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

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

20%
of U.S. adults have
pancreatitis—pain that
affects their sleep a few
nights a week
Source: National Sleep Foundation, 2000

Annual cost of chronic pain in U.S. healthcare, 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
Source: National Center for Health Statistics, Centers for Disease Control & Prevention, 2011

28% low back pain

15% severe headaches or migraines

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: World of Chronic Pain in a survey of 300 chronic pain sufferers conducted for the American Pain Foundation and supported by Pfizer PharmaRx, 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

1. Pain persisting or increasing
   - Nonopioid +/- Adjuvant

2. Pain persisting or increasing
   - Opioid for mild to moderate pain
     +/- Nonopioid
     +/- Adjuvant

3. Freedom from (cancer) pain
   - Opioid for moderate to severe pain
     +/- Nonopioid
     +/- Adjuvant

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:

- Methadone
- Oxycodone (e.g., OxyContin)
- Hydrocodone (e.g., Vicodin)

The information contained in this infographic is not intended as legal or medical advice. Please consult a professional for more information. ©2018 Shandro Group, all rights reserved.
Dosage

• Tolerable dose vs therapeutic dose (serum levels vs empiric recommendations)
• Combinations may reduce the tolerable dose
Treatment ladder (Modified....)
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 1962 used 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.
<table>
<thead>
<tr>
<th>Condition</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central Neuropathic Pain</td>
<td>2.5mg-5mg/kg, 30-40 minutes</td>
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</tbody>
</table>
| 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                                                     |
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

<table>
<thead>
<tr>
<th>Lipid Emulsion 20%</th>
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<tbody>
<tr>
<td>(Precise volume and flow rate are not crucial)</td>
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<table>
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<tr>
<th>Greater than 70 kg patient</th>
<th>Less than 70 kg patient</th>
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<tbody>
<tr>
<td><strong>Bolus 100 mL Lipid Emulsion 20% rapidly over 2-3 minutes</strong></td>
<td></td>
</tr>
<tr>
<td>• Lipid emulsion infusion 200-250 mL over 15-20 minutes</td>
<td></td>
</tr>
<tr>
<td><strong>Bolus 1.5 mL/kg Lipid Emulsion 20% rapidly over 2-3 minutes</strong></td>
<td></td>
</tr>
<tr>
<td>• Lipid emulsion infusion ~0.25 mL/kg/min (ideal body weight)</td>
<td></td>
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</tbody>
</table>

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 hippocampus.
- 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 affecting 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.
<table>
<thead>
<tr>
<th>Condition</th>
<th>Treatment Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central Neuropathic Pain</td>
<td>bolus 60 μg/kg, 6 μg/kg/min, 17-21 minutes</td>
</tr>
<tr>
<td></td>
<td>0.4 mg/kg, 40 minutes</td>
</tr>
<tr>
<td>Peripheral Neuropathic Pain</td>
<td>0.4 mg/kg, over 1 hour</td>
</tr>
<tr>
<td></td>
<td>60 μg/kg bolus, followed by 6 μg/kg/min infusion, 20 minutes</td>
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<tr>
<td></td>
<td>0.2 mg/kg bolus over 10 minutes, followed by 0.3 mg/kg/hr, one hour or less</td>
</tr>
<tr>
<td>Postherpetic Neuralgia and Peripheral Nerve Injury</td>
<td>0.15 mg/kg, 10 minutes</td>
</tr>
<tr>
<td></td>
<td>0.24 mg/kg, 30 minutes</td>
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<tr>
<td>CRPS</td>
<td>5mg/hr to a maximum dose of 30 mg/hr, 4.2 days</td>
</tr>
<tr>
<td></td>
<td>25 mg/hr for 4 hours daily, 10 days</td>
</tr>
<tr>
<td>Fibromyalgia</td>
<td>0.3 mg-0.5mg/kg, 10- 30 minutes</td>
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</table>
## Ketamine- contraindications

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

- 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 (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.

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)


• 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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