Infusion Therapies in Pain
“present and future”

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Session Goals

- Overview on the management of chronic pain with commonly used intravenous infusions.
- Alternatives to tackle opioid crisis.
- Evolving future infusion therapies.

Pain

- *"An unpleasant sensory and emotional experience associated with actual or potential tissue damage, and lasts beyond the normal time for healing."*


CHRONIC PAIN
ONE OF THE MOST
UNDERESTIMATED
HEALTH CARE
PROBLEMS IN
THE WORLD TODAY

According to a 2011 report titled Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research by the Institute of Medicine of the National Academies, pain not only exacts its toll on people's lives but also on the economy with an estimated annual economic cost of at least $560 - 635 billion in health care costs and the cost of lost productivity attributed to chronic pain.

Pain Physician 2013; 16:231-249

100 million
people in the U.S. have chronic pain

Source: Institute of Medicine, National Academies, 2011

1.5 billion
people have chronic pain worldwide

Source: Global Industry Analysts Inc., 2011

20%
of U.S. adults have painsomnia—pain that affects their sleep a few nights a week

Source: National Sleep Foundation, 2000

Nearly three-fifths
of adults 65 and older with pain said it lasted for 1 year or more

Source: National Center for Health Statistics, Centers for Disease Control & Prevention, 2006

Annual cost of chronic pain in U.S. health care, lost wages, and lost productivity

$560 billion–$635 billion

Source: Institute of Medicine, National Academies, 2011

Most common types of chronic pain

15% neck pain

28% low back pain

15% severe headaches or migraines

Source: National Center for Health Statistics, Centers for Disease Control & Prevention, 2015

Quality of life for people with chronic pain

59% report an impact on their overall enjoyment of life

77% report feeling depressed

70% report trouble concentrating

Source: "Voices of Chronic Pain," a survey of 303 chronic pain sufferers conducted for the American Pain Foundation and sponsored by Endo Pharmaceuticals, 2006

Chronic pain

From symptom to disease

Pain exceeds onset (3 months)

Exceeds beyond the healing period

No protective function

Degrades health and function

Affects mood and causes depression.

Acute pain

Obvious tissue damage

Autonomic system activity increased

Pain resolves after specific treatment

Protective in nature

Why bother measuring pain

Might help improve pain management

Adjust analgesia

Analgesia may reduce but not eliminate pain, so a graded scale is more

helpful than- Pain/No Pain

Barriers

- Lack of knowledge
- Lack of access
- Lack of resources
- Lack of commitment
- Inadequate assessment

Pain: The 5th Vital Sign

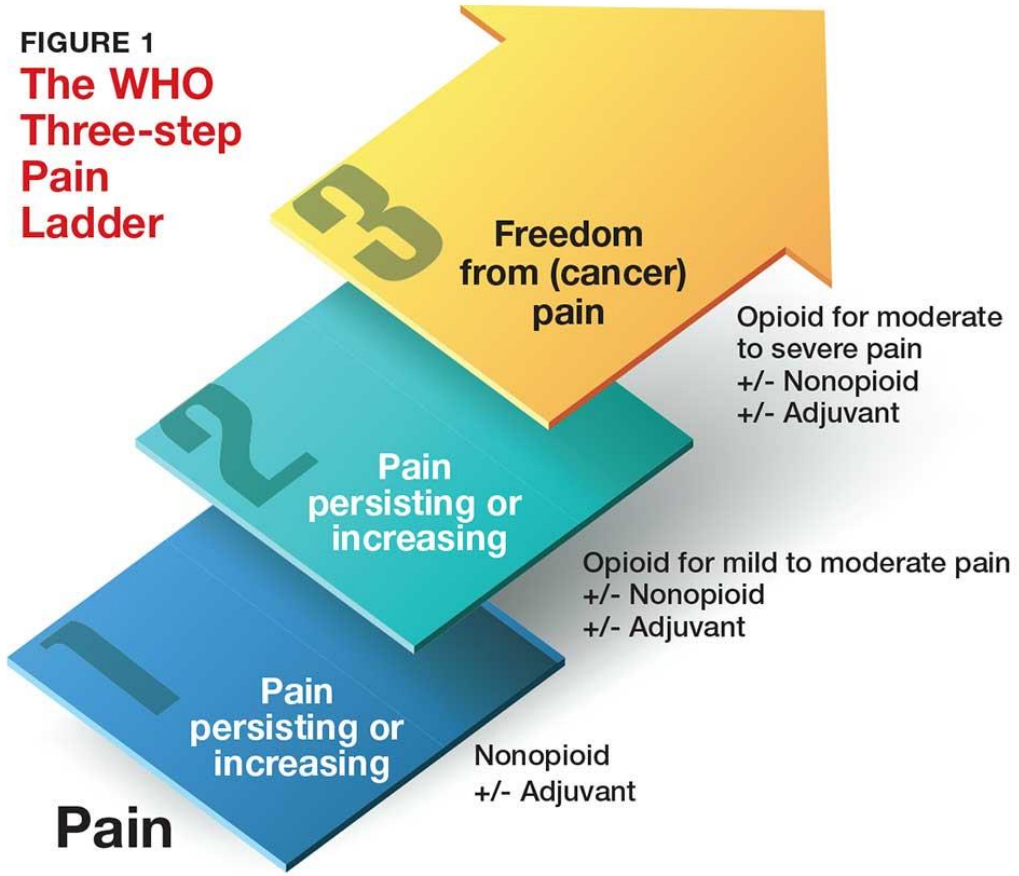
1. Temperature
2. Blood Pressure
3. Pulse
4. Respiratory Rate

