Pioneering Technologies For Lifestyle Based Medicine

Innovative Treatment Options in the Chronic Pain Patient

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Dr. Swidan obtained her Doctor of Pharmacy degree from the University of Michigan and completed a 3-year research fellowship in Bio-Pharmaceutics at the University of Michigan. Previously, she was the Director of Pharmacy at the Chelsea Community Hospital and the clinical pharmacist for the inpatient head and chronic pain service. Currently, she is the President and CEO of Pharmacy Solutions in Ann Arbor, MI, which is a unique, personal and educational specialty pharmacy. She is also the Clinical Associate Professor of Pharmacy at the University of Michigan, College of Pharmacy, and is a board certified and advanced fellow in anti-aging and regenerative medicine.

Dr. Swidan is an internationally-known speaker in the areas of pain management and BHRT, and has authored several books, articles and patient education material in the area of pain management and functional medicine. Currently, Dr. Swidan is completing a Master’s program in Cardio-Metabolic and Functional Medicine.

Sahar Swidan, Pharm.D., BCPS, ABAAHP, FACA
Objectives

1. Review the physiology of pain transmission
2. Review the use of topical medications in various pain syndromes
3. Review common doses of topical medications
Pain

- Nociceptive
- Neuropathic
- CRPS
Pain

- Nociceptive
- Neuropathic
- CRPS

Photo courtesy: perioperativepain.com
Pain

- Nociceptive
- Neuropathic
- CRPS

- Peripheral nerve fiber
- Noxious stimuli of harmful intensity
- Mechanical
- Thermal
- Chemical
- Somatic pain
- Visceral pain
Pain

- Nociceptive
- Neuropathic
- CRPS

• Lesion or dysfunction of the somatosensory nervous system
• Peripheral sensitization
• Central sensitization
• Deafferentation hypersensitivity
• Central lesion
Pain

- Nociceptive
  - Lesion or dysfunction of the somatosensory nervous system
  - Peripheral sensitization
  - Central sensitization
  - Deafferentation
  - Hypersensitization

- Neuropathic
  - Central lesion

- CRPS
  - Pain source
  - Peripheral nerves
  - Spinal tracks
  - Dorsal horn

Photo courtesy: perioperativepain.com
Pain

- Nociceptive
- Neuropathic
- CRPS

- Peripheral neuropathy
- Diabetic neuropathy
- Herpes-zoster infection
- Physical trauma
- Central neuropathy
- Spinal cord injury
- Stroke
Pain

- Nociceptive
- Neuropathic
- CRPS

*Peripheral neuropathy
- Diabetic neuropathy
- Herpes-zoster infection
- Physical trauma
- Central neuropathy
- Spinal cord injury
- Stroke

Burning, stabbing, tingling, pin and needles, electrical
Receptor Location

- \( \alpha \) and glutamate receptors—periphery
- Opioid and \( \alpha-2 \)-locally
- NMDA-epidermal-dermal junction—various subtypes
- GABA-\( \beta \) associate with NMDA for sensory input
- AMPA-local to NMDA
Chronic Neuropathic Pain

- Glutamate and Aspartate are neuro-agonists
  - Transmitter of excitation between primary afferent and spinal neurons
- Endorphins, Glycine, GABA, Zinc, and Mag are inhibitors
- Ampa and NMDA receptors are key
Neuropathic Pain Treatment

- Block the physiologic nerve pathways with various mechanism
  - NMDA Antagonist
  - MU receptor agonist
  - Calcium channel blockers
  - Magnesium channel blockade
  - AMPA antagonist
  - GABA agonist
What is NMDA?

