Updates on the Opioid Epidemic

Chairperson: Kenji Saito, MD, JD, FACOEM

Tuesday, March 29th, 2022

2:35-3:25pm

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Kenji Saito, MD, JD, FACOEM

Roberto Feliz, MD

What We Know Now
That We Didn't
Know Before

Jan Gellis, MD

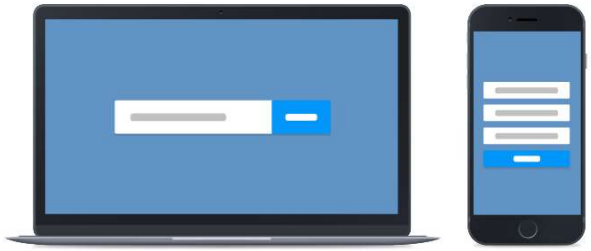
A Multi-Modal Approach
to Pain Management:
Prescription, OTC, &
Topical Medications

Dean Hashimoto, MD, JD

Oxycontin and the Purdue
Pharma Bankruptcy

How to join

Web



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Is the opioid epidemic a concern at your workplace?

Yes

No

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Text **MEDLAW** to **22333** once to join

Is the opioid epidemic a concern at your workplace?

Yes

No

Is the opioid epidemic a concern at your workplace?

Yes

No

What are some word(s) that comes to mind when managing workplace concerns around the opioid epidemic?

What are some of the challenges you face in the workplace due to the opioid epidemic? (up vote - click thumbs up on the answers you agree with)

Top

What are some best practices you have at your workplace to address the opioid epidemic?

Top

What We Know Now
That We Didn't Know Before

Roberto Feliz, MD

Boston Pain Center
Hyde Park, MA

OPIOID: What we know now that we did not know before

- What do we know now?
- **Old Theory of NO ceiling effect**: Is WRONG. There is a ceiling effect.
- In fact, chronic ingestion of **opioids lose their effectiveness over time**.

Opioid: What we know now, that we did not know before

- What do we know now?

- **Chasing the pain** with escalating doses of opioid **is WRONG**: Tolerance develops.

- Patient reports 7/10 pain now, similar to their reports of 7-10 years ago of 7/10, despite escalation of to maximum higher dose.

2022
Work Related Injuries Workshop

Opioid: what we know now that we did not know before

- What do we know now?

- We now better understand **Opioid Induced Neuroinflammation**

Opioid: What we know now that we did not know before

- **NEUROINFLAMMATION**:
- Microglia/Astroglia neurons Cells: Secretion of Pro-inflammatory, pain causing/prolonging substances: TNF, PG, interleukins, 2, 6.

- **Neuroinflammation (in the CNS) is = to chronic Pain perpetuation**.

- A patient with **an inflamed brain/CNS, feels and experiences more pain.**

Opioid: What we know now that we did not know before

- What do we know now?
- **Opioid Induced Hyperalgesia** at the level of nociceptors of skin sensory receptors.
- Patient on chronic opioid feel and report more sensitivity to pain, even to light touch, than patients who minimize opioid.

Opioid: What we know now that we did not know before

- My observation:

- For chronic pain, **opioids provide 30% to 40% relief at best (20% to 40% range**). The rest: Covers **Anxiety and End-of-Dose, early signs of withdrawals at end of each dose, forcing patient to seek the next dose**.

Living within the **Comfort Zone vs Discomfort Zone.**

Opioid: What we know now that we did not know before

- What do we know now?

- We better understand **Hormonal suppression**: Testosterone/Estrogen leading to generalized weakness, de-conditioning, fatigue/malaise, lack of libido and an overall **lack of "get up and go."**

Opioid: what do we know that we did not know before

- What do we know now?

- We are beginning to understand: **Personalized, Patient-centric, precision, DNA/Genetic based prescribing** : Using CP 450 isoenzymes: ultra slow metabolizers, rapid metabolizers, ultra-rapid metabolizers.

- Prescribing directly to the individual patient and not the general population.

Opioid: what we know now that we did not know before

- What do we know now?
- **Drug Holiday**:
- Not detrimental to the pain (my observation). In fact, most patients feel better as the tolerance improves, the neuroinflammation decreases, the hyperalgesia decreases, the hormonal suppression improves.
- **Encourage a Drug Holiday**. Patient feels better.
- The difficulty relies in convincing most patients that weaning away from a medication designed to relief pain is beneficial to reducing or relieving the actual pain (**the paradoxical effect**).

A Multimodal Approach to Pain Management

Pharmacologic Options

Janice E. Gellis, MD

Assistant Professor of Anesthesiology
Geisel School of Medicine at Dartmouth

Attending Physician Center for Pain and Spine
Dartmouth Hitchcock Medical Center

2022
Work Related Injuries Workshop

Disclosures

- I have nothing to disclose.

