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presents

Innovative Treatment Options in the Chronic Pain Patient

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Objectives

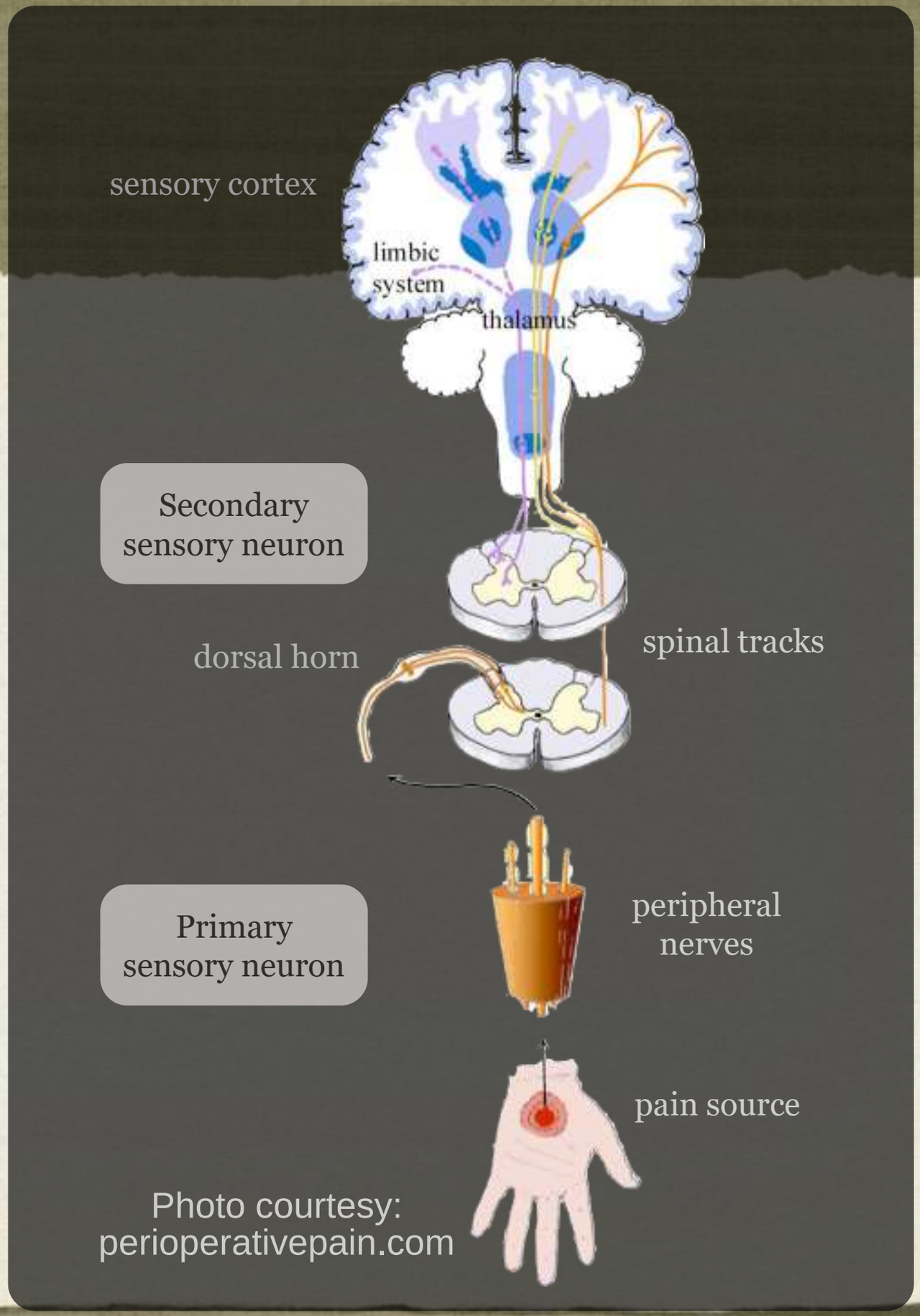
1. Review the physiology of pain transmission
2. Review the use of topical medications in various pain syndromes
3. Review common doses of topical medications

