Update in Pain Management 2025

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Objectives

- Updates in Pharmacology
- Review of Current Recommendations
- Update of Interventional Techniques in Pain Management
- Correlation of Interventional Pain Management and Osteopathic Principles

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Today's Presenter

- Joseph R. Reyes DO
- Interventional Pain Management Physician
- American Board of Anesthesiology Board Certified in Pain Medicine
- American Board of Anesthesiology Board Certified in Anesthesiology

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Education

- WVSOM Class of 1999
- Traditional Osteopathic Internship – WVSOM
- St. Louis University – Anesthesiology
- Tufts University - Pain Management Fellowship
- Boston – Las Vegas - Wisconsin

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Disclosures

No financial relationships to disclose

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Should we still prioritize pain?

- Prevalence of Chronic Pain – 11-40% of US population
- Epidemiological studies have shown that chronic pain
  - Increases with age
  - Significant socioeconomic differences with pain related disability and impact on quality of life

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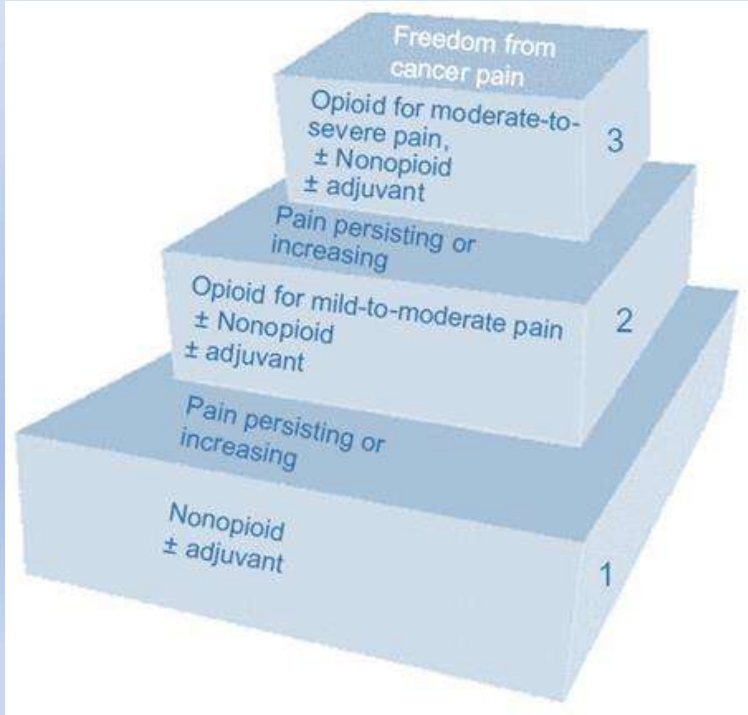
Interventional Pain Management

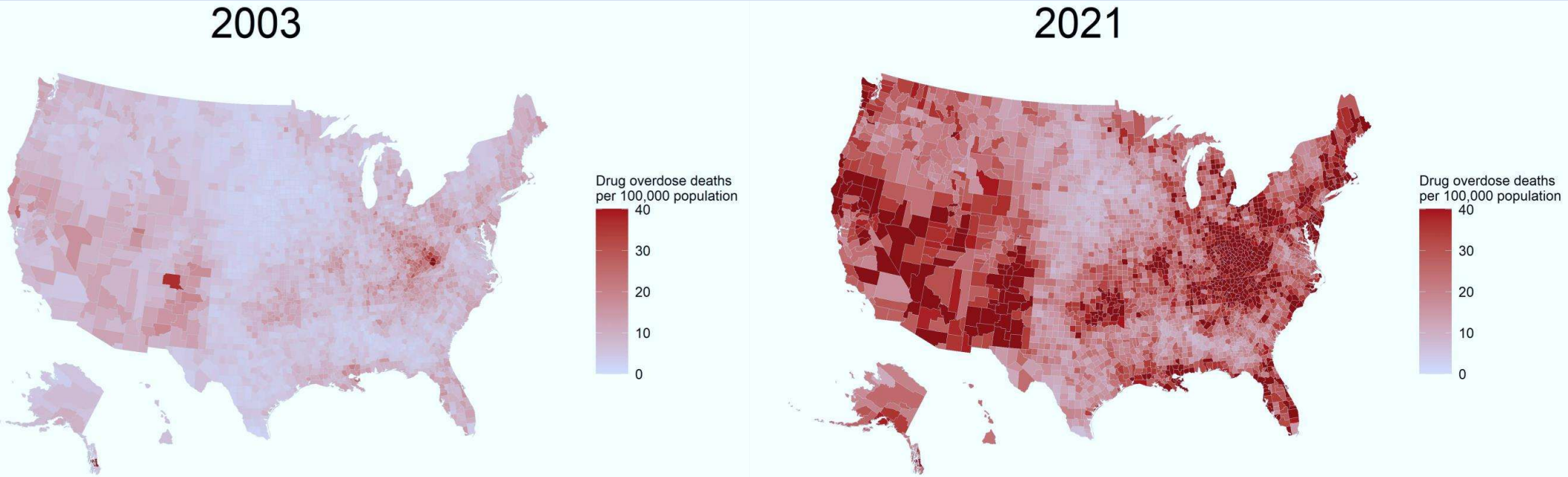


World Heath Organization ladder

Where does IPM fit in the progression of pain management

Drug Overdoses

Model-based crude death rates for drug overdose per 100,000 population by county and year.



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SOURCE: National Center for Health Statistics, National Vital Statistics System, mortality data (http://www.cdc.gov/nchs/deaths.htm).