Pain is Multimodal

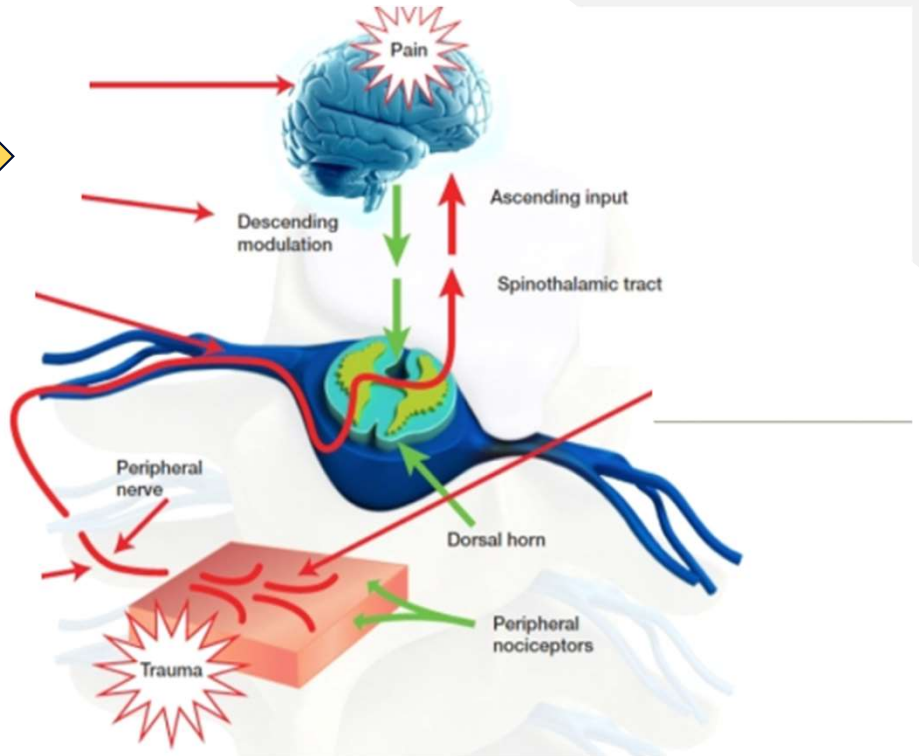
Multiple categories

- Acute
- Chronic
- Nociceptive
- Neuropathic
- Nociplastic

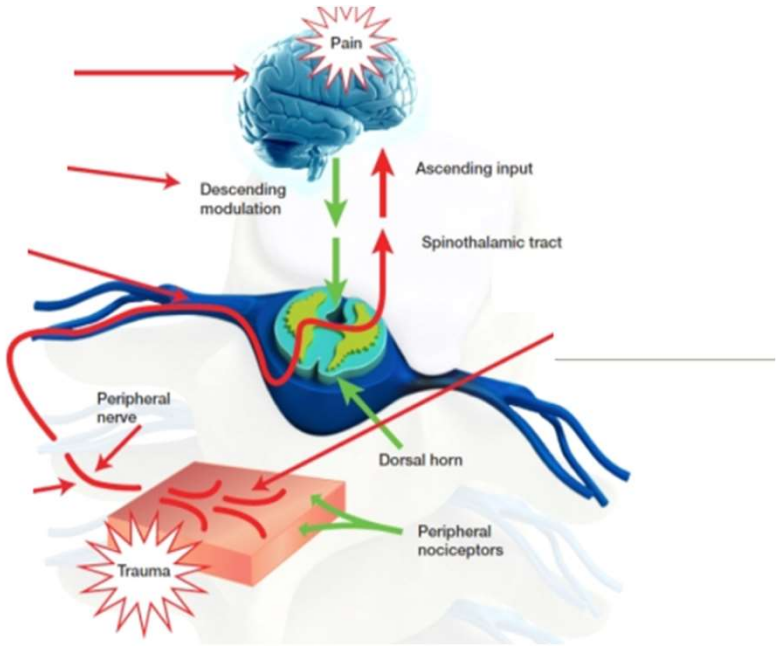
Multiple locations

- Central
- Peripheral
- Myofascial
- Visceral

Multimodal interactions



Pain is Multimodal



- Involves complex interactions that perpetuate pain

Cohen, S.P., L. Vase, and W.M. Hooten. The Lancet, 2021. **397**(10289): 2082-2097
Garland, E.L.. Primary Care: Clinics in Office Practice. 2012. **39**(3): 561-571