Pain

- Nociceptive
- Neuropathic
- CRPS

Pain

- Nociceptive
- Neuropathic
- CRPS



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

sensory cortex

Secondary sensory neuron

- Nociceptive

dorsal horn

- Neuropathic
- CRPS

Primary sensory neuron

Photo courtesy: perioperativepain.com

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

Pain

- Nociceptive
- Neuropathic
- CRPS

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

Pain

- Nociceptive
- Neuropathic
- CRPS

Burning, stabbing, tingling, pin and needles, electrical

Receptor Location

- ά and glutamate receptors-periphery
- Opioid and ά-2-locally
- NMDA-epidermal-dermal junction-various subtypes
- GABA-ß 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
- Neuropathic
- CRPS

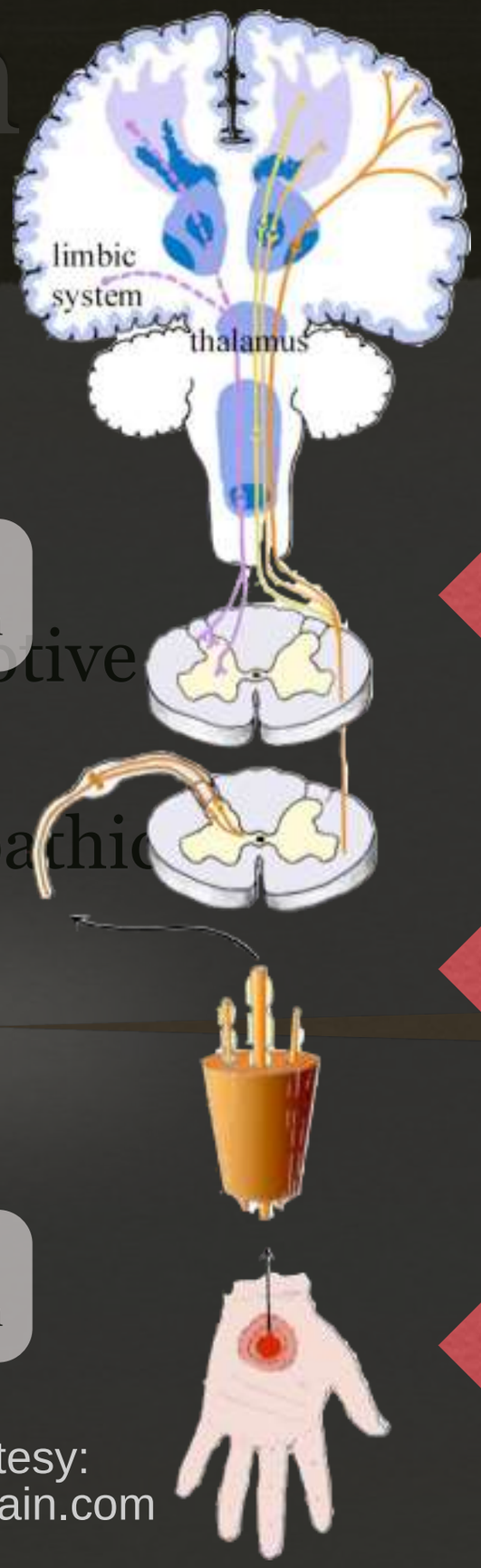
- Complex Regional Pain Syndrome
- Burning pain in extremities
- Skin sensitivity
- Changes in skin temperature, color, and texture
- Changes in hair and nail growth
- Muscle spasms, weakness, atrophy
- Stiff and swollen joints

Pain

- Nociceptive
- Neuropathic
- CRPS

- Pathophysiology not well understood
- Starts peripherally
- Sensitization of pain transmission neurons throughout neuraxis
- Inflammation
- NMDA agonization
- Sympathetic dysfunction