SUGGESTED CITATION: Rossen LM, Bastian B, Warner M, Khan D, Chong Y. Drug overdose mortality: United States, 2003–2021. National Center for Health Statistics. 2022. (Available from: https://www.cdc.gov/nchs/data-visualization/drug-poisoning-mortality/).

Previous Overdose Data Conclusions...

- Prior data led CDC to conclude that prescription opioids are the principal determinate for opioid overdose deaths, total overdose deaths and addiction
- "...Overprescribing opioids-largely for chronic pain-is a key driver of America's drug overdose epidemic"- Tom Frieden, CDC director

Centers for Disease Control and Prevention. Press release.
CDC releases Guideline for Prescribing Opioids for Chronic Pain.
March 15, 2016

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International Opioid Consumption

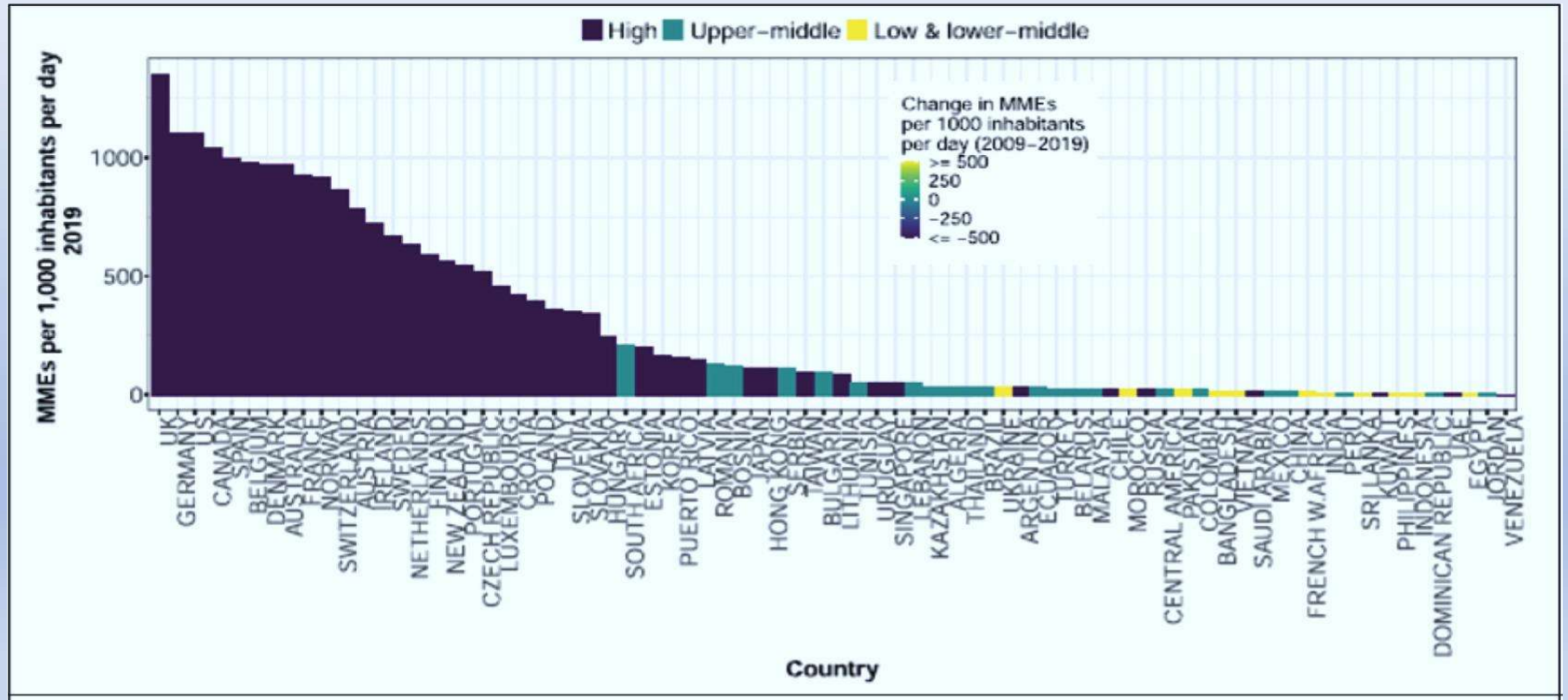
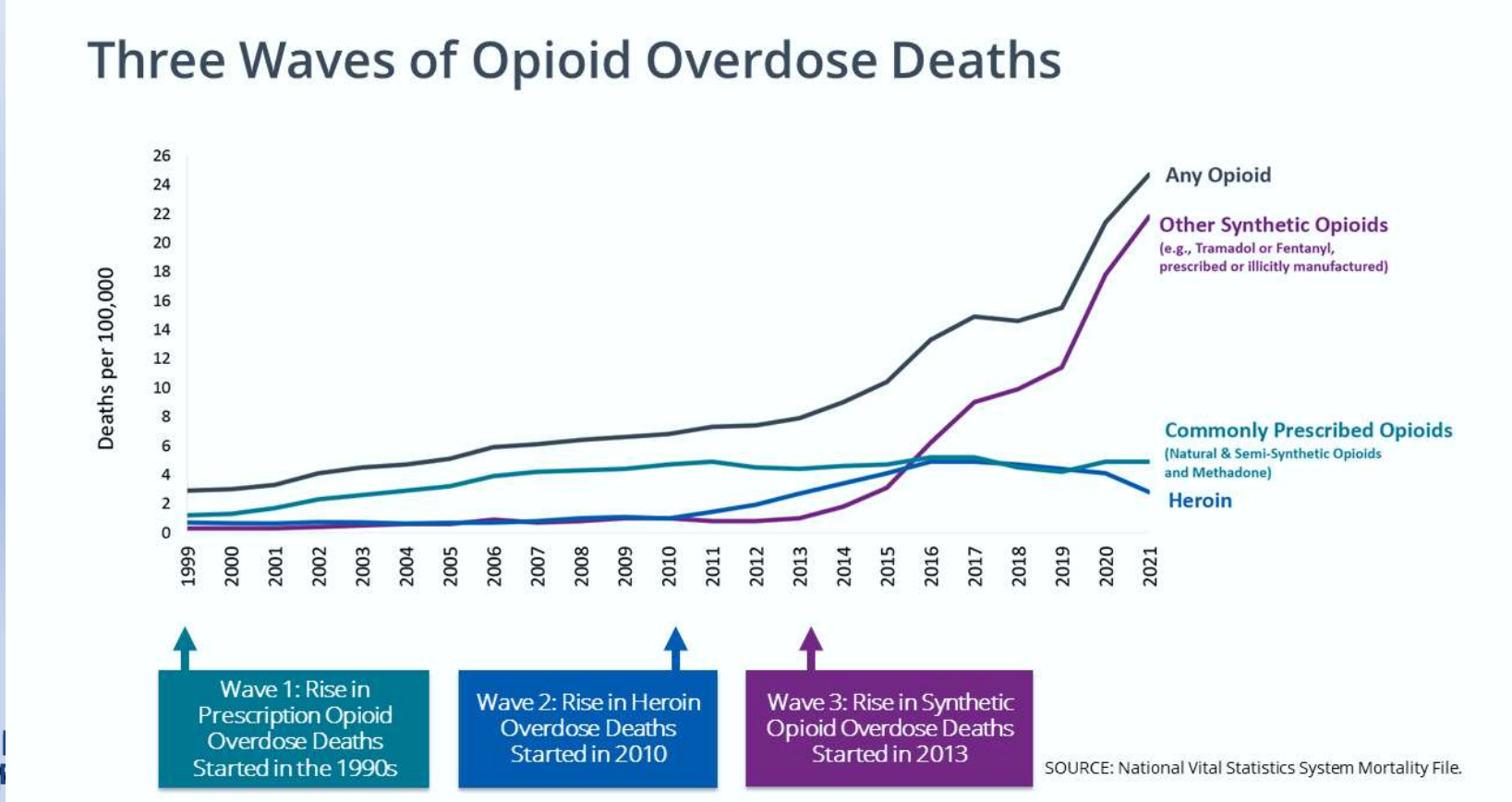