5. Pain Assessment

American Pain Society. 1998

FIGURE 1

The WHO Three-step Pain Ladder

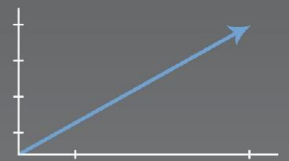


Source: World Health Organization. 2017.[12]

OPIOID EPIDEMIC

FACT SHEET

Deaths from prescription opioids are more than **four times** higher than the 1999 rate.

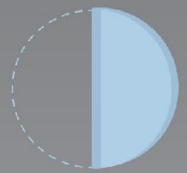


91 Americans die every day from an opioid overdose.

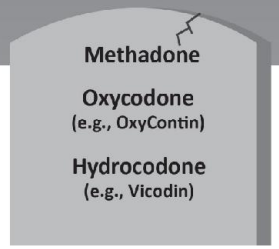
Every day, over **1,000 people** are treated in emergency departments for misusing prescription opioids.

25% of people who receive opioid prescriptions for long-term, non-cancer pain struggle with addiction.

Nearly **half** of all opioid overdoses involve a prescription opioid.



Most commonly abused opioids:

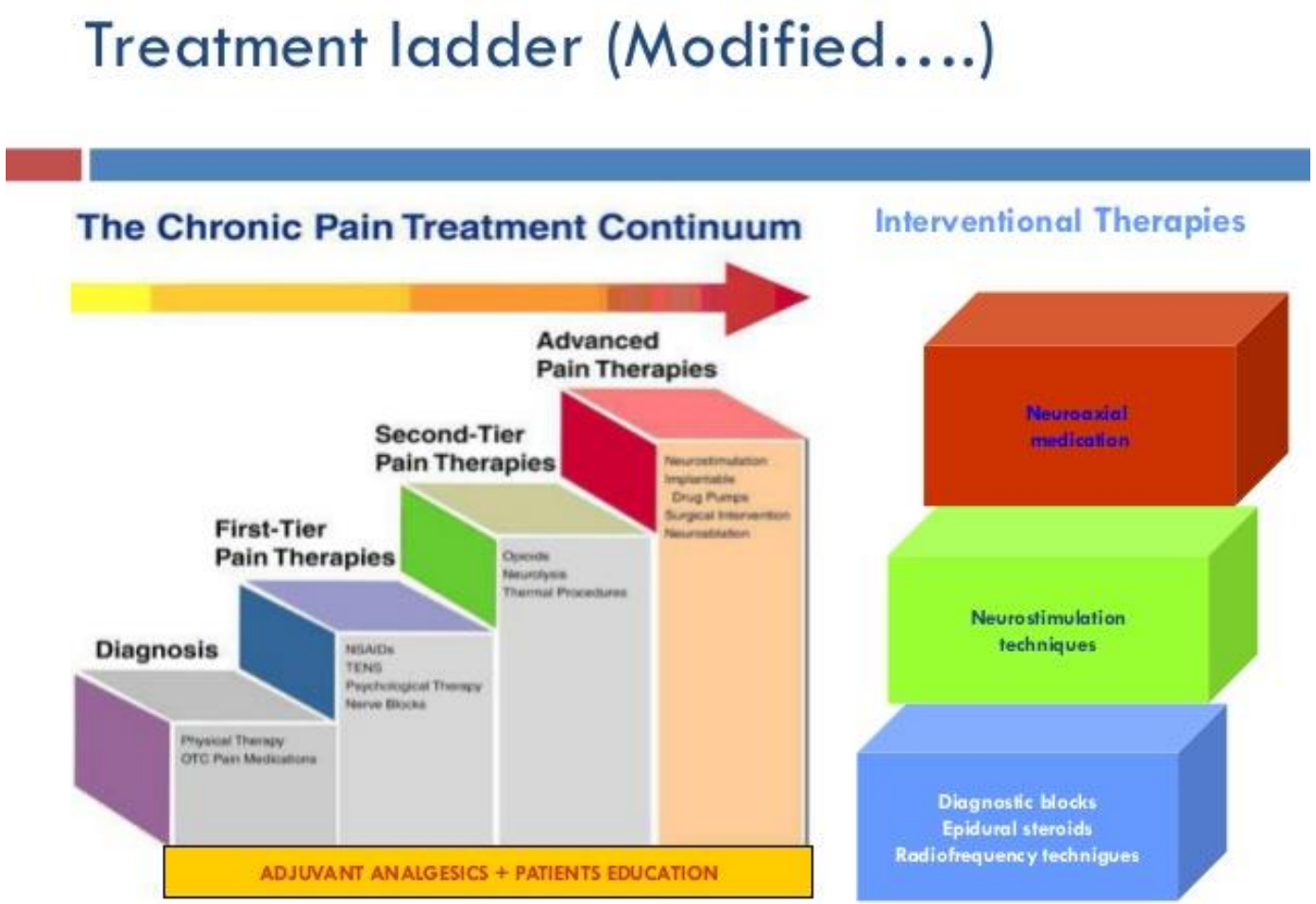


Shandro group

Dosage

- **Tolerable dose vs therapeutic dose (serum levels vs empiric recommendations)**
- **Combinations may reduce the tolerable dose**

Treatment Ladder



Infusion therapy

Infusion therapy involves the administration of medication through a needle or catheter

- Intravenous
- Epidural
- Intrathecal
- Perineural
- Subcutaneous
- Intraventricular

Intravenous therapies in pain

- Acute Pain – Opioids, Lidocaine, Ketamine, Dexmedetomidine
- Chronic Pain– Lidocaine, Ketamine, Bisphosphonate's

Intravenous therapy

- The fastest onset of drug action and optimal bioavailability.
- Worse side-effect profile because of the rapid rise in plasma drug concentration.
- Need for experienced trained staff.
- Need secondary care (e.g. hospitals) with immediate access to resuscitation teams and equipment.
- Problems with IV access —infection, thrombosis, air embolism.

Lidocaine

- **1943 Lidocaine**, the first amino amide–type local anesthetic, was first synthesized under the name 'xylocaine' by Swedish chemist Nils Löfgren..
- **1949** It was first marketed.
- **1962**- Bartlett et al - Systemic lidocaine was first reported in 1962used to treat postoperative pain.
- **1980**- Boas et al demonstrated that IV lidocaine attenuated central pain, refractory to more conventional treatment.
- **1998**-Groudine and colleagues (Intravenous lidocaine decreased postoperative pain, but may also shorten the hospital stay in patients undergoing radical retro pubic prostatectomy.