Preventing the Transition to Chronic Pain

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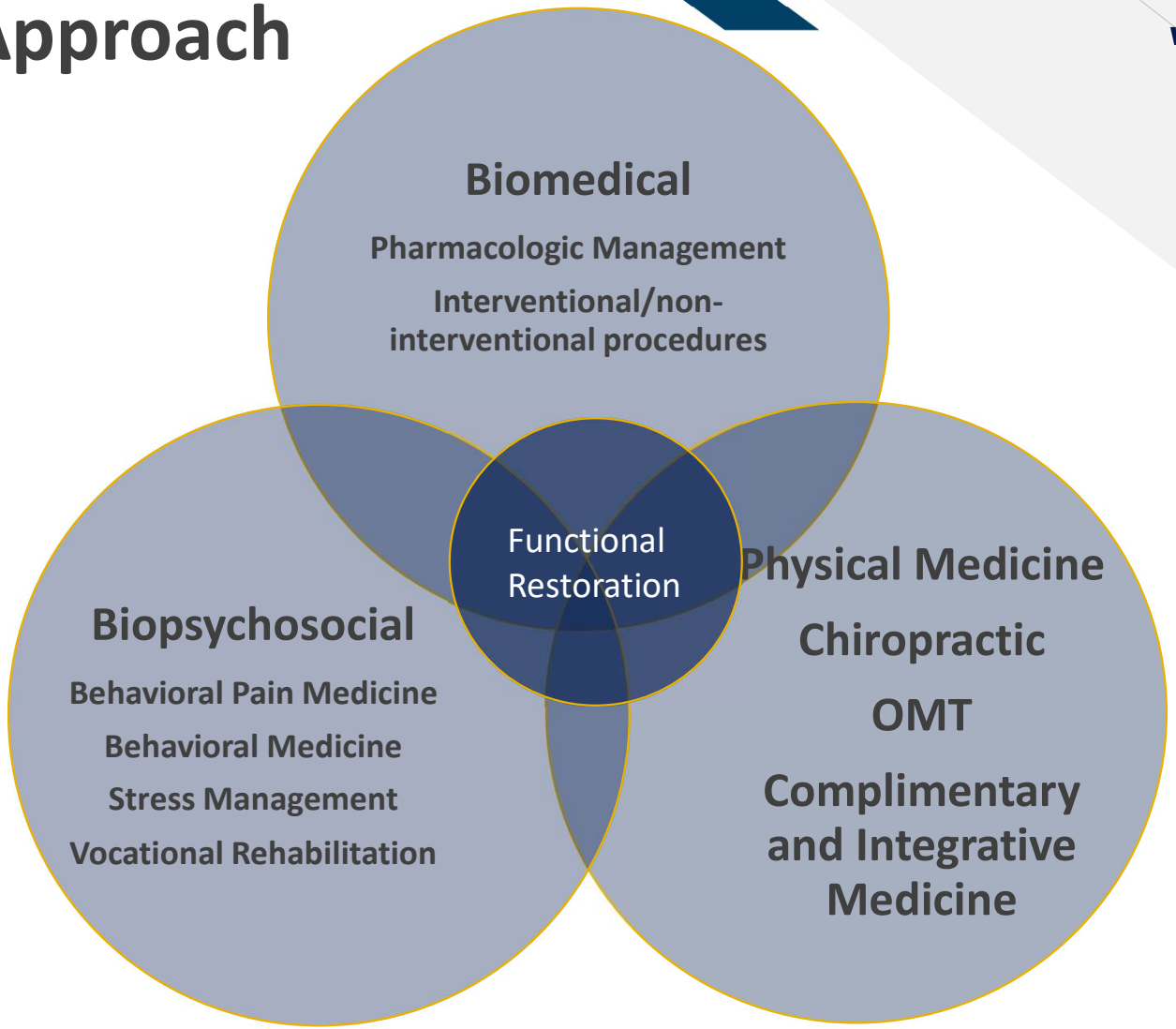
- The nervous system is “plastic” and ongoing barrage of pain signals can lead to peripheral and central sensitization.
- Managing pain promptly and in a multimodal fashion is important in preventing this transition
- Changes occur in the nervous system as pain persists, that can make medication less effective.
- Opioids can contribute to this due to opioid induced hyperalgesia.
- Medication along with a multimodal approach can help to remodel the nervous system.

Price, T.J., et al. Nature Reviews Neuroscience, 2018. **19**(7): p. 383-384.
Cohen, S.P., L. Vase, and W.M. Hooten. The Lancet, 2021. **397**(10289): 2082-2097