- Glutamate receptor
  - Glutamate is a stimulatory signaling molecule
- Plays a big role in excitotoxicity
- Responsible for memory formation through synaptic plasticity, long term potentiation and long term depression
Pain

- Nociceptive
  - Burning pain in extremities
  - Skin sensitivity

- Neuropathic
  - Changes in skin temperature, color, and texture
  - Changes in hair and nail growth
  - Muscle spasms, weakness, atrophy
  - Stiff and swollen joints

- CRPS
  - Complex Regional Pain Syndrome
Pain

- Nociceptive
  - Pathophysiology not well understood
  - Starts peripherally

- Neuropathic
  - Sensitization of pain transmission neurons throughout neuraxis

- CRPS
  - Inflammation
  - NMDA agonization
  - Sympathetic dysfunction
- Nociceptive
- Neuropathic
- CRPS

- Inflammation
- NMDA agonization
- Sympathetic dysfunction

Photo courtesy: perioperativepain.com
Pain

- Nociceptive
- Neuropathic
- CRPS

- Complications
  - Irreparable damages
    - Muscle and skin atrophy
    - Contracture
  - Spread
Why Topical?

- Topical vs transdermal
  - Topical: Minimal systemic absorption
  - Transdermal: Significant systemic absorption
    - May administer multiple drugs in one dosage form
    - Treatment is focused on peripheral ganglia
- High local concentration
- Less systemic side effects
Pharmacokinetics Following Transdermal Administration

- Transdermal Drugs
  - Pharmacokinetic associated with metabolism and disposition of drug
    Similar in transdermal or oral administration of same drug
Why Topical?

- **Topical vs Transdermal**
  - **Topical:** Minimal systemic absorption
  - **Transdermal:** Significant systemic absorption

- **High local concentration**
- **Less systemic side effects**
- **Psychological effects**

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<table>
<thead>
<tr>
<th>Treatment</th>
<th>( C_{\text{max}} ) % of Oral</th>
<th>AUC % of Oral</th>
</tr>
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<tbody>
<tr>
<td>Voltaren Gel 160 mg/d</td>
<td>0.6%</td>
<td>5.8%</td>
</tr>
<tr>
<td>Voltaren Gel 480 mg/d</td>
<td>2.2%</td>
<td>19.7%</td>
</tr>
<tr>
<td>Diclofenac PO 150 mg/d</td>
<td>100%</td>
<td>100%</td>
</tr>
</tbody>
</table>

Source: Voltaren Gel Prescribing Information 2010
Why Topical?

- Topical vs transdermal
  - Topical: Minimal systemic absorption
  - Transdermal: Significant systemic absorption
- High local concentration
- Less systemic side effects
- Psychological effects

Geriatric patients!
Transdermal

- Needs to penetrate stratum corneum
- Small molecular size
- Lipophylic
- Vehicle, penetration enhancers
Transdermal

- Needs to penetrate stratum corneum
- Small molecular size
- Oxybutynin 359 Da
- Lipophylic
- Vehicle, penetration enhancers

We want topical!
Does not matter as much
Nociceptive pain

- Salicylate
- NSAIDs
- Capsaicin
- Opioids (topical vs transdermal)
- Local anesthetics
- Lidocaine
Nociceptive pain

- Salicylate
- NSAIDs
- Capsaicin
- Opioids (topical vs transdermal)
- Local anesthetics
Nociceptive pain

- Salicylate
  - Low dose topical ointments
  - Commercially available OTC: 0.025% to 0.075%
  - Applied TID to QID for 2-4 weeks
  - Depletes substance P
  - "Burning sensation"

- NSAIDs

- Capsaicin
  - "Makes you comfortable by first making you uncomfortable."

- Opioids (topical vs transdermal)

- Local anesthetics
Nociceptive pain

- Salicylate
- NSAIDs
- Capsaicin
- Opioids (topical vs transdermal)
- Local anesthetics

- Opioid receptors present in inflamed issues
- Pressure sores (10mg once daily with occlusive dressing)
- Chemo-associated mucositis (15mL 2% morphine vs magic mouthwash Q3H 6 times/day)
Nociceptive pain

- Salicylate
  - Used on broken skin and mucosal membranes
  - Does not address inflammation
  - Tachyphylaxis in ~3 days
  - NMDA antagonist (ketamine) can reverse tolerance in mice
  - Concomitant use of topical cannabinoids increases efficacy in mice
- NSAIDs
- Capsaicin
- Opioids (topical vs transdermal)
- Local anesthetics
Nociceptive pain

- Salicylate
- NSAIDs
- Capsaicin
- Opioids (topical vs transdermal)
- Local anesthetics
Neuropathic pain

- High dose capsaicin
  - Amitriptyline
- Tricyclic antidepressants
- Anticonvulsants
  - Gabapentin
  - Lidocaine
- Local anesthetics
  - Ketamine
- NMDA-antagonists
Neuropathic pain

- High dose capsaicin
- Tricyclic antidepressants
- Anticonvulsants
- NMDA-antagonists

Watch for cardiac AE

- QT Prolongation
- Other meds that prolong QT?