Pain



Secondary sensory neuron

- Nociceptive
- Neuropathic
- CRPS

INFLM

NMDA

INFLM

NE

Primary sensory neuron

INFLM

Photo courtesy: perioperativepain.com

- Inflammation
- NMDA agonization
- Sympathetic dysfunction

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
- Psychologi

Treatment	C_{max} % of Oral	AUC % of Oral
Voltaren Gel 160 mg/d	0.6 %	5.8%
Voltaren Gel 480 mg/d	2.2%	19.7%
Diclofenac PO 150 mg/d	100%	100%

Source: Voltaren Gel Prescribing Information 2010

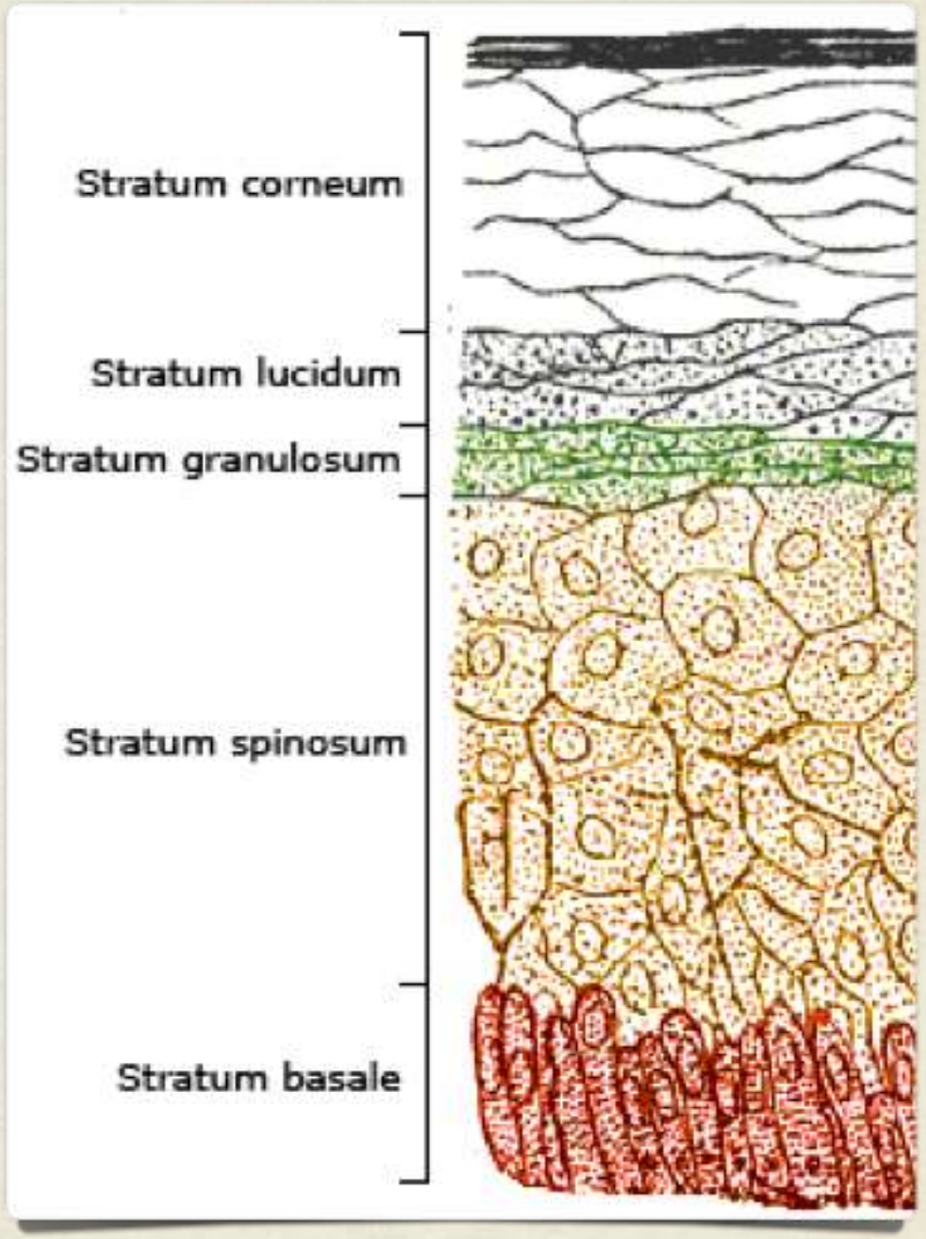
Why Topical?