Mechanism of action

- Acts on Voltage-gated sodium channels -The activation of voltage-gated sodium channels may play a role in the pathogenesis and maintenance of both neuropathic and inflammatory pain.
- Blocks conduction of nerve impulses mediated by action potential (AP) generation along axon.
- Binds at inner surface of Na+ channel – preventing Na+ influx which initiates AP → blockade of nerve impulses(Pain signals)
- Bind to the open form of the Na+ channel from the cytoplasmic side of the neuronal membrane

Chronic pain

- The **activation of voltage-gated sodium channels** may play a role in the pathogenesis and maintenance of both neuropathic and inflammatory pain. ***Pain 2004; 108:237-247***
- the **proliferation** and **activation of sodium channels** after nerve injury and inflammatory pain causing ectopic discharges stemming from the site of injury, dorsal root ganglia, or even in adjacent uninjured neurons. ***Pain* 2004; 108:237-247**
- **Spontaneous discharges** can develop in both myelinated and unmyelinated nerve fibers, and ectopic activity can arise in both nociceptors and low-threshold mechanoreceptors. ***Pain 1983; 17:321-339.***

Central Neuropathic Pain	2.5mg-5mg/kg, 30-40 minutes
Peripheral Neuropathic Pain	5 and 7.5mg/kg, 4 hour 5mg/kg, 30 minutes 1, 3, and 5mg/kg/hr, 6 hours 5mg/kg, 60 minutes
CRPS	targeted plasma concentrations 1, 2, and 3 µg/ml, 20 minutes 1, 3, and 5 mg/kg, 6 hours
PPSP	1.5mg/kg bolus followed by 1.5mg/ kg/hr, duration of surgical procedure; stopped one hour after skin closure 1mg/kg bolus followed by 4 mg/kg, 40 minutes
Fibromyalgia	5mg/kg, 30 minutes

Pain Physician 2013; 16:231-249

Side effects

- Allergic reactions
- Cardiovascular – arrhythmias, cardio depression, hypotension
- CNS: metallic taste, excitability, agitation, increased talkativeness, convulsions followed by coma.

Lidocaine systemic toxicity treatment

- Stop Lidocaine infusion
- Airway management
    - Ventilate with 100% oxygen / avoid hyperventilation / advanced airway device if necessary
- Control seizures with benzodiazepines

Lipid Emulsion 20% (Precise volume and flow rate are not crucial)	
Greater than 70 kg patient	Less than 70 kg patient
Bolus 100 mL Lipid Emulsion 20% rapidly over 2-3 minutes • Lipid emulsion infusion 200-250 mL over 15-20 minutes	**Bolus 1.5 mL/kg Lipid Emulsion 20%** rapidly over 2-3 minutes • Lipid emulsion infusion ~0.25 mL/kg/min (ideal body weight)
If patient remains unstable: • Re-bolus once or twice at the same dose and double infusion rate; be aware of dosing limit (12mL/kg) • Total volume of lipid emulsion can approach 1 L in a prolonged resuscitation (e.g., > 30 minutes)	

Ketamine

- **1958** -Pharmacologist Graham Chen (Parke Davis) and his associates obtained the compound from Maddox.
- **1964**- first administered to 20 volunteers from a prison population and produced dissociative anesthesia, and effective analgesia in doses ranging from 1 to 2 mg/kg.
- **August 3, 1964**- The first human was given ketamine via an IV sub anesthetic dose, by Guenter Corssen, MD, an anesthesiologist at the University of Alabama at Birmingham.
- **1970**- Ketamine was approved by the FDA.

Mechanisms of Action

- Acts as a **noncompetitive antagonist** at the phencyclidine binding site of N-methyl-D-aspartate (NMDA) receptors in the central nervous system (CNS), at the prefrontal cortex and hippo- campus.
- Acts by decreasing the frequency of channel opening and duration of time spent in the active, open state.
- The NMDA receptor is **a ligand-gated channel** whose major endogenous agonist is glutamate, the predominant excitatory neurotransmitter in the CNS.
- NMDA channel activation plays a major role in cognition, chronic pain, opioid tolerance, and mood regulation and also the principal receptor involved in phenomena of central sensitization and windup.