Amitriptyline

Lorkhart 2004 (abstract):
- Significant effects in higher dose
- N=118 (responders in 7-day open-label study)
- AMI 4% + KET 2%, AMI 2% + KET 1%, or placebo
- Significantly lower pain intensity in higher dose group
- Significantly more subjects attaining 30% reduction in pain intensity
Neuropathic pain

- High dose capsaicin
  - Pharmacology not well understood
- Tricyclic antidepressants
  - Potential for peripheral actions
- Anticonvulsants
  - Most research focus on vulvodynia
- Local anesthetics
  - Stinging, burning, sharp pain
- NMDA-antagonists
  - 2-6% of gabapentin TID for weeks
Neuropathic pain

- High dose capsaicin
  - Boardman et al 2008
  - Retrospective, N = 51, 8-week or longer
- Gabapentin
  - 2%, 4% or 6% gabapentin cream (in Lipoderm base) TID
- Anticonvulsants
  - 4 to 5 points improvement of 10-point pain score (p < 0.001)
- Local anesthetics
- NMDA-antagonists
  - No systemic side effects reported
Neuropathic pain

- High dose capsaicin
- Tricyclic antidepressants
- Anticonvulsants
- Local anesthetics
- NMDA-antagonists

More research needed
Limited AE and systemic absorptions
Sharp, burning, tingling pain

- Boardman et al 2008
  - Retrospective, N = 51, 8-week or longer
  - 2%, 4% or 6% gabapentin cream (in Lipoderm base) TID
  - 4 to 5 points improvement of 10-point pain score (p < 0.001)
  - No systemic side effects reported
Neuropathic pain

- High dose capsaicin
  - Effective in post-herpetic neuralgia
- Tricyclic antidepressants
  - Burning, jabbing, or deep, aching
- Local anesthetics
  - Some evidences for other types of neuralgia
- NMDA-antagonists
  - Rare systemic side effects
Neuropathic pain

- High dose capsaicin
- Tricyclic antidepressants
- Anticonvulsants
- Local anesthetics
- NMDA-antagonists

Patch indicated for post-herpetic neuralgia

May work for other neuropathic pain

Sharp, burning or dull, aching
Neuropathic pain

- High dose capsaicin: Intravenous, epidural, and intranasal routes have been shown to produce analgesic effects.
- Tricyclic antidepressants: Opioid sparing effects.
- Anticonvulsants: Relieve allodynia & hyperalgesia.
- Local Ketamine: Noncompetitive NMDA antagonist.
- NMDA-antagonists: Topically, may interact with local Na-K channels and opioid receptors.
CRPS

- NSAIDs
- $\alpha_2$ agonists
- Tricyclic antidepressants
- Anticonvulsants
- Local anesthetics
- NMDA-antagonists
CRPS

- NSAIDs
- α2 agonists
- Tricyclic antidepressants
- Anticonvulsants
- Local anesthetics
- NMDA-antagonists

Photo courtesy: perioperativepain.com
CRPS

- **Clonidine**
  - Antagonizes the sympathetic nervous system
  - Coupling of sympathetic and somatosensory nervous system in CRPS
  - Suppresses sympathetic stimulation of pain transmission neurons

- **α2 agonists**
- **Tricyclic antidepressants**
- **Anticonvulsants**
- **Local anesthetics**
- **NMDA-antagonists**
CRPS

- NSAIDs
- α2 agonists
- Tricyclic antidepressants
- Anticonvulsants
- Ketamine
- NMDA-antagonists

- NMDA agonization causes change in gene expression in secondary pain transmission neurons
- That changes synaptic conductance
- NMDA antagonist can suppress this change in gene expression
Combo therapy