Fig. 16. *Global opioid consumption by country:2009-2019. (A) Change in the national opioid consumption rate between 2009 and 2019 in morphine milligram equivalents (MME) per 1,000 inhabitants per day. The color scale is continuous with darker shades indicating negative values and lighter shades indicating positive values. Countries with no data shaded in grey. (B)*

Overdose Deaths by Type - 3 Waves 1999 to 2021



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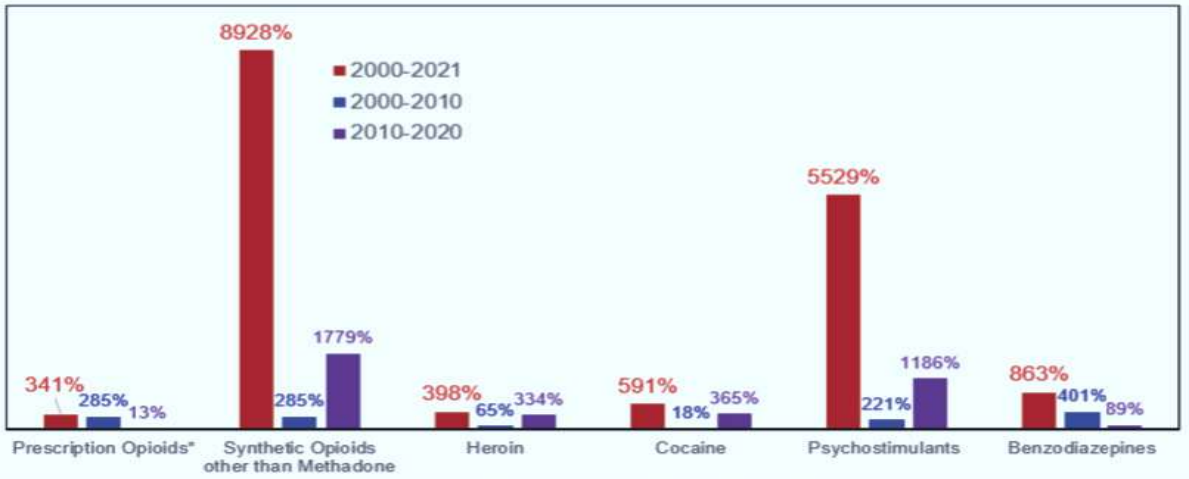
Deeper Dive - Quantification of Opioid Deaths 2000-2021



	2000	2010	2017	2018	2019	2020	2021	Change 2000-2021	Change 2000-2010	Change 2010-2020	Change 2019-2020	Change 2020-2021
Prescription Opioids (natural & semi-synthetic opioids & methadone)	3,785	14,583	17,029	14,975	14,139	16,416	16,706	341%	285%	13%	16%	2%
Synthetic Opioids other than Methadone (primarily fentanyl)	782	3,007	28,466	31,335	36,359	56,516	70,601	8928%	285%	1779%	55%	25%
Heroin	1,842	3,036	15,482	14,996	14,019	13,165	9,173	398%	65%	334%	-6%	-30%
Cocaine	3,544	4,183	13,942	14,666	15,883	19,447	24,486	591%	18%	365%	22%	26%
Psychostimulants	578	1,854	10,333	12,676	16,167	23,837	32,537	5529%	221%	1186%	47%	36%
Benzodiazepines	1,298	6,497	11,537	10,724	9,711	12,290	12,499	863%	401%	89%	27%	2%

