Central Sensitization and Ketamine Infusions

Jay Joshi, MD, DABA, DABA-PM, FABA-PM

Disclosure

- Nothing to disclose
Learning Objectives

- Discuss the landscape of pain management
- Discuss the various types of pain
- Discuss central sensitization
- Discuss ketamine and the mechanism of action
- Discuss ketamine infusions
- Discuss barriers to treatment

Definition of Pain

- According to the International Association for the Study of Pain (IASP), “pain” is defined as:
  - An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage

- According to the Underground Dictionary, “pain” and “painful” are defined as:

<table>
<thead>
<tr>
<th>pain</th>
<th>Painful</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAIN IS FRENCH BREAD see below</td>
<td>See “reality TV”</td>
</tr>
<tr>
<td><em>WHAT IS PAIN?</em> &quot;FRENCH BREAD!&quot; from Remember the Titans</td>
<td>Survivor is painful to watch.</td>
</tr>
<tr>
<td>by wrestlerbob February 21, 2005</td>
<td>by jondapicam November 05, 2003</td>
</tr>
</tbody>
</table>
Other Definitions by IASP

- Allodynia: Pain due to a stimulus that does not normally provoke pain.
- Dysesthesia: An unpleasant abnormal sensation, whether spontaneous or evoked.
- Hyperalgesia: Increased pain from a stimulus that normally provokes pain.
- Hyperesthesia: Increased sensitivity to stimulation, excluding the special senses.
- Hyperpathia: A painful syndrome characterized by an abnormally painful reaction to a stimulus, especially a repetitive stimulus, as well as an increased threshold.
- Neuralgia: Pain in the distribution of a nerve or nerves.
- Neuritis: Inflammation of a nerve or nerves.

Other Definitions by IASP (cont’d)

- Neuropathic pain: Pain caused by a lesion or disease of the somatosensory nervous system.
- Central neuropathic pain: Pain caused by a lesion or disease of the central somatosensory nervous system.
- Peripheral neuropathic pain: Pain caused by a lesion or disease of the peripheral somatosensory nervous system.
- Neuropathy: A disturbance of function or pathological change in a nerve: in one nerve, mononeuropathy; in several nerves, mononeuropathy multiplex; if diffuse and bilateral, polyneuropathy.
Other Definitions by IASP (cont’d)

- Nociceptive pain: Pain that arises from actual or threatened damage to non-neural tissue and is due to the activation of nociceptors.
- Sensitization: Increased responsiveness of nociceptive neurons to their normal input, and/or recruitment of a response to normally subthreshold inputs.
- Central sensitization: Increased responsiveness of nociceptive neurons to their normal input, and/or recruitment of a response to normally subthreshold inputs.
- Peripheral sensitization: Increased responsiveness and reduced threshold of nociceptive neurons in the periphery to the stimulation of their receptive fields.

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 pain\(^2\)
  - ~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

---

Types of Pain

While pain management crosses the health care spectrum, for the purposes of this assessment we have classified pain treatment services into three generally accepted categories:

- **Acute**
  - Focused on symptomatic relief of acute pain (ie, post-operative, obstetrical)

- **Chronic**
  - Pain that persists beyond the time of normal healing and can last from 6 months onward (ie, headaches, low back, pelvic pain, arthritis, RSD/CRPS)

- **Palliative**
  - Severe pain in those suffering and dying from progressive diseases (ie, cancer)
Who Provides These Services

- Physician specialties involved with pain treatment include:
  - Anesthesiology
  - Emergency Medicine
  - General Surgery
  - Interventional Pain Management/Anesthesiology
  - Oncology
  - Neurology
  - Neurosurgery
  - Orthopedics
  - Psychiatry
  - Primary Care/Internal Medicine/Hospitalists
  - Radiology
  - Rheumatology
  - Trauma Surgery