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

Geriatric patients!

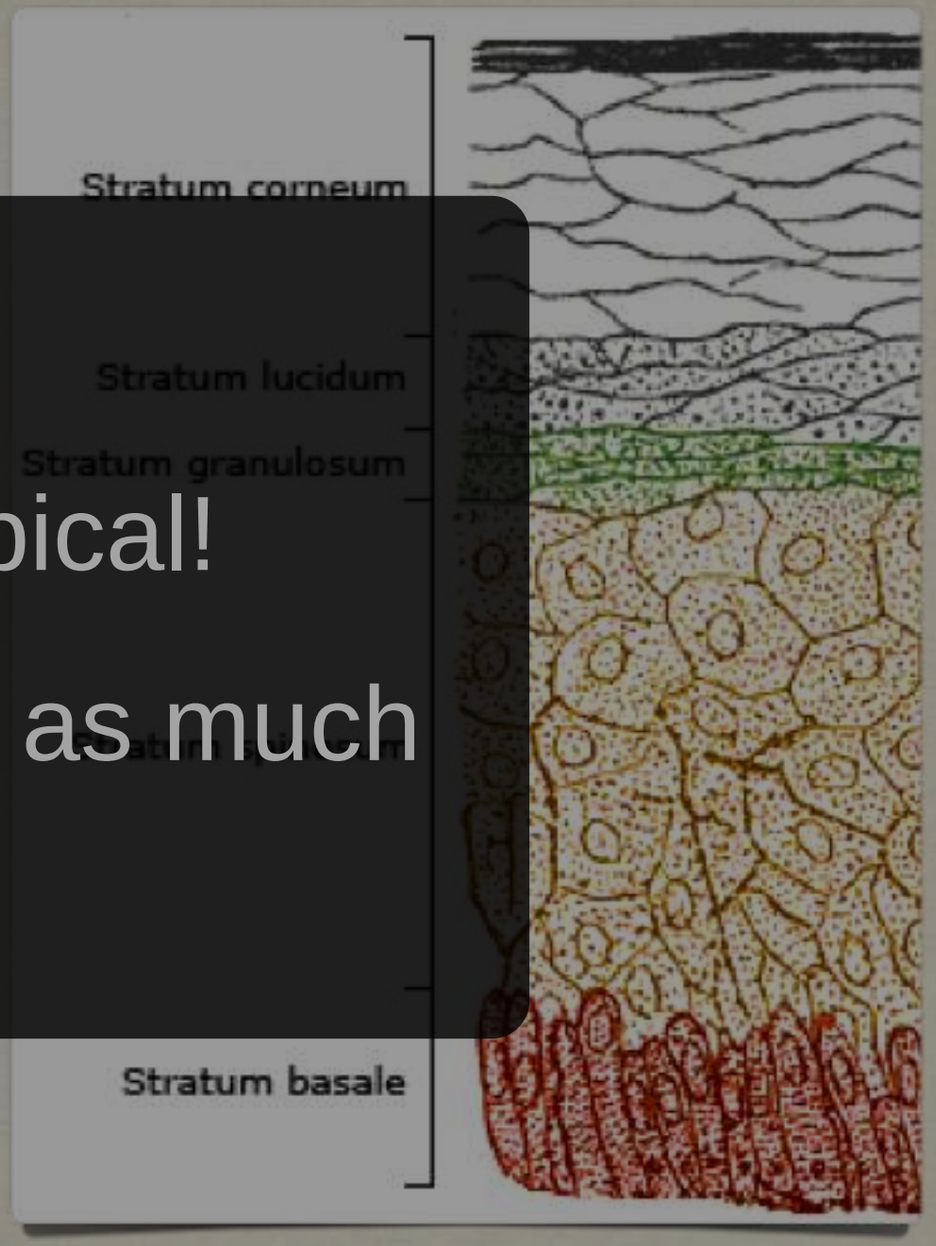
Transdermal

- 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

Morphine

Lidocaine

Nociceptive pain

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

Nociceptive pain

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

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

Nociceptive pain

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

Morphine

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

Morphine

- 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

Nociceptive pain

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

Neuropathic pain

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

Amitriptyline

Gabapentin

Lidocaine

Ketamine

Neuropathic pain

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

Amitriptylin
e

Watch for cardiac AE

QT Prolongation

Other meds that prolong QT?