Fig. 18. *Quantification of opioid deaths 2000-2021.*

Source: Centers for Disease Control and Prevention, National Center for Health Statistics. Multiple Cause of Death 1999-2021 on CDC WONDER Online Database, released 2/9/2023. Accessed on 5/3/2023
https://www.cdc.gov/nchs/products/databriefs/db428.htm

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Deeper Dive - Overdose
Death by Drug

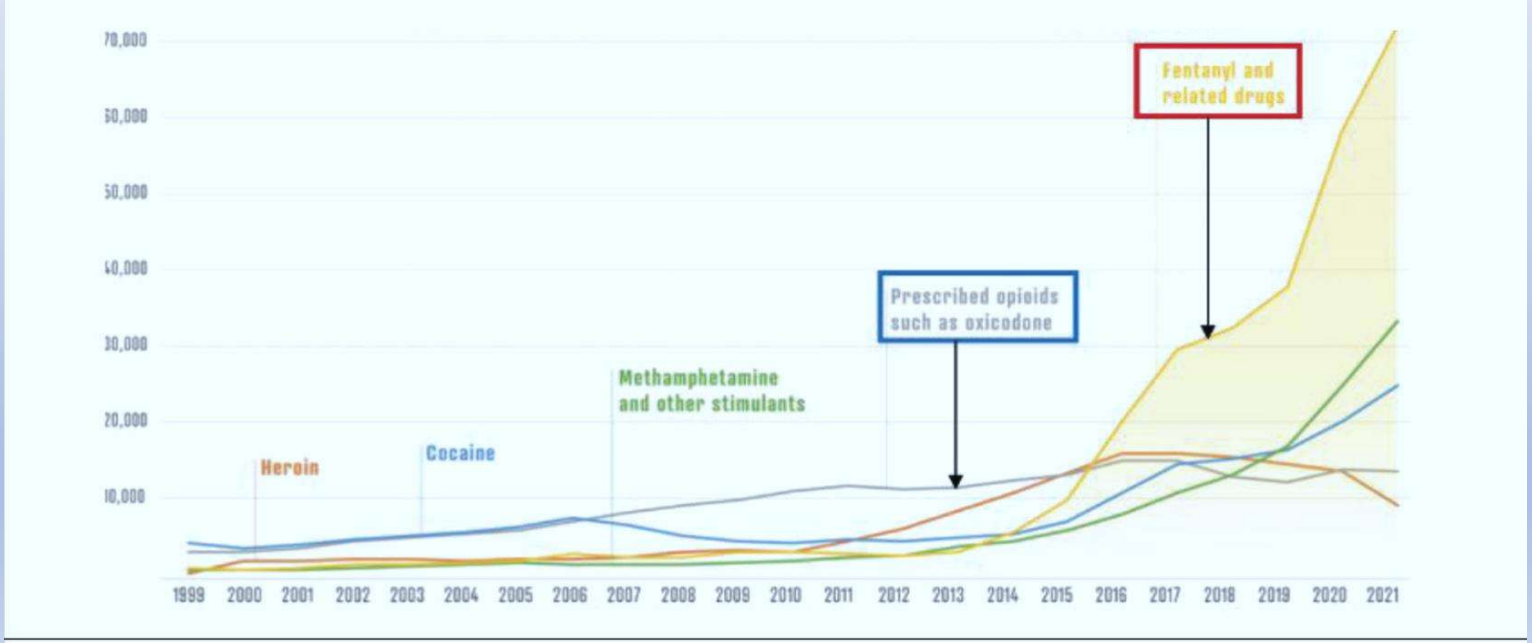

Fig. 17. ***Overdose deaths by drug – clearly and accurately portrayed.***

"Semi-synthetic opioids" has been replaced by "prescribed opioids, such as oxycodone [sic]. The category formerly titled "Synthetic opioids other than methadone" is now "fentanyl and related drugs." Quite a difference. Both of these categories are now clearly defined. Credit: B. Hayes/NIST (March 2021) based on data from the U.S. Centers for Disease Control and Prevention.