Pharmacodynamics and Pharmacokinetics

- Ketamine exists as a racemic mixture of R(−) and S(+) stereoisomers. The S(+) stereoisomer is approximately 3 to 4 times more potent than its R(−) stereoisomer.
- The **S Ketamine** has a shorter duration of action and possesses greater neuroprotective and analgesic properties than its R(−) counterpart, **S Ketamine** is a more ideal analgesic.
- Both **water and lipid soluble- extensive** rapid distribution throughout the body and rapid crossing of the blood-brain barrier.
- Ketamine's **half-life** is approximately 2.3 ± 0.5 hours.
- Ketamine causes analgesia and sedation (low doses), whereas in high doses, it produces general anesthesia.

Chronic pain

- Ketamine “resets the CNS,” by reversing the deleterious effects of central sensitization by virtue of its NMDA-receptor antagonistic effects. ***Woolf CJ, Thompson SW. Pain. 1991;44:293–299***
- Ketamine may exert its profound analgesic effects by not only af-fecting the sensory-discriminative system, but also modulating the affective-motivational component of pain.
- Ketamine used as an antidepressant and also as a treatment for PTSD.

AbdallahCG *Depress Anxiety. 2016;33:689–697*; Juven-Wetzler A et al *Eurneuropsychopharmacol. 2014;24:469–479.*

Barriers

- an “anesthetic agent,” - induce general anesthesia and ablate protective airway reflexes.
- Most hospitals prohibit its use as a “bolus” by nonanesthesiologists, and many require an anesthetist to oversee its use in any context.
- Lack of large-scale, valid studies to guide treatment.
- Lack of treatment standards.
- Lack of safe-use recommendations, guidelines to inform safe practice.

Central Neuropathic Pain	**bolus 60 µg/kg, 6 µg/kg/min, 17-21 minutes** **0.4 mg/kg, 40 minutes**
Peripheral Neuropathic Pain	**0.4 mg/kg, over 1 hour** **60 µg/kg bolus, followed by 6 µg/kg/min infusion, 20 minutes** **0.2 mg/kg bolus over 10 minutes, followed by 0.3 mg/kg/hr, one hour or less**
Postherpetic Neuralgia and Peripheral Nerve Injury	**0.15 mg/kg, 10 minutes** **0.24 mg/kg, 30 minutes**
CRPS	**5mg/hr to a maximum dose of 30 mg/hr, 4.2 days** **25 mg/hr for 4 hours daily, 10 days**
Fibromyalgia	**0.3 mg-0.5mg/kg, 10- 30 minutes**

Ketamine- contraindications

Category	Contraindication/Precaution
Cardiovascular	• Unstable angina • Poorly controlled hypertension • High-risk coronary vascular disease
Neurological and ophthalmic	• Elevated intracranial pressure, including secondary traumatic brain injury or tumor • Elevated intraocular pressure, acute globe injury, or glaucoma
Endocrinological (due to possible potentiation of sympathomimetic effects)	• Hyperthyroidism • Pheochromocytoma
Metabolic	• Severe liver disease
Gastrointestinal	• Full stomach aspiration risk
Pregnancy	• Lack of data on safety
Psychiatric	• Intoxication with alcohol or other substances • Active substance abuse • Delirium • Psychosis • Refusal or inability to consent

DEXMEDETOMIDINE

- Dexmedetomidine is chemically related to clonidine, about 8 times more specific for α-2 adrenoceptors.
- Has α-2:α-1 selectivity ratio of 1620:1, (200:1 for clonidine)
- Its effects are dose-dependent.
- It appears to exert analgesic effects at the spinal cord level and at supraspinal sites.
- Provide antinociception through non-spinal mechanisms eg intra-articular administration during knee surgery improves postoperative analgesia.
- Can activate α2A receptors , inhibition of the conduction of nerve signals through C and Aδ fibers, and the local release of enkephalin.
- Dosage- 0.2 or 0.6 µg/kg/hr.