- Amitriptyline and ketamine
- High-dose capsaicin and lidocaine
- Morphine and ketamine?
- Morphine and cannabinoids?
Treatment options

- Dull, chronic pain — amitriptyline
- Sharp, burning, tingling (neuropathic) — gabapentin
- Allodynia — lidocaine
- Inflammatory — salicylate, NSAIDs
- Refractory peripheral neuropathic — ketamine, lidocaine
## Transdermals

<table>
<thead>
<tr>
<th>Drug</th>
<th>%</th>
<th>Frequency</th>
<th>MOA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ibuprofen</td>
<td>10-30%</td>
<td>TID-QID</td>
<td>NSAID</td>
</tr>
<tr>
<td>Ketoprofen</td>
<td>5-15%</td>
<td>TID</td>
<td>NSAID</td>
</tr>
<tr>
<td>Piroxicam</td>
<td>0.5-3%</td>
<td>BID</td>
<td>Oxicam NSAID</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>2-5%</td>
<td>TID</td>
<td>NSAID</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>5-10%</td>
<td>BID</td>
<td>NSAID</td>
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</table>
## Transdermals

<table>
<thead>
<tr>
<th>Drug</th>
<th>%</th>
<th>Frequency</th>
<th>MOA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclobenza</td>
<td>1-2%</td>
<td>BID-TID</td>
<td>Muscle Relaxant</td>
</tr>
<tr>
<td>Guiafenesin</td>
<td>10%</td>
<td>TID-QID</td>
<td>Muscle relaxanat/Expectorant</td>
</tr>
<tr>
<td>DM</td>
<td>10%</td>
<td>BID-QID</td>
<td>NMDA Antagonist</td>
</tr>
<tr>
<td>Ketamine</td>
<td>0.5-15%</td>
<td>BID-QID</td>
<td>NMDA Antagonist</td>
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</table>
# Transdermal

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<tr>
<th>Drug</th>
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<th>Frequency</th>
<th>MOA</th>
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<tbody>
<tr>
<td>Nifedipine</td>
<td>1-5%</td>
<td>TID</td>
<td>CA channel blocker</td>
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<tr>
<td>Clonidine</td>
<td>0.1-0.3%</td>
<td>TID</td>
<td>Alpha 2 Agonist</td>
</tr>
<tr>
<td>Phenoxybenzamine</td>
<td>1-1.5%</td>
<td>QD-BID</td>
<td>Irreversible Alpha 2 antagonist</td>
</tr>
<tr>
<td>Capsaicin</td>
<td>0.025-0.1%</td>
<td>TID-QID</td>
<td>Substance P blocker</td>
</tr>
<tr>
<td>Pentoxyfylline</td>
<td>5-10%</td>
<td>TID</td>
<td>TNF-A inhibitor Peripheral dilator</td>
</tr>
</tbody>
</table>
## Transdermal

<table>
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<th>Drug</th>
<th>%</th>
<th>Frequency</th>
<th>MOA</th>
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<tbody>
<tr>
<td>Amitriptyline</td>
<td>1-2%</td>
<td>TID</td>
<td>TCA</td>
</tr>
<tr>
<td>Baclofen</td>
<td>2-3%</td>
<td>TID</td>
<td>GABA Agonist</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>3-10%</td>
<td>TID</td>
<td>Glutamate Antagonist</td>
</tr>
<tr>
<td>Diphenhydramine</td>
<td>5-10%</td>
<td>TID-QID</td>
<td>Na/Ca channel blockade</td>
</tr>
</tbody>
</table>
# Transdermal

<table>
<thead>
<tr>
<th>Drug</th>
<th>%</th>
<th>Frequency</th>
<th>MOA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine</td>
<td>2-5%</td>
<td>TID</td>
<td>Na channel blocker, Membrane stabilizer</td>
</tr>
<tr>
<td>Lidocaine</td>
<td>2-5%</td>
<td>TID</td>
<td>Anesthetic</td>
</tr>
<tr>
<td>MS</td>
<td>1-5%</td>
<td>QID</td>
<td>Mu agonist</td>
</tr>
<tr>
<td>DMSO</td>
<td>10-50%</td>
<td>TID</td>
<td>Penetration enhancer/ Anti-inflammatory</td>
</tr>
<tr>
<td>2-DDG</td>
<td>1-2%</td>
<td>TID</td>
<td>Antiviral</td>
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</tbody>
</table>
Transdermal L-Arginine