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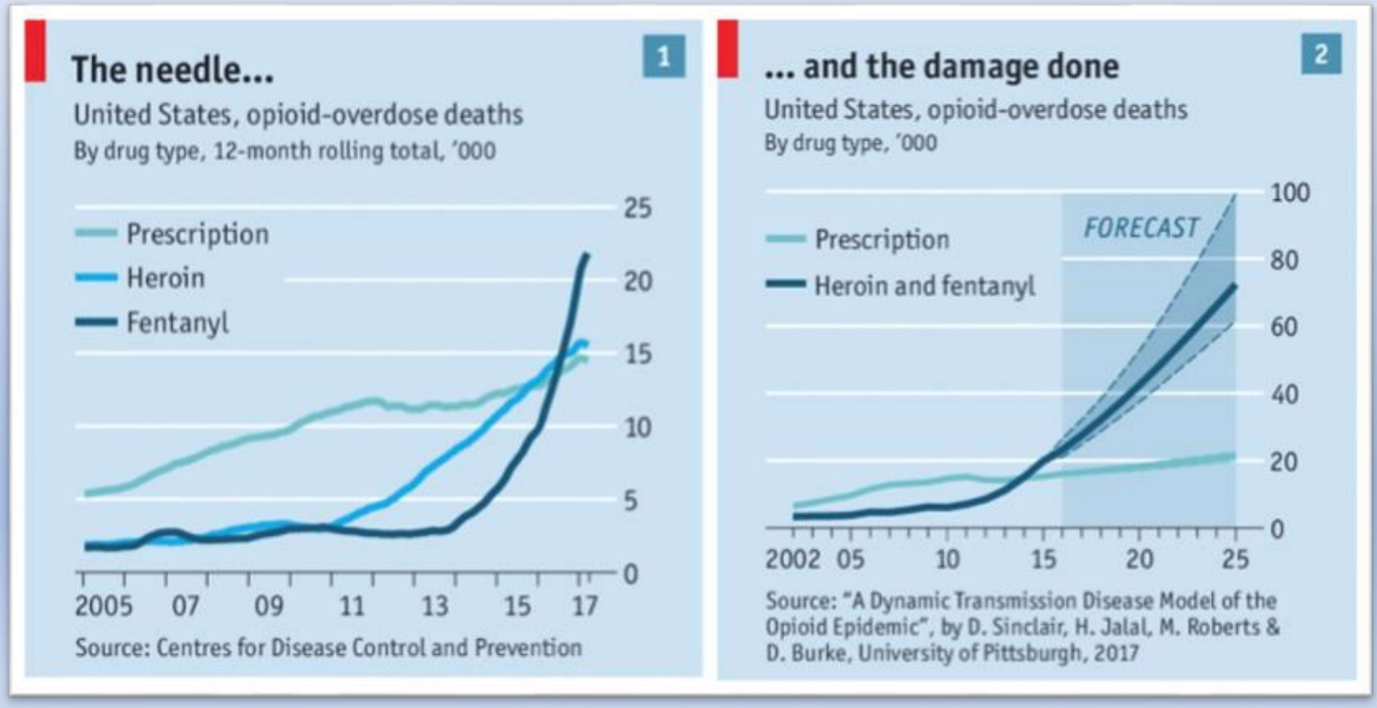
Where We Were…What We Feared



Of the 65,000 drug-overdose victims in 12 months from March 2017, 80% died from opioids. The death toll now exceeds the height of the aids epidemic.

www.economist.com/news/united-states/21730690-when-will-it-peak-and-how-many-will-it-kill-forecasting-opioid-epediemic

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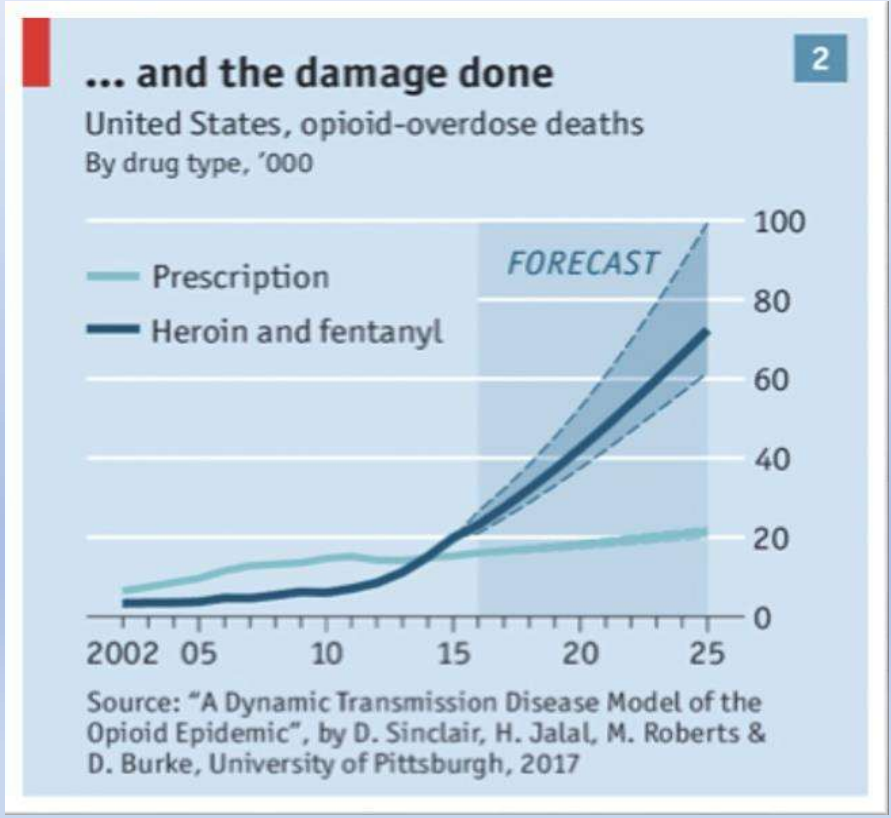
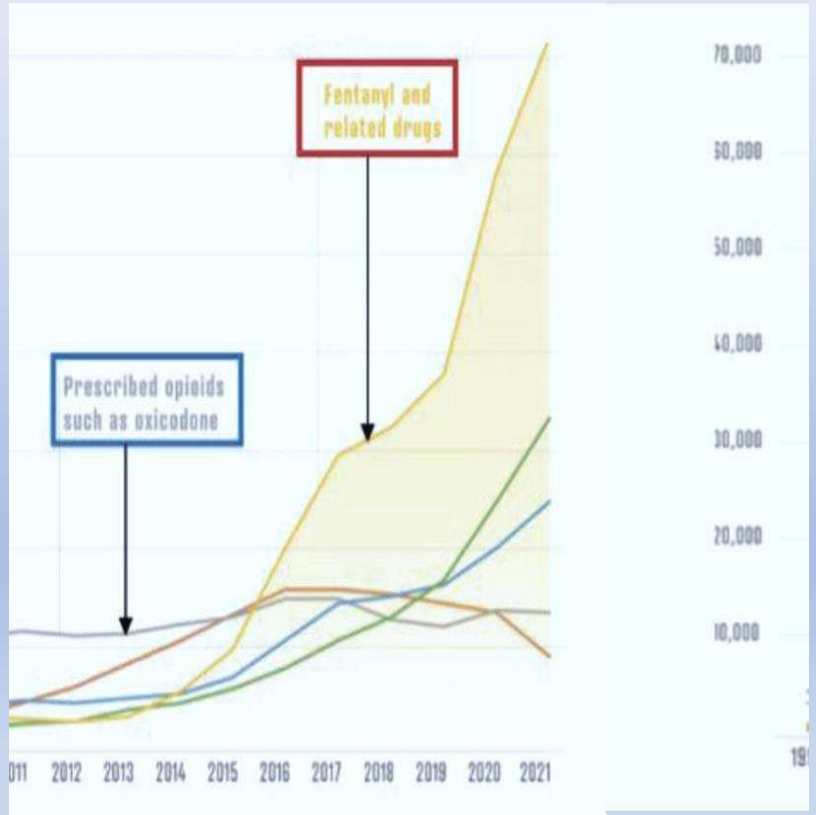
Unfortunately…pretty much nailed it