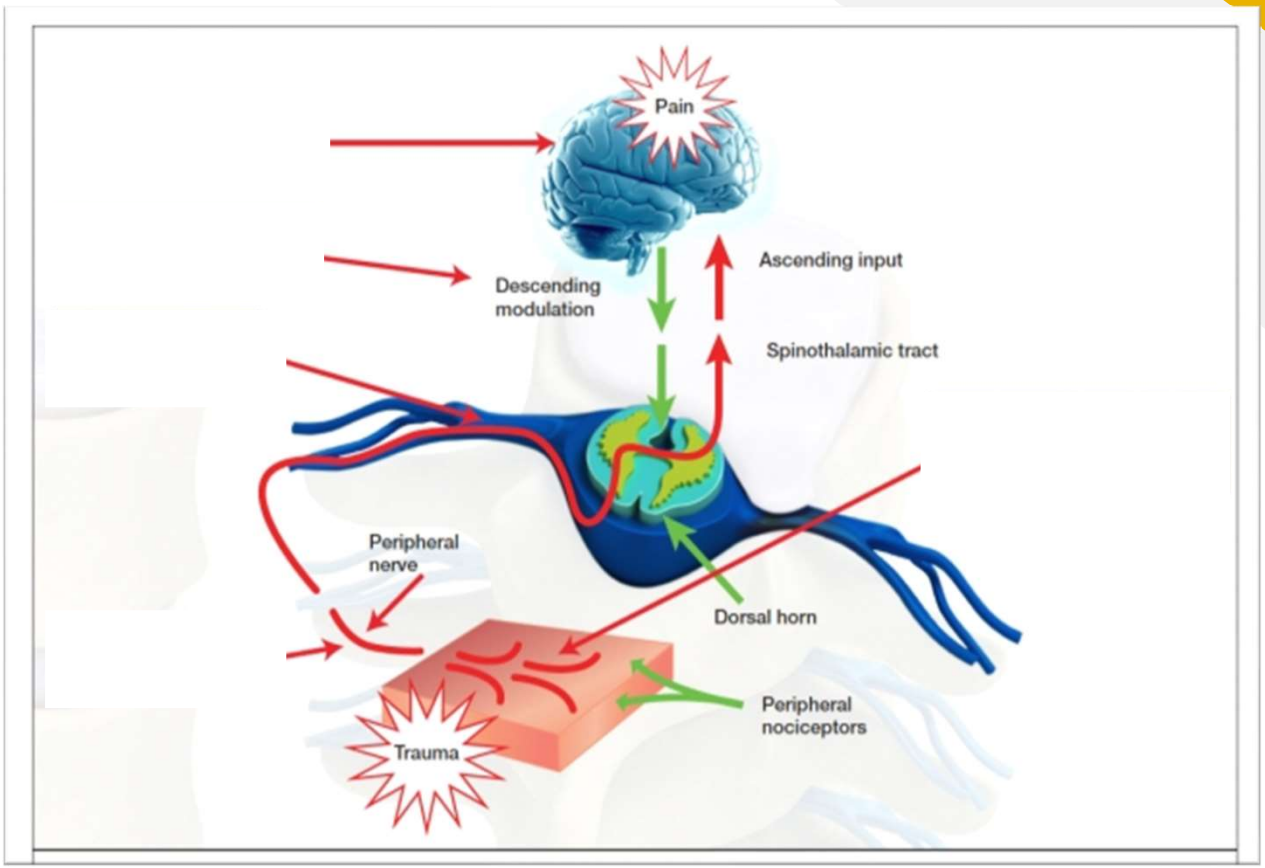
Multimodal Approach



Multimodal Approach

Multimodal Approach-Pharmacologic

- Prescription
  - Membrane stabilizers
    - Pregabalin
    - Gabapentin
  - Antidepressants
    - SSRIs
    - SNRIs
    - Tricyclic antidepressants
  - NSAID
  - Topical Preparations
- OTC medication
- Herbs and Supplements



Cohen, S.P. and J. Mao. BMJ, 2014. 348: f7656.

Low Dose Naltrexone

Microglial Cells and Pain

What are they?

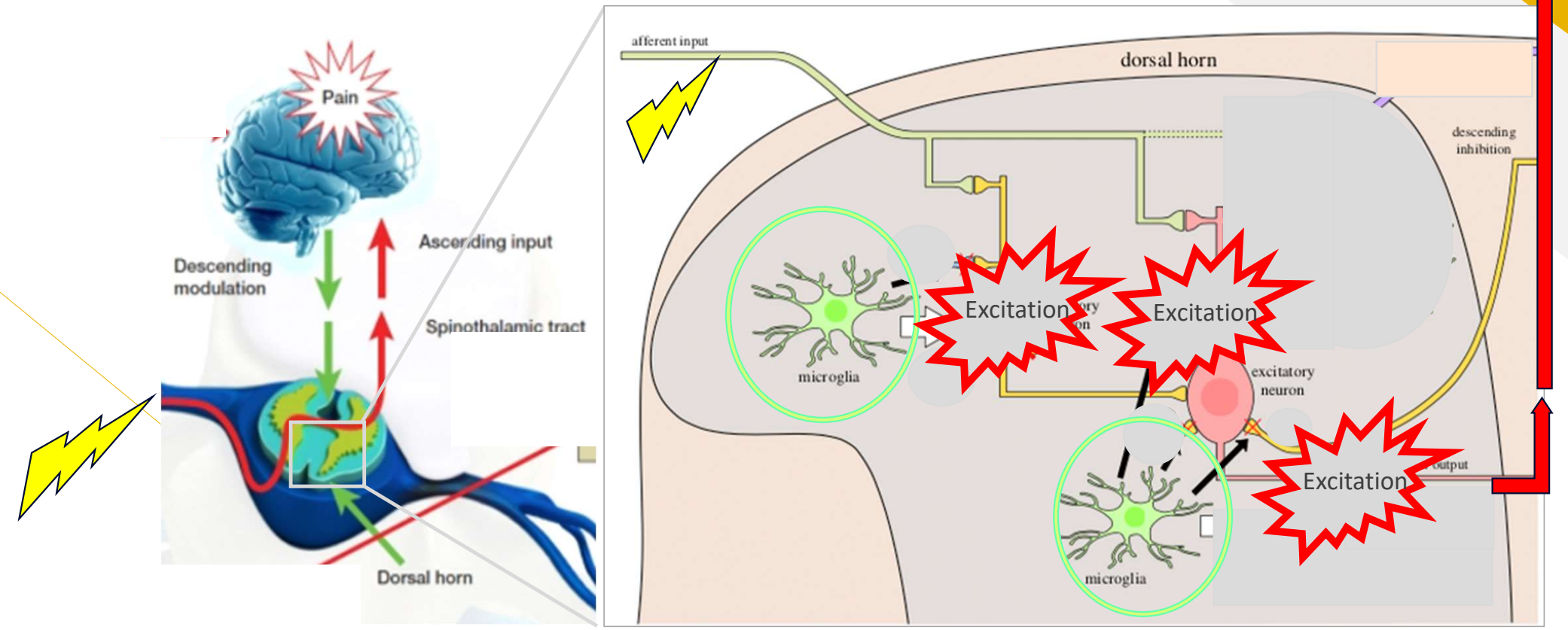
- Cells in the CNS that are involved in nerve cell inflammation via activation of Toll-like receptors
- Involved in neuronal signaling
- “Remodelers” that affect synapses and neurons

Why do we care?

- At one time felt only role was neuro-immune response to nerve damage
- May have a role in chronicity of pain

Ward H, West SJ. R. Soc. Open Sci. 2020. 7: 200260

Microglial Cells and Pain



Adapted from Ward H, West SJ. R. Soc. Open Sci. 2020. 7: 200260

Low Dose Naltrexone (LDN)

What is it?

- Naltrexone-opioid receptor antagonist (50-100 mg daily)
- In low doses (1-6 mg/day) it binds to and Toll-like receptors in microglial cells, where it acts as an antagonist

Clinical applications

- Neuropathic pain,
- Complex regional pain syndrome,
- Chronic inflammation
- Other painful conditions (fibromyalgia, multiple sclerosis)

Toljan K, Vrooman B.. Med. Sci. 2018, 6, 82
Kim PS. Current Pain and Headache Reports. 2020, 24: 64

Low Dose Naltrexone (LDN)

Prescribing info

- Available as compounded formulation.
- Patient cannot be taking opioids.
- Few or no side effects.
- Usually started at 1.5 mg.

Toljan K, Vrooman B.. Med. Sci. 2018, 6, 82
Kim PS. Current Pain and Headache Reports. 2020, 24: 64

Subanesthetic Ketamine

Ketamine

What is it?