- 12.5% L-arginine HCl (4mg L-arginine/cm²) applied twice a day to feet x 2 weeks

- Water-based moisturizing vehicle containing choline chloride 10%, sodium chloride 5%, and magnesium chloride 5%

- Improved blood flow and temperature

- Long lasting effect

  - High local concentration may cause inactive eNOS to form active dimers
Diabetic Neuropathy

- Agents to increase circulation
  - Nifedipine transdermal
  - Pentoxifylline transdermal
  - α-Lipoic acid (thioctic acid)
    - 300 to 600 mg daily po
  - Modulates nitric oxide within cells
  - Stimulates glucose uptake by muscle cells
  - Helps prevent diabetic neuropathy by decreasing lipid peroxidation of nerve tissue
Raynaud’s Syndrome

- Calcium channel blockers
  - Nifedipine PO 10-20 mg tid
  - Side effects in 1/3 (headache, flushing, dizziness, reflex tachycardia, peripheral edema)
  - Transdermals (0.2 to 0.5%) cream
- Pentoxifylline 5 to 15%
- Primrose oil and fish oil
Hydroxycobalamin

- Prophylaxis of migraine
  - Nitric oxide scavenger
  - Pilot study used 1 mg intranasal hydroxycobalamin daily for 3 months
  - 19 patients
  - Reduction in frequency >50% seen in 53%
Anal Fissures and Spasms

- 30-40% of population suffers from proctologic pathologies once in lifetime

- Nifedipine
  - 20 mg p.o. bid x 8 wks, 9 of 15 healed,
  - orally: flushing and headache
  - 0.2% topical gel: q 12 hrs x 21 days, 95% total remission

- Diltiazem 3% and Bethanecol 0.1%

- Albuterol for spasms
Topical Treatments of Vulvodynia

- Amitriptyline 2% / Baclofen 2%
- Gabapentin 3-6%
- Ketamine 2.5-5%
- Doxepin 1%

All in oil-in-water emulsion cream bases

- Dose ½ mL at HS to BID
Pain Management and Hormones

- Optimize levels of hormones in males and females
- Progesterone has great anti-inflammatory and pain modulating effects
- Testosterone in Males- Anti-inflammatory
- DHEA- Lots of data in rheumatology literature
The most effective therapies for chronic pain are often not used in clinical practice

- Education
- Exercise
- Cognitive therapy
- Medications in conjunction with other therapies

Chronic pain may be both “peripheral” and “central”
Questions???

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The Role of Ketamine in Psychiatry, Addiction, and Pain Management
Background

- Ketamine first synthesized in 1960s as alternative to phencyclidine
- Initially, used as a dissociative anesthetic
- Limited use in contemporary anesthesia due to side effects, namely psychedelic symptoms (Niesters et al. 2013)
- More commonly used in animal anesthesia (Morgan, Curran 2012)
- At subanesthetic doses, produces analgesia
Pharmacology

- A non-competitive antagonist of the NMDA receptor – blocks glutamate action

- $S(+) \text{ isomer has higher affinity for NMDA receptor than } R(-) \text{ isomer}$ (Morgan, Curran 2012)

- Also interacts with monoaminergic, muscarinic, and opioidergic receptors (Niesters et al. 2013)
Psychiatric effects

- Emergence symptoms after IV infusion – hallucinations, delusions, ‘out-of-body’ experiences

- Induces transient symptoms of schizophrenia in healthy patients but no evidence linking chronic ketamine use to diagnosis of psychiatric disorders

- Frequent users exhibited profound impairment of long and short term memory (Morgan, Curran 2012)
Reward and Dependence

- Increases dopaminergic modulation in the brain (similar to other addictive substances) $\Rightarrow$ activates reward pathway

- Interaction with $\mu$ opioid receptors may contribute to its rewarding properties