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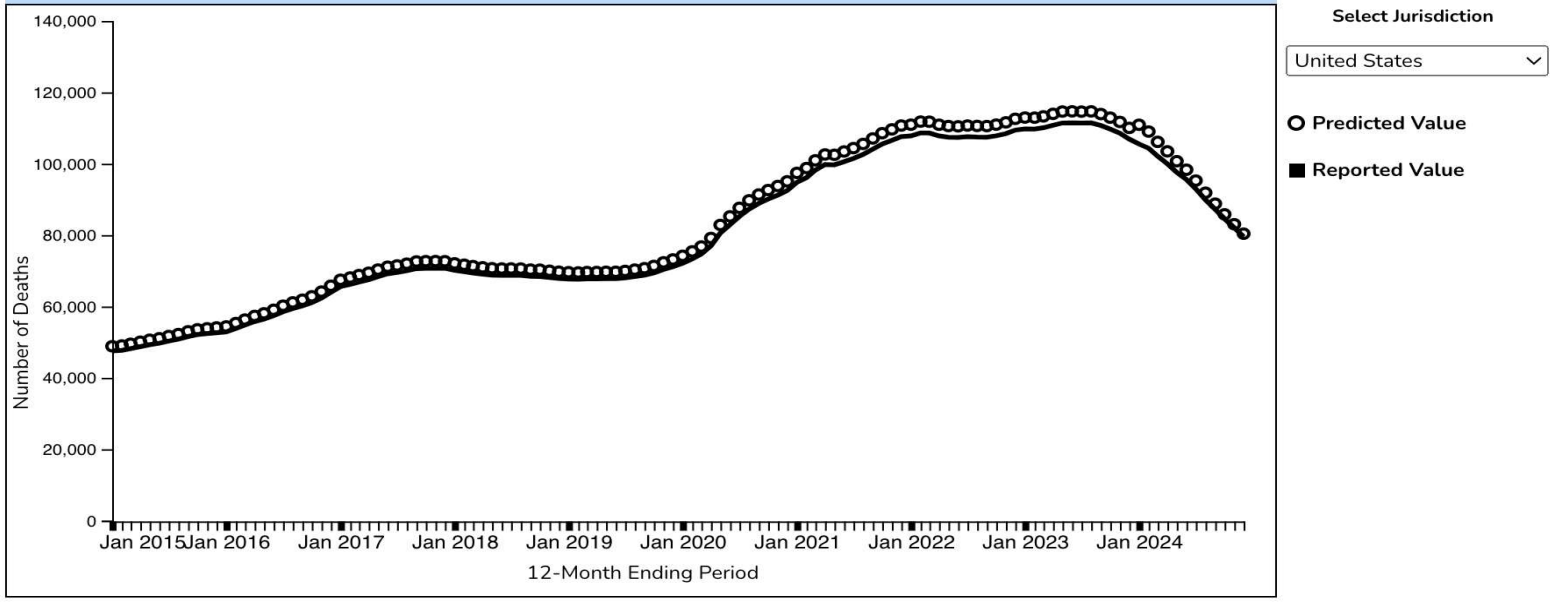
Overdose Data 2024