Neuropathic pain

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

Gabapentin

- Pharmacology not well understood
- Potential for peripheral actions
- Most research focus on vulvodynia
- Stinging, burning, sharp pain
- 2-6% of gabapentin TID for weeks

Neuropathic pain

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

Gabapentin

- 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
- Tricyclic antidepressants
- Gabapentin
- Anticonvulsants
- Local anesthetics
- NMDA-antagonists

More research needed

Limited AE and systemic absorptions

Sharp, burning, tingling pain

Neuropathic pain

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

Neuropathic pain

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

Lidocaine

Patch indicated for post-herpetic neuralgia

May work for other neuropathic pain

Sharp, burning or dull, aching

Neuropathic pain

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

Ketamine

•Intravenous, epidural, and intranasal routes have been shown to produce analgesic effects

•Opioid sparing effects

•Relieve allodynia & hyperalgesia

•Noncompetitive NMDA antagonist

•Topically, may interact with local Na-K channels and opioid receptors

CRPS

- NSAIDs
- α2 agonists

Clonidine

- Tricyclic antidepressants
- Anticonvulsants
- Local anesthetics
- NMDA-antagonists

CRPS

- NSAIDs
- α2 agonists
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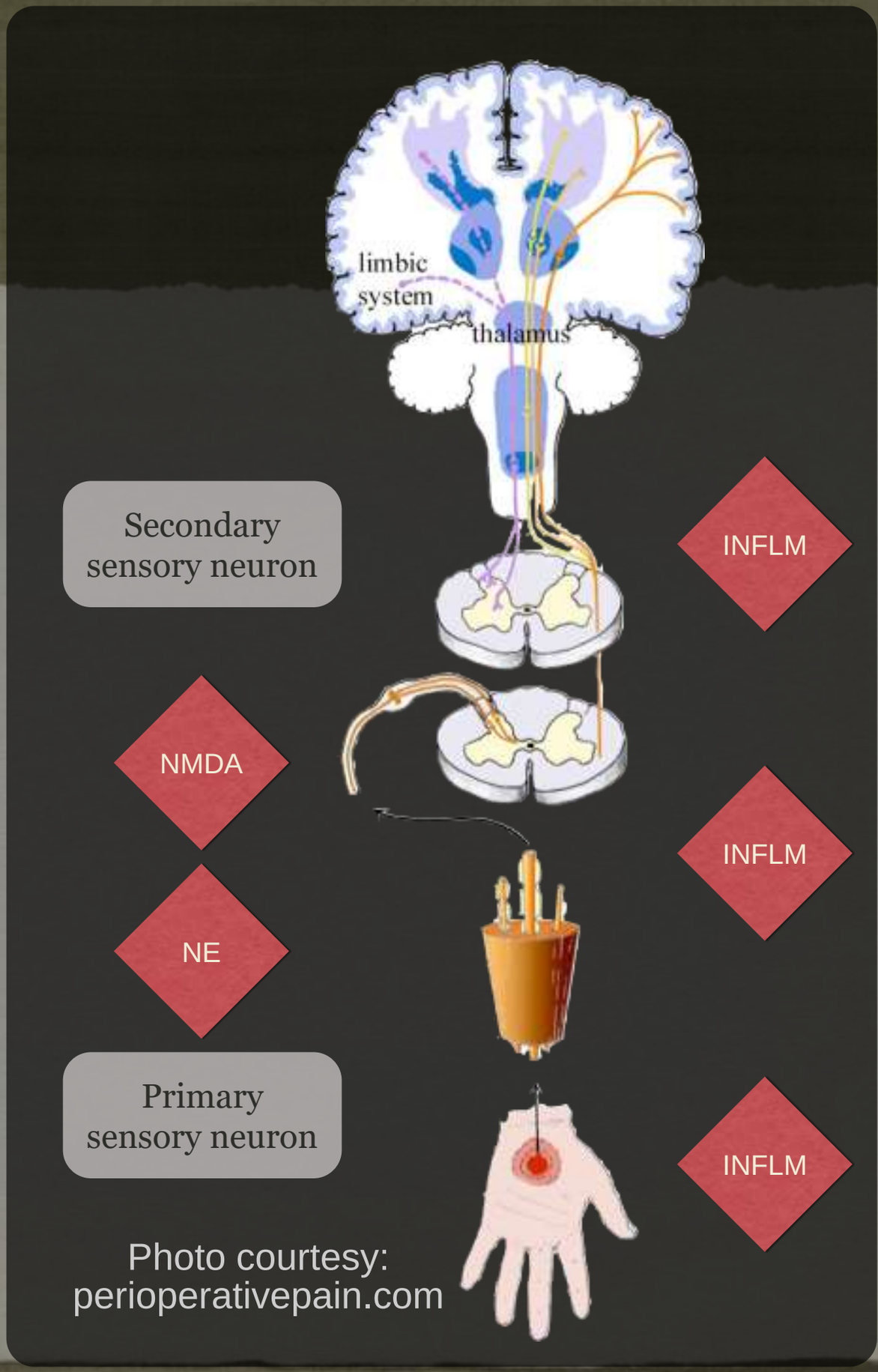