- Anesthetic agent in higher doses
- Phencyclidine derivative
- N-methyl-D-aspartate receptor **antagonist** (NMDAr)
- Ketamine blocks the NMDAr to decrease neuronal excitation

What is the NMDAr

- Gate keeper of neuronal activity
- Activated by glutamate an excitatory neurotransmitter
- Once activated can cause central sensitization.
- NMDAr excitation plays a key role in ongoing perpetuation of pain.

Zhou, J.Y., et al. Adv Anesth, 2020. 38: 97-113.
Cohen, S.P., et al. Regional Anesthesia and Pain Medicine, 2018. **43**(5): 521-546

Ketamine: Administration and Uses

How is it administered?

- Oral, intranasal, topical (compounded)
- Intravenously
- Sub-anesthetic doses are used

Clinical Applications

- Management of pain, particularly that associated with peripheral and central sensitization.
- Intraoperatively (opioid sparing)

Orhurhu, V., et al. Anesth Analg, 2019. **129**(1): 241-254
Cohen, S.P., et al. Regional Anesthesia and Pain Medicine, 2018. **43**(5): 521-546
Schwartzman, R.J., et al. Pain, 2009, 147(1-3): p. 107-15.
Sigtermans, M.J., et al.. Pain, 2009, **145**(3): p. 304-11.

Ketamine: Side Effects

Route dependent

- Topical (compounded)< Oral or Intranasal< Intravenous

CNS

- Hallucinations
- Dysphoria
- Nightmares
- Sedation

Cardiac

- High Blood Pressure
- Tachycardia

Azari, P., et al. CNS Drugs, 2012. **26**(3): 215-28.

Ketamine: Side Effects

Organ effects

- Liver
- Bladder

Psychiatric

- Psychosis

Topical Preparations

Topical Preparations

Advantages

- Minimal or no systemic effects
- Compounding can allow for tailored formulations

Disadvantages

- Skin reactions
- No systemic effects
- Often have to be compounded

Leppert. Molecules (2018) 23:681
Casale. Curr Pain Headache Rep (2017) 21:15

Topical Preparations

Develop a high concentration in joint structures

Local anti-inflammatory effect

- NSAIDS

Act locally in tissues: receptors or ion channels

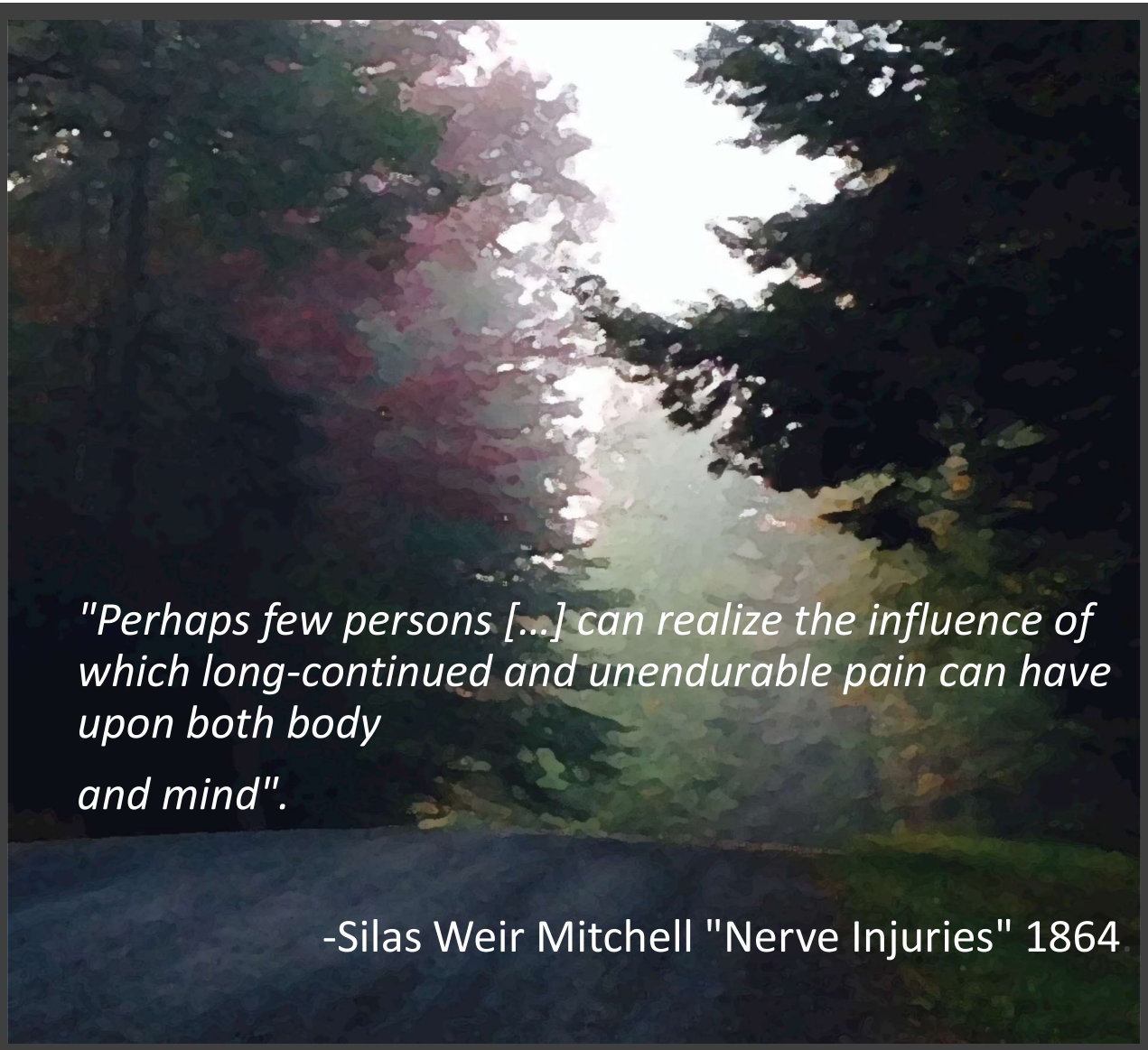
- Ketamine
- Lidocaine
- Amitriptyline
- Capsaicin
- Gabapentin