12 Month-ending Provisional Number and Percent Change of Drug Overdose Deaths

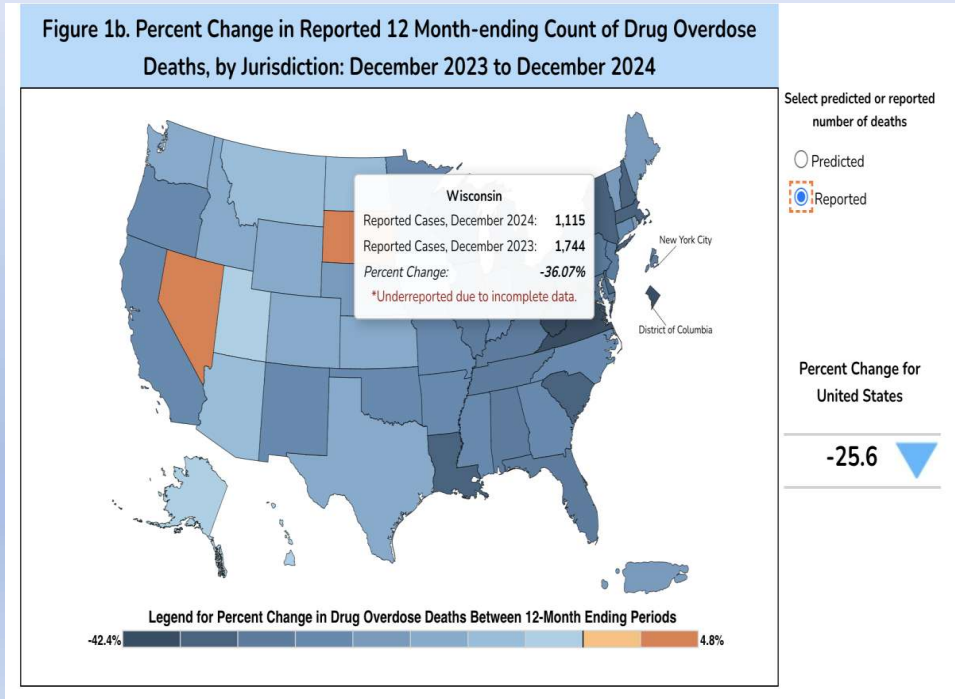
Based on data available for analysis on: May 4, 2025

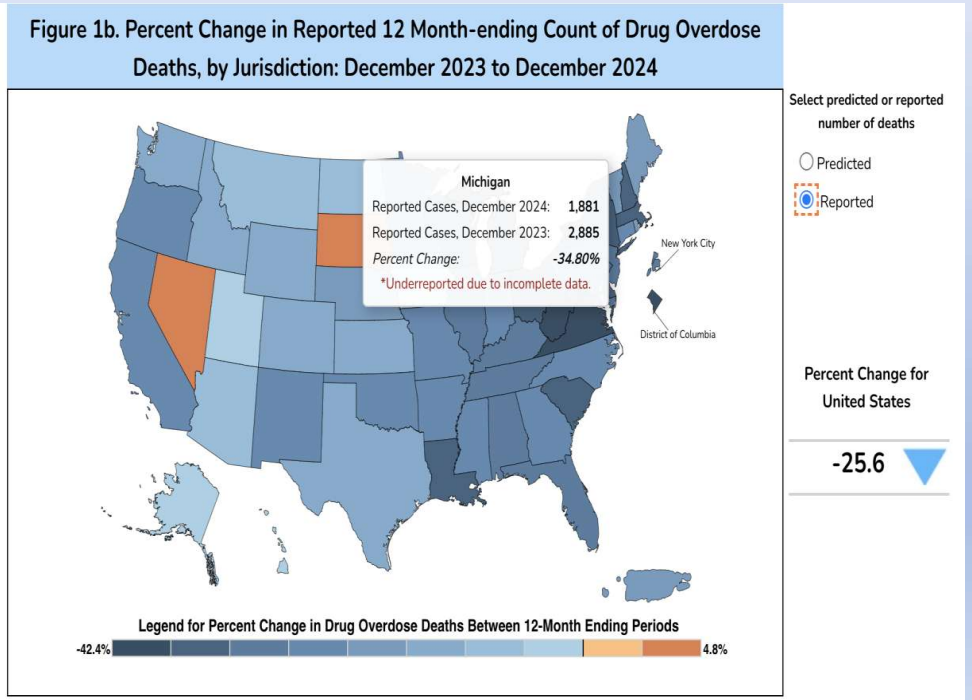
Figure 1a. 12 Month-ending Provisional Counts of Drug Overdose Deaths: United States



https://www.cdc.gov/nchs/nvss/vsrr/drug-overdose-data.htm

2024 Overdose Data





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https://www.cdc.gov/nchs/nvss/vsrr/drug-overdose-data.htm

Michigan Overdose Data to Action Dashboard

Home

Explore data

Current Trends

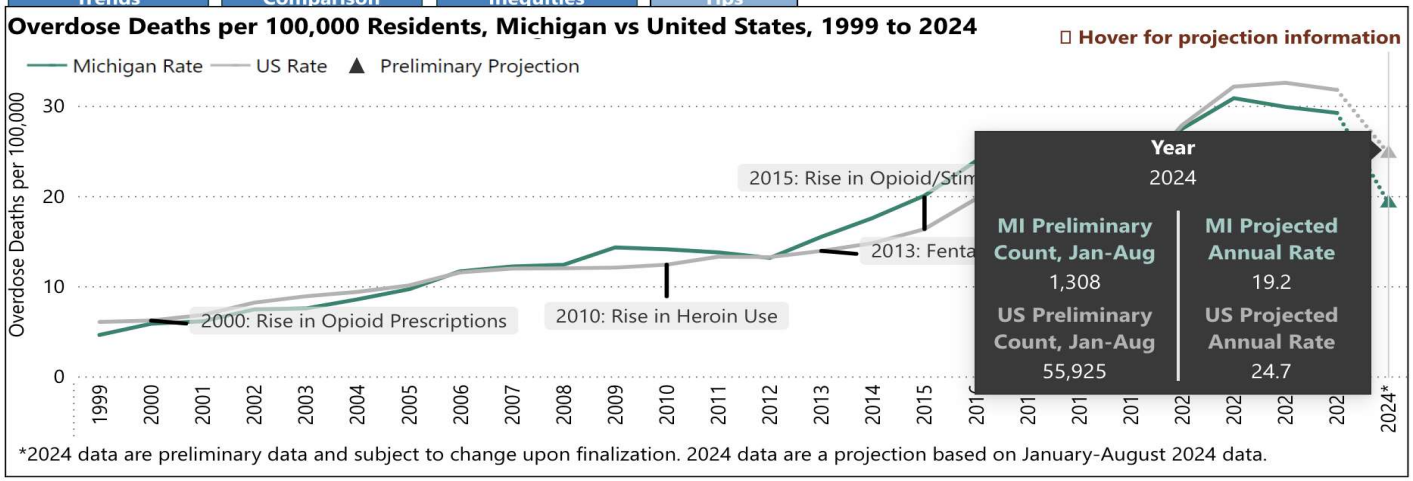
Technical Notes

Frequently Asked Questions

If you are in crisis, or know someone who needs help, contact the National Suicide Prevention Lifeline NOW at:
1-800-273-TALK (8255)
www.suicidepreventionlifeline.org