Other Providers

- In addition to physicians, Pain Management Services can be provided by:
  - Chiropractors
  - CRNAs
  - Nurse Practitioners
  - Physician Assistants
  - Physical Therapists
  - Massage Therapists
  - Acupuncturists
  - Holistic/Homeopathic “Doctors”
  - DME providers
  - Hospice and Home Health providers
The Big Picture

- The psychiatrist sees depression
- The gastroenterologist sees IBS
- The gynecologist sees PMS
- The cardiologist sees noncardiac chest pain
- The rheumatologist sees FM
- The neurologist sees chronic headache
- The otolaryngologist sees TMJ syndrome


Interventional Pain Specialist

- Ideally for patients, an Interventional Pain Specialist is:
  - Typically Anesthesiologist who has done a fellowship in Interventional Pain Management
  - Can skillfully perform over 100 minimally invasive procedures
  - Diagnostician first
  - Multi-dimensional treatment options
  - Strong fund of multimodal pain knowledge
  - Practice with integrity holding patient safety and outcome as the priority
Reality of Pain Management

- Of all “pain” doctors, over 90% have not had any formal advanced training in Pain Management
- Many pain board certifications can be bought (no formal accredited fellowship is required)
- In the past, Interventional Pain Management training programs had variable quality of training
- Many unaccredited programs
- Many “trained” and board certified pain physicians have a variable practice patterns
- Specialty of Interventional Pain Management recognized by Medicare only in 2002
- Hardly any physicians, including Interventional Pain Management physicians have been formally educated and trained on central sensitization and Ketamine Infusions

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
Surgical Referral vs Pain Referral

- **Surgical referral**
  - Patient cannot move extremities
  - Lack of bowel control
  - Lack of bladder control
  - Failed all other pain management options

- **Pain management referral**
  - Patient experiences chronic pain
  - Recent trauma
  - Chronic neck, thoracic, back pain
  - Arm or leg pain
  - CRPS
  - Whiplash
  - Chronic neuropathic headaches
  - Postlaminectomy/failed back surgery syndrome
  - Initial radiculopathy (<3 months)
  - Increased function and quality of life desired
  - Minimally invasive options/nonsurgical options desired

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 upregulated and in a persistent state of high reactivity.
  - Central vs peripheral

- **Organic vs inorganic**
What is Central Sensitization? (cont’d)

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? (cont’d)

- Central sensitization is a manifestation of activity-dependent plasticity due to an increase in synaptic strength, driven to a substantial extent, by N-methyl-d-aspartic acid glutamatergic receptors.1

- Central sensitization operates after noxious stimuli, peripheral inflammation, and nerve injury in the spinal cord and higher brain centers, and involves multiple presynaptic and postsynaptic changes producing changes in transmitter release and action, as well as synthesis of novel neuromodulators.2,3


Samad, TA Moore, KA Sapirstein, A Bille! S Allchorne, A Poole, S Bonventre, JV Woolf, CJ
What is Central Sensitization? (cont’d)

- Many features of central sensitization resemble those that are responsible for memory.  

- 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.

- It has been suggested that central neuronal sensitization plays an important role in postoperative pain.


What Causes Central Sensitization

- Potential mechanisms implicated in central sensitization:
  - NMDA receptor activation
  - Altered gene expression in dorsal horn neurons
  - Decreased inhibition
  - Microglial activation
  - Thalamic and somatosensory cortex changes

Types of Central Sensitization

- Anxiety
- Chronic pain (in general)
- CRPS/RSD
- Depression
- Fibromyalgia
- Headaches
- Opioid induced hyperalgesia
- Phantom limb pain
- PTSD

Neurophysiology of Central Sensitization

(A) Transfer of information about the intensity, duration, and location of peripheral noxious stimuli.

(B) Activity-dependent synaptic plasticity driven by high levels of nociceptor input that results in activation of intracellular kinases that phosphorylate ion channels and receptors, altering their distribution and function and increasing excitability and thereby pain sensitivity.

(C) Changes in transcription in dorsal horn neurons. Some alterations in gene expression are activity driven and others are widespread, like the induction of (Cox-2).