Leppert. Molecules , 2018 23:681
Casale. Curr Pain Headache Rep, 2017. 21:15
Sawynok, J.Anesth Analg, 2014. 119(1): 170-8.
Sawynok, J. Eur J Pain, 2014. 18(4): 465-81.

References

- Azari, P., et al., *Efficacy and safety of ketamine in patients with complex regional pain syndrome: a systematic review.* CNS Drugs, 2012. **26**(3): p. 215-28.
- Casale, R., Z. Symeonidou, and M. Bartolo, *Topical Treatments for Localized Neuropathic Pain.* Curr Pain Headache Rep, 2017. **21**(3): p. 15.
- Cohen, S.P., et al., *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.* Reg Anesth Pain Med, 2018. **43**(5): p. 521-546.
- Cohen, S.P. and J. Mao, *Neuropathic pain: mechanisms and their clinical implications.* BMJ, 2014. **348**: p. f7656.
- Cohen, S.P., L. Vase, and W.M. Hooten, *Chronic pain: an update on burden, best practices, and new advances.* The Lancet, 2021. **397**(10289): p. 2082-2097.
- Garland, E.L., *Pain Processing in the Human Nervous System.* Primary Care: Clinics in Office Practice, 2012. **39**(3): p. 561-571.
- Kim, P.S. and M.A. Fishman, *Low-Dose Naltrexone for Chronic Pain: Update and Systemic Review.* Current Pain and Headache Reports, 2020. **24**(10).
- Leppert, W., et al., *Transdermal and Topical Drug Administration in the Treatment of Pain.* Molecules, 2018. **23**(3).
- Orhurhu, V., et al., *Ketamine Infusions for Chronic Pain: A Systematic Review and Meta-analysis of Randomized Controlled Trials.* Anesth Analg, 2019. **129**(1): p. 241-254.
- Price, T.J., et al., *Transition to chronic pain: opportunities for novel therapeutics.* Nature Reviews Neuroscience, 2018. **19**(7): p. 383-384.
- Sawynok, J., *Topical and peripheral ketamine as an analgesic.* Anesth Analg, 2014. **119**(1): p. 170-8.
- Sawynok, J., *Topical analgesics for neuropathic pain: preclinical exploration, clinical validation, future development.* Eur J Pain, 2014. **18**(4): p. 465-81.
- Schwartzman, R.J., et al., *Outpatient intravenous ketamine for the treatment of complex regional pain syndrome: a double-blind placebo controlled study.* Pain, 2009. **147**(1-3): p. 107-15.
- Sigtermans, M.J., et al., *Ketamine produces effective and long-term pain relief in patients with Complex Regional Pain Syndrome Type 1.* Pain, 2009. **145**(3): p. 304-11.
- Toljan, K. and B. Vrooman, *Low-Dose Naltrexone (LDN)-Review of Therapeutic Utilization.* Med Sci (Basel), 2018. **6**(4).
- Ward, H. and S.J. West, *Microglia: sculptors of neuropathic pain?* Royal Society Open Science, 2020. **7**(6): p. 200260.
- Zhou, J.Y., et al., *Update on Ketamine.* Adv Anesth, 2020. **38**: p. 97-113.

Thank you


"Perhaps few persons [...] can realize the influence of which long-continued and unendurable pain can have upon both body
and mind".
-Silas Weir Mitchell "Nerve Injuries" 1864