CRPS

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

Clonidine

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

CRPS

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

Ketamine

•NMDA agonization causes change in gene expression in secondary pain transmission neurons

•That changes synaptic conductance

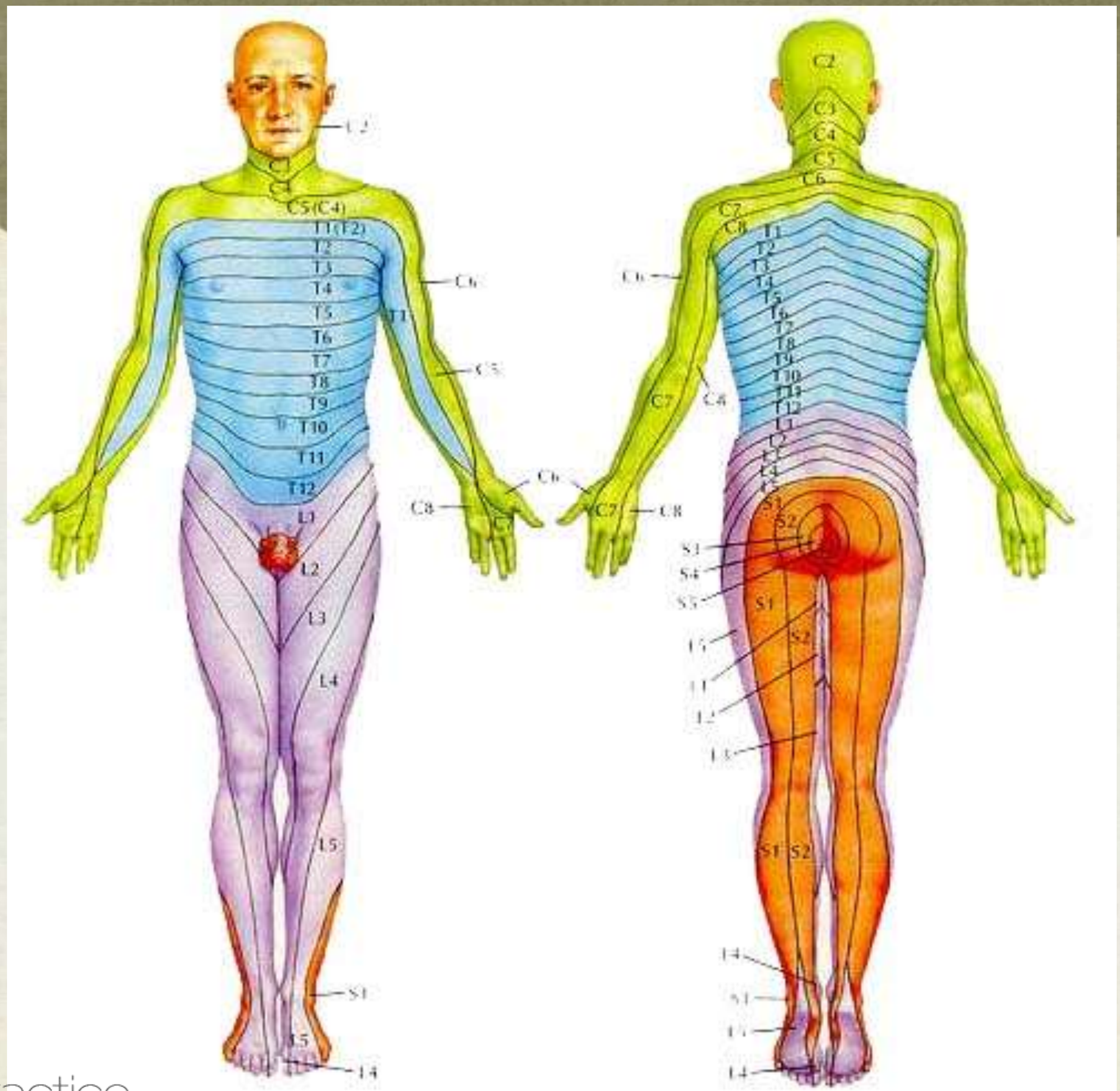
•NMDA antagonist can suppress this change in gene expression