(D) Inhibitory interneurons play a major role in damping down sensory processing. After peripheral nerve lesions, there is a reduction in the action of inhibitory transmitters and a loss of γ-aminobutyric acid–mediated interneurons, resulting in a loss of inhibition (disinhibition) producing pain hypersensitivity.

AA = arachidonic acid; AMPA = α-amino-3-hydroxy-5-methyl-4-isoxazole propionate; EP = prostaglandin receptor; IL1β = interleukin 1β; NK1 = neurokinin 1; NMDA = N-methyl-D-aspartic acid; PGE2 = prostaglandin E2; TrkB = tyrosine kinase

What is Central Sensitization?

Constructing the Brain Acute Pain Representation Map from Resting State Brain Activity

(A) Brain regions identified by pain, which identifies 311 PubMed studies in the Neurosynth meta-analysis tool (Yarkoni et al., 2011). The map is localized to six brain regions: bilateral secondary somatosensory cortex (S2), anterior cingulate (ACC), bilateral anterior and posterior insula (aINS, pINS), thalamus (TH), and periaqueductal gray (PAG).

(B) Resting state functional connectivity associated with the term pain. Functional connectivity is derived from resting state activity from 1,000 subjects (Biswal et al., 2010), generated in Neurosynth. Essentially the same network is identified when ACC, aINS, or S2 are used as seeds. The pINS seed identifies bilateral pINS as well as posterior cingulate/supplementary motor area. The TH network is limited to bilateral thalamus, and PAG seed only shows connectivity limited to itself.

(C) Overlap between the map for the term “pain” and sum of six resting state networks. Blue is the same map shown in (A). Red is the sum of all functional connections identified in (B). The overlap between red and blue maps is 72% of the blue map.

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

What is Central Sensitization

Low Back Pain

Osteoarthritis

Postherpetic Neuralgia

Pelvic Pain

fMRI Imaging in CRPS (A Model for Central Sensitization)


Chronic Pain and Central Sensitization

Brain Reorganization

Time Scale of Pain
Neural connections between the stellate ganglion and the hypothalamus, amygdala, and regions of the prefrontal cortex, in particular the insular cortex, might explain the effect of stellate ganglion block on Central Pain conditions.

Treatment 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 (cont’d)

- 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

- 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.

Properties of Ketamine

- Highly lipophilic (44% non-ionized at physiological pH)
- Racemic mixture of two stereoisomers: S(+) and R(-)
- Onset—IV: 30 seconds; IM: 3-4 minutes
- Duration—IV: 5-15 minutes; IM: 12-25 minutes
- Half-Life/Elimination half-life: 2.5 hours; Distribution half-life: 11-16 hours
- Metabolism: Hepatic via hydroxylation and N-demethylation; the metabolite norketamine is 33% as potent as parent compound
- Excretion: primarily urine
**Ketamine Structure**

(R)-ketamine

(S)-(−)-ketamine

(S)-(+)−ketamine hydrochloride

(S)-Ketamine has about 3-4 times greater affinity for the NDMA receptor than (R)-Ketamine

---

**NMDA Receptor**

- NMDA receptor (N-Methyl-D-Aspartate), a specific inotropic glutamate receptor, mediates neuronal signaling and regulates gene expression.
- Present in all neurons in the CNS - specifically in the dorsal horn of the spinal cord.
- Highly permeable to and allows flow of Na+ and Ca2+ into cell and K+ out of cell. Mg2+ blocks NMDA channels.
- NMDA signaling is important in anesthesia: involved in pain processing, neuronal plasticity and generation of central sensitization
- The NMDA receptor is very important for controlling synaptic plasticity and memory function
- NMDAR antagonists reduce neuropathic, wind-up and spontaneous pain.
NMDA Receptor (cont’d)

- Various NMDAR compounds have differing relative potency on the different NMDA receptor subtypes (commonly termed GluN1, GluN2A, GluN2B, GluN2C, and GluN2D—also called NR1, NR2A-D) with resultant different spectra of action.