Oxycontin and the Purdue Pharma Bankruptcy

Dean Hashimoto, MD, JD

Chief Medical Officer, Workplace Health & Wellness, Mass General Brigham

Professor of Law, Boston College

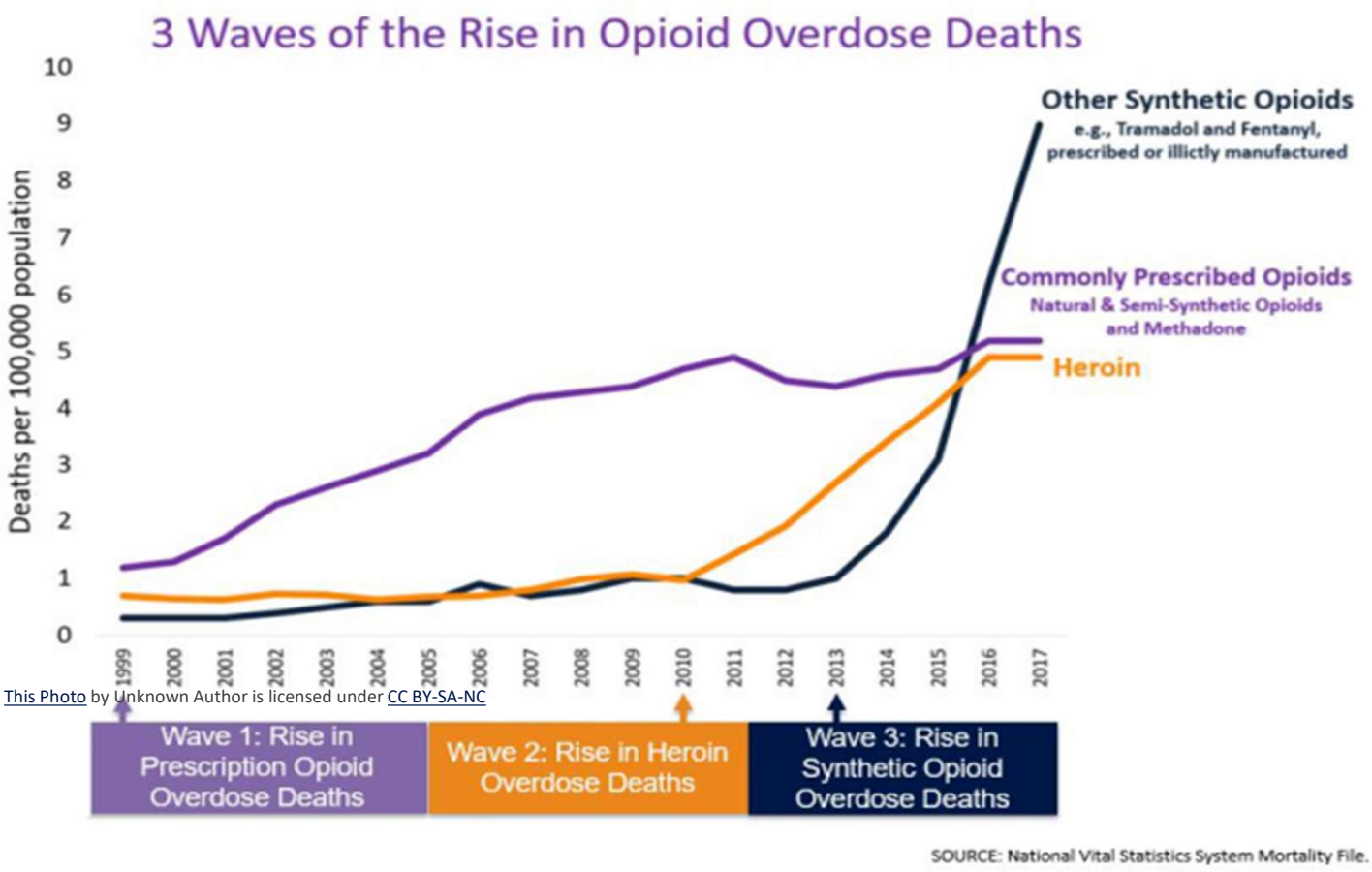
Issues:

Opioid Pharmaceutical Litigation

- Description of Purdue Pharma, Oxycontin, and the opioid epidemic
- What is the opioid litigation?
- What are the key legal issues?
- What is the significance of the settlement of the Purdue Pharma litigation?
- What are the future issues that need resolution?

Opioid Epidemic and Purdue Pharma

- In 1995, FDA approved Oxycontin based on the representation that it was less addictive than other opioids and may be widely prescribed.
- Purdue Pharma engaged in intense marketing to medical providers and the public.
- By 1999, the death wave from opioid prescriptive medications began to rise.
- The first wave from prescription opioids was closely associated with the following waves.



November 2020: Department of Justice Settlement Resulting in Purdue Pharma's Admission of 3 Felony Offenses and Civil Liability of Shareholders

3 felony offenses including:

- Selling to providers even though believed that these providers were diverting to abusers;
- Misleading FDA about steps it had taken to prevent diversion;
- Giving kickbacks to providers such as through doctor speaker programs to encourage recommending its prescription opioids.

Civil law suits against shareholders including Sackler family

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Failure of Government Regulation and Abusive Practices by the Drug Industry

The opioid epidemics resulted from the failure of government regulation and abusive practices by the drug industry:

- No industry or federal guidelines for the promotion of prescription drugs;
- FDA approved opioids for “around-the-clock” pain relief without support based on scientific data;
- Close relationship between FDA and Purdue Pharma due to revolving door to jobs.
- Aggressive marketing by industry was tolerated.

Ultimately, 400,000 Americans have died as a result of 100 billion pain pills distributed from manufacturers

What Is the Opioid Litigation?

4 Main Categories

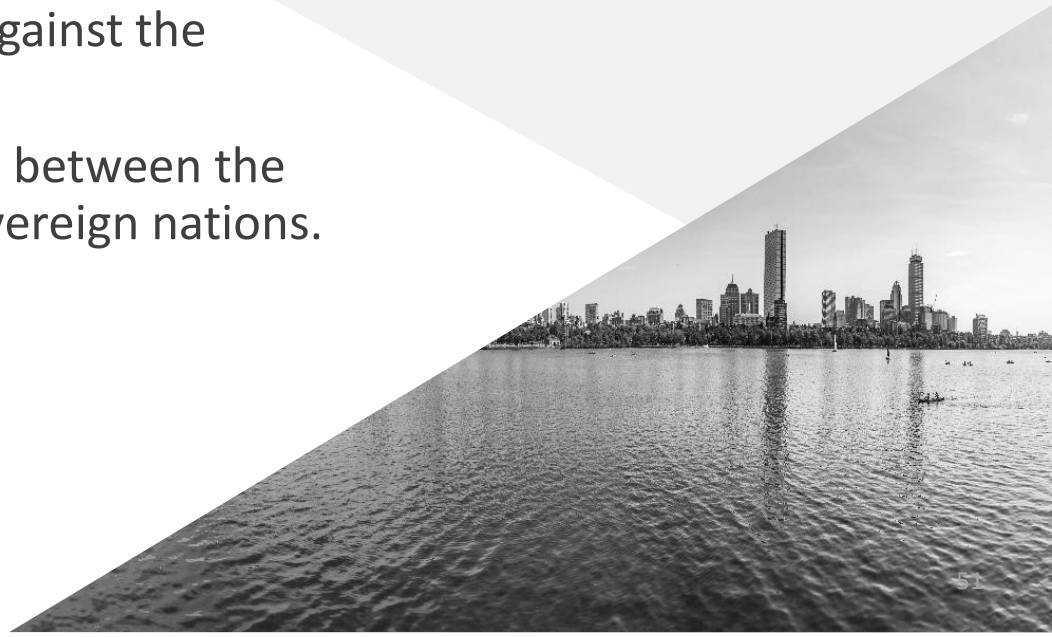
1. Civil enforcement actions and criminal prosecutions;
2. Civil lawsuits by local governments (city, county) and tribal sovereign nations against manufacturers, distributors, and retailer ("multidistrict litigation" = MDLs);
3. Civil lawsuits by states' attorneys general.
4. Purdue Pharma's civil bankruptcy;

