronic back pain.
- Implications:
  - Reduced acute pain
  - Reduced chronic pain
  - Reduced peripheral sensitization
  - Reduced central sensitization
  - Reduced opioid induced hyperalgesia

Intraoperative ketamine reduces perioperative opiate consumption in opiate-dependent patients with chronic back pain undergoing back surgery. Loftus RW, Yeager MP, Clark JA, Brown JR, Abdu WA, Sengupta DK, Beach ML. Anesthesiology. 2010 Sep;113(3):639-46.

# Ketamine and PTSD

- Ketamine infusion was associated with significant and rapid reduction in PTSD symptom severity, compared with midazolam
- Ketamine was also associated with reduction in comorbid depressive symptoms and with improvement in overall clinical presentation
- Ketamine was generally well tolerated without clinically significant persistent dissociative symptoms.
- To date, few pharmacotherapies have demonstrated sufficient efficacy in PTSD; selective serotonin reuptake inhibitors, serotonin norepinephrine reuptake inhibitors, and other medications are associated with significant levels of nonresponse and persistent residual symptoms, even in responders.
- Accumulating evidence for the role of glutamate in mediating stress responsivity, the formation of traumatic memories, and the pathophysiology of PTSD, suggests a potential benefit for ketamine for PTSD

Efficacy of Intravenous Ketamine for Treatment of Chronic Posttraumatic Stress Disorder, A Randomized Clinical Trial Adriana Feder, MD; Michael K. Parides, PhD; James W. Murrough, MD; et. al. JAMA Psychiatry. 2014;71(6):681-688. doi:10.1001/jamapsychiatry.2014.62

# Challenges to Treatment

- Physician Lack of Education
- Physician Stereotypes
- Physician Egos
- Physician Laziness
- Facility Logistical Issues
- Complexity of Science
- Complexity of Treatment
- Lack of Coverage
- Minimal Reimbursement

In the USA there is some following, even absent "FDA approval" for use of ketamine infusions, in documented CRPS-criteria meeting cases. Ms. [redacted] did not meet diagnostic criteria for CRPS and therefore, use of ketamine infusions was not indicated. She also does not have "central sensitization" (purely speculative diagnosis) nor does she have peripheral neuropathy (all EMGs are normal). She therefore is NOT a candidate for ketamine infusions.

# NATIONAL PAIN CENTERS

## Interventional Spine and Pain Specialists

Proper pain management is the comprehensive integration of multiple complex treatment options that yields an effective and safe patient outcome.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