- These subtypes show markedly heterogeneous distributions in the brain, which may account for the variations in clinical effects caused by different NMDA blocking compounds.

- The GluN2A subtype is found throughout the brain, whereas GluN2B is primarily confined to the limbic system, thalamus, and spinal cord, GluN2C to the thalamus and cerebellum, and GluN2D in the brain stem, diencephalon, and spinal cord.
Ketamine Mechanism of Action (cont’d)

- Ketamine has been shown to result in suppression of immediate early gene expression at the site of mechanical injury (zif/268, c-fos, junB, fosB, c-jun, junD).

- It also alters the regulation of NMDA receptor1 phosphorylation 22 and NMDA receptor1 mRNA expression in rat and mouse models of hyperalgesia, and also limits astrocytic and microglial activation as seen in reduced glialfibrillary acidic protein (GFAP) expression; effects that correlate with a reduction in neuropathic pain.

Ketamine Mechanism of Action (cont’d)

- At concentrations within the clinical dose range, ketamine directly affects a wide range of cellular processes, including:
  - Blockade of NMDA channels
  - Neuronal hyperpolarisation-activated cationic currents (Ih, also known as hyperpolarisation-activated cyclic nucleotide channels (HCN1))
  - Nicotinic acetyl-choline ion channels
  - Delta and mu-opioid agonism and opioid potentiation
  - Nitric-oxide (NO) cyclic guanosine-mono-phosphate (cGMP) system
  - Non-NMDA glutamate receptors (a-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA))
  - Metabotropic glutamate receptors (mGluR)
  - Reduction in cholinergic neuromodulation
  - Increased release of aminergic neuromodulators (dopamine and noradrenaline)
  - Neurosteroids

- L-Type Ca2b channels.
Ketamine Mechanism of Action (cont’d)

- Ketamine has also been shown to enhance brain-derived neurotrophic factor (BDNF) and mammalian target of rapamycin (mTOR) protein levels in the rat hippocampus, resulting in modification to the number and function of synaptic connections.
- Norketamine has been shown to actually have anti-analgesic effects and ketamine may actually facilitate endogenous pain pathways in some circumstances.
- In the setting of chronic neuropathic pain syndromes, there is some evidence for prolonged post-drug analgesia that markedly outlasts the effective drug levels, which would be mediated by downstream mechanisms.


Ketamine Mechanism of Action (cont’d)

- Ketamine also has direct effects on the delta opioid receptor, and acts to augment opioid mu-receptor function.
- Ketamine’s analgesia is not reduced by naloxone; which would argue against the primary opioid mechanisms of action.
- In vitro, ketamine prevented and even reversed opioid mu-receptor desensitization.
- Ketamine augments endogenous anti-nociceptive systems presumably, in part, via its aminergic (serotonergic and noradrenergic) activation and inhibition of re-uptake.
- Ketamine directly inhibits nitric-oxide synthase which probably contributes in part to its analgesic effects.
Ketamine Mechanism of Action (cont’d)

- Ketamine has both acute and prolonged effects on chronic neuropathic pain syndromes.
- A single low analgesic dose of ketamine can rapidly and transiently reduce ongoing pain of neuropathic origin, including allodynia and hyperalgesia.
- This may be due to a reduction in NMDA-mediated “wind-up”.
- Ketamine applied around the time of surgery as a single infusion has even been reported to limit the development of chronic pain up to 180 days postoperatively.
- Ketamine’s pre-emptive reduction in neuropathic pain is a corollary of its antidepressant effect which endures well after the drug has been eliminated.
- Ketamine may set in chain cell signaling cascades that interrupt the gradual propagation of pathophysiologica changes associated with chronic pain development.


Ketamine Mechanism of Action (cont’d)

- Ketamine has 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.

For Consultants Use Only
Ketamine Perioperatively (cont’d)

- 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


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

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.