Civil lawsuits by city, county, and tribal sovereign nations

- Initiated in 2014, local governments sought recoveries from manufacturers, distributors, and retailors
- They want to ensure fair distribution that is not reliant on state legislatures and is focused on resolving the opioid epidemic.
- Previous history of tobacco litigation settlement of $200 billion with state AGs that resulted in only 2.7% being spent on smoking treatment and prevention

Civil lawsuits by state attorney generals

- As an alternative to class action suits by private individuals, the state attorney general may bring *parens patriae* lawsuits on behalf of a state for violations against the health and well-being of its residents.
- A “global settlement” requires collaboration between the states and the cities, counties, and tribal sovereign nations.



Legal Issues: Defining "public nuisance" and determining legal causation

Did manufacturers and others create a "public nuisance"?

- Oklahoma Supreme Court on November 2021 overturned earlier court ruling that imposed $465 million in liability to state residents.
- The state supreme court held that public nuisance law as not intended to address a large public health crisis and would be impermissibly vague law.

Did drug companies cause an illegal rise in prescription opioids?

- California court held that drug manufacturers marketing and promotion efforts were appropriate and responsible and did not cause a public nuisance.
- Not a direct link to prescription decisions made by medical providers and abuse by patients.

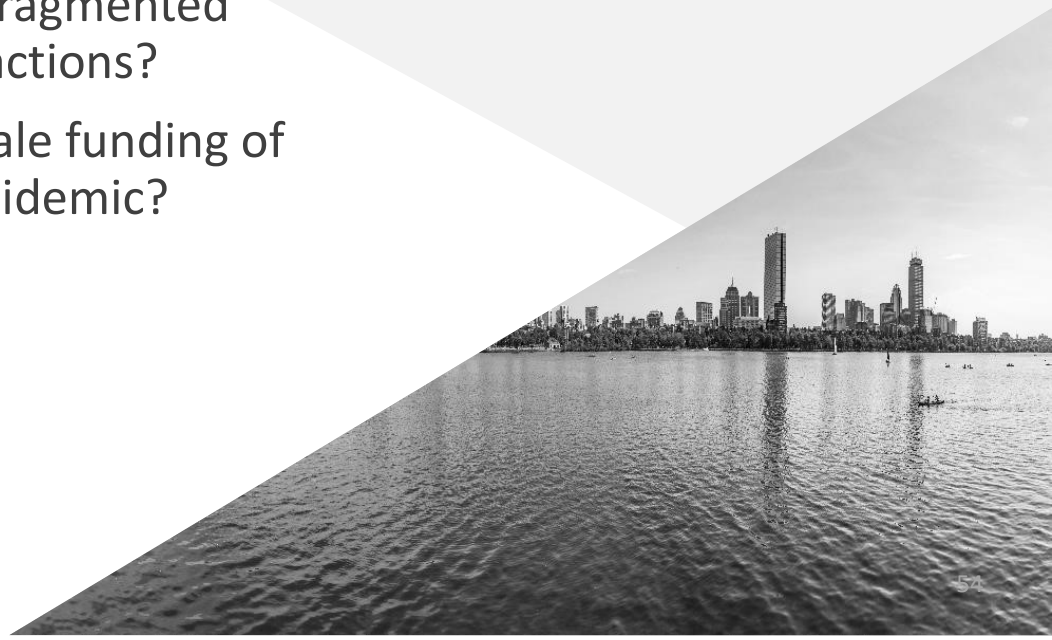
Settlements have been reached: $26 billion settlement involving J&J and 3 distributors, but many more still need to be made.

Purdue Pharma's Civil Bankruptcy Settlement

- Purdue will be renamed Knoa Pharma and overseen by a public board. Knoa will evolve into a manufacturer of medications for addiction reversal and treatment.
- Sackler family contribution will be $5.5 billion plus $500 million more contingent on future sale of international pharmaceutical companies.
- In exchange, the Sackler family will receive a shield from future litigation over opioid lawsuits. Earlier settlement for $4.8 billion was initially overturned based on this issue of providing protection since Sacklers' themselves are not filing for bankruptcy.

Future Issues

- How will future courts rule on “public nuisance” actions and legal causation?
- Will global settlements prevail over more fragmented approaches by states, localities, and class actions?
- Will the legal settlements result in large scale funding of programs directly addressing the opioid epidemic?



What are some of the challenges you face in the workplace due to the opioid epidemic? (up vote - click thumbs up on the answers you agree with)

Top

What are some best practices you have at your workplace to address the opioid epidemic?

Top

Questions? Discussion?