Combo therapy

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

Treatment options

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



Transdermals

Drug	%	Frequency	MOA
Ibuprofen	10-30%	TID-QID	NSAID
Ketoprofen	5-15%	TID	NSAID
Piroxicam	0.5-3%	BID	Oxicam NSAID
Diclofenac	2-5%	TID	NSAID
Indomethacin	5-10%	BID	NSAID

Transdermals

Drug	%	Frequency	MOA
Cyclobenza	1-2%	BID-TID	Muscle Relaxant
Guiafenesin	10%	TID-QID	Muscle relaxanat/ Expectorant
DM	10%	BID-QID	NMDA Antagonist
Ketamine	0.5-15%	BID-QID	NMDA Antagonist

Transdermal

Drug	%	Frequency	MOA
Nifedipine	1-5%	TID	CA channel blocker
Clonidine	0.1-0.3%	TID	Alpha 2 Agonist
Phenoxybenzamine	1-1.5%	QD-BID	Irreversible Alpha 2 antagonist
Capsaicin	0.025-0.1%	TID-QID	Substance P blocker
Pentoxyfylline	5-10%	TID	TNF-A inhibitor Peripheral dilator

Transdermal

Drug	%	Frequency	MOA
Amitriptyline	1-2%	TID	TCA
Baclofen	2-3%	TID	GABA Agonist
Gabapentin	3-10%	TID	Glutamate Antagonist
Diphenhydramine	5-10%	TID-QID	Na/Ca channel blockade

Transdermal

Drug	%	Frequency	MOA
Carbamazepine	2-5%	TID	Na channel blocker, Membrane stabilizer
Lidocaine	2-5%	TID	Anesthetic
MS	1-5%	QID	Mu agonist
DMSO	10-50%	TID	Penetration enhancer/ Anti-inflammatory
2-DDG	1-2%	TID	Antiviral

Transdermal L-Arginine

- 12.5% L-arginine HCl (4mg L-arginine/cm^2) 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 effecs
- Testosterone in Males- Anti-inflammatory
- DHEA- Lots of data in rheumatology literature

Summary

- 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 phencyclinde
- 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(+) isomer has higher affinity for NMDA receptor than R(-) 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) → activates reward pathway
- Interaction with μ 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)

Role in Alcohol Dependence

- 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 effecive
  - 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

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Thank You!

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

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