- Some case reports of ketamine dependence but no large scale studies undertaken so incidence of ketamine dependence is unknown

- Frequent users report increasing dose over time (tolerance) (Morgan, Curran 2012)
• Study by Krupitsky and Grinenko 1997 demonstrated benefit of adding ketamine psychedelic therapy (KPT) to standard therapy

• 65.8% of KPT group showed total abstinence > 1 year compared to 24% of standard treatment group
Role in Depression

- IV infusion of ketamine resulted in rapid antidepressant effect, but only lasted 1-2 weeks
  - 0.5 mg/kg dosing was used in one study
  - Response rates 24 h after ketamine infusion (71%) matched the rates after 6-8 weeks (65%) of standard monoaminergic therapy (Naughton et al. 2014)
- Rapid reduction in suicidal ideation independent of antidepressant effect (Caddy et al. 2014)
Role in Depression

• Dissociative and psychotomimetic effects followed ketamine infusion but did not last longer than 80 min (Caddy et al. 2014)

• Bottom line: ketamine’s antidepressant effects peak at 24 h post infusion and generally last 1-2 weeks
Role in Depression

• Clinical use?
  
• Can provide immediate relief until monoaminergic therapy takes effect
  
  • Prevent loss of work or school days

  • Reduce suicide

  • Shorten hospital stays

• Overall, good safety profile associated with single dose of ketamine (not enough info on repeated infusions) (Naughton et al. 2014)
Role in Pain Management

- Antagonism of NMDA receptor thought to modulate pain
- Potent analgesic at sub-anesthetic doses (0.5-1 mg/kg/hr) that prevents sensitization of spinal neurons to painful stimuli (Morgan, Curran et al. 2012)
- Roles in acute, chronic, and cancer/palliative care pain
Role in Pain Management

- **Acute pain**
  - Recommended to start 0.1 mg/kg i.v. ketamine and titrating up with a limit of 0.5 mg/kg
  - Dose required for treating acute pain can lead to loss of consciousness in patients (Persson 2013)

- **Chronic Pain**
  - A 2003 review of chronic neuropathic pain conditions concluded that evidence for the efficacy of ketamine is moderate to weak
  - Long-term efficacy and safety of ketamine is not well-studied (Persson 2013)
Role in Pain Management

• Not well-established in cancer/palliative care pain (Persson 2013)
  • May be used as adjuvant therapy if standard therapy is not effective
  • Caution since ketamine may upregulate mTor, which accelerates tumor growth (Naughton et al. 2014)

• Complex Regional Pain Syndrome (CRPS)
  • Current level of evidence is 2B – weak recommendation, moderate quality evidence
  • Need large, well-designed controlled trials (Azari et al. 2012)
Role in Pain Management

- Ketamine in postoperative pain systematic review by Laskowski et al. 2012
  - Treatment group: ketamine + opioid if necessary
  - Placebo group: just opioid
- IV ketamine effective at reducing opioid consumption and delaying time to first analgesic dose in patients with postoperative pain
- Increased neuropsychiatric effects associated with ketamine but reduced postoperative nausea/vomiting (PONV) (Laskowski et al. 2011)
Role in Pain Management

• Postoperative pain (cont.)

• IV ketamine better in some situations
  
  • Least opioid reduction in head and neck surgery
  
  • Upper thoracic and abdominal surgeries had greater opioid reduction
  
  • VAS pain scores > 7/10 showed greatest reduction in opioid use
  
  • Site of surgery and intensity of pain affect the degree of opioid reduction

• Despite using more opioid, 78% of placebo groups experienced significantly more pain than ketamine treatment groups
  
  • Implies that ketamine improves overall quality of pain control (Laskowski et al. 2011)
Summary/Conclusion

• Ketamine is still undergoing experimental study in regards to its antidepressant effects, not ready for consistent clinical use

• Ketamine has analgesic properties but has limited use in treating various types of pain

• Well-designed, randomized clinical trials required to corroborate case reports of efficacy

• Further investigation into ketamine’s mechanisms of action may elucidate how to better utilize ketamine


We will email you a copy of this presentation and recording tomorrow!

Thank You!

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