BISPHOSPHONATES

- Mainly used in the treatment of pathologic conditions associated with abnormal bone metabolism, such as osteoporosis, Paget's disease, and cancer-related bone pain.
- Bisphosphonates has a **role in the treatment of CRPS.**
- Bisphosphonates exert biological effects through osteoclasts and their precursors, and on macrophages, dendritic cells, and microglia.
- They suppress bone resorption via osteoclast inhibition and shorten osteoclast life span

BISPHOSPHONATES dose - CRPS

- 60 mg pamidronate ***Robinson et al***
- 100 mg neridronate in 2 hours, given 4 times over 10 days ***Varenna et al***
- 300 mg clodronate, 10 days ***Varenna et al***

Immunoglobulin G

Immunoglobulin G (IgG) concentrates are immune-modulating, anti-inflammatory human blood plasma-derived products.

Used for the treatment of some peripheral neuropathies and a range of other pain disorders.

Mechanism of Action

- the analgesic effect of IgG in chronic pain conditions is thought to be secondary to the modulation of cytokine expression and function and immuno- suppression.
- pathological auto- antibodies to components of the voltage-gated potassium channel complex (VGKC complex) are thought to be involved in chronic pain.

Clinical Indications

- CRPS
- Lumbosacral radiculoplexus neuropathy
- Diabetic neuropathic pain
- Sjögren's syndrome-associated neuropathy,
- Fibromyalgia
- Postpolio syndrome
- Pain secondary to pathological autoantibodies

The “Liverpool protocol”

Initially be treated with a lower dose of 0.5 g/kg, and if greater than 40% pain relief is achieved, patients should then, 2 weeks later, be offered a trial of 6–12 months of low-dose maintenance treatment.

Tamburin S, Borg K, et al. Immunoglobulin G for the treatment of chronic pain: report of an expert work- shop. Pain Med. 2014;7:1072–82.

Administration

Intravenously (intravenous immunoglobulin [IVIg]) or subcutaneously (subcutaneous immunoglobulin [SCIg])

Doses vary with condition is being treated, but generally:

IVIg 0.5–2 g/kg SCIg 0.5 g/kg/mo

Duration

Onset of action ranges from 2 days to 2 weeks, while the peak effect is typically 1–2 months. The half-life of IVIg varies from 18 to 32 days, which is the same range for native IgG.

Remission may be achieved through continuous IgG treatment.

R.J. Yong et al. (eds.), Pain Medicine, DOI 10.1007/978-3-319-43133-8_51

Stem Cell therapy

- preliminary open-labeled study showed autologous administration of stem cells for neuropathic trigeminal pain significantly reduced pain intensity at 6 months and is a safe and well tolerated intervention. e
  Russell Vickers et al *Journal of Pain Research 2014:7 255–263*

- Multipotent Mesenchymal Stem Cell Treatment for Disco genic Low Back Pain and Disc Degeneration.
  Jeffrey Zeckser et al Stem Cells International
  Volume 2016, Article ID 3908389

Questions?

References

- Boleslav Kosharskyy et al Pain Physician: May/June 2013; 16:231-249

  Xu, Jijun ***Yang, Jing*** ***Lin, Peirong*** ***Rosenquist, Ellen*** ***Cheng, Jianguo*** ***Anesthesia & Analgesia*****,** Volume 122, Number 3, March 2016, pp. 843-856(14)
- Noppers I, Niesters M, Swartjes M, Bauer M, Aarts L, Geleijnse N, Mooren R, Dahan A, Sarton E. Absence of long- term analgesic effect from a short-term S-ketamine infusion on fibromyalgia pain: A randomized, prospective, double blind, active placebo-controlled trial. *Eur J Pain* 2011; 15:942-949.
- Venn RM, Karol MD, Grounds RM. Pharmacokinetics of dexmedetomidine infusions for sedation of postoperative patients requiring intensive care. *Br J Anaesth* 2002; 88:669-675.
- Sigtermans MJ, van Hilten JJ, Bauer MC, Arbous MS, Marinus J, Sarton EY, Da- han A. Ketamine produces effective and long-term pain relief in patients with complex regional pain syndrome type 1. *Pain* 2009; 145:304-311
- Consensus Guidelines on the Use of Intravenous Ketamine Infusions for Chronic Pain From the American Society of Regional Anesthesia and Pain Medicine, the American Academy of Pain Medicine, and the American Society of Anesthesiologists, Regional Anesthesia and Pain Medicine • Volume 43, Number 5, July 2018

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