Click here for information on programs and resources to prevent overdose and treat substance use disorder.

View Historical Trends | View Monthly Comparison | View Health Inequities | (?) Helpful Tips



The Michigan Overdose Data to Action (MODA) Team

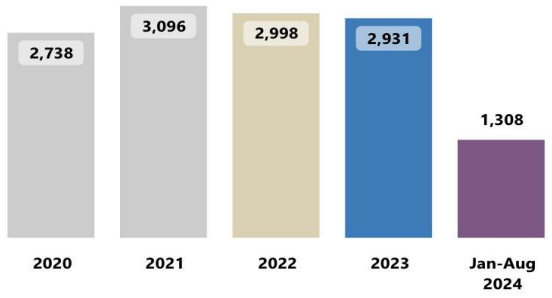
Please send questions about this dashboard to MDHHS-MODAsurveillance@michigan.gov.

The Michigan Department of Health and Human Services (MDHHS) MODA team is funded by the Centers for Disease Control and Prevention (CDC) Overdose Data to Action (OD2A) grant to bring surveillance and prevention efforts together to decrease rates of drug misuse, substance use disorder, fatal

Historical Trends, Monthly Comparison and Health Inequities Data

The charts above display the most recent Michigan overdose data available compared to US data, the previous year by month, and data regarding inequities in overdoses by race/ethnicity group in Michigan. On the inequities graph, NH stands for "non-Hispanic", API stands for "Asian/Pacific Islander" and

Number of Overdose Deaths by Year



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Michigan Overdose Data to Action Dashboard

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Explore Data

Specific Drug Trends

Helpful Tips

Technical Notes

Frequently Asked Questions

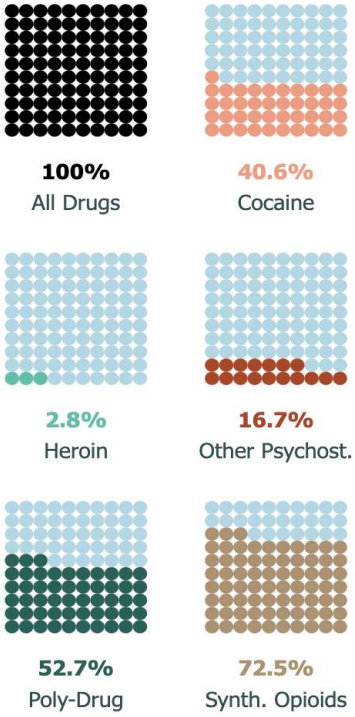
Data Notes
Deaths and ED Visits represent all drug overdoses. EMS Responses represent probable opioid overdoses only. Due to the differences in how frequently each data source is updated, the time period shown may vary by indicator.

Select Geographic Category: Statewide

Select Sub-Category: All

Go to... Historical Trends | Geographic Patterns | Demographic Patterns

Percent of Overdose Deaths with Specified Drug Involved in Michigan, 2023



100% All Drugs

40.6% Cocaine

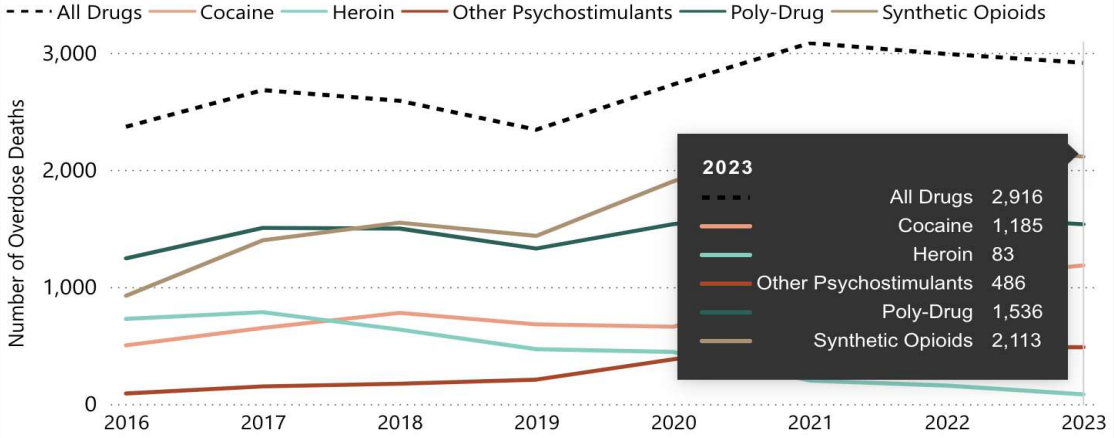
2.8% Heroin

16.7% Other Psychost.

52.7% Poly-Drug

72.5% Synth. Opioids

Overdose Deaths by Drug* by Year in Michigan



*Drug categories are not mutually exclusive; multiple drugs may be involved in a death. Poly-drug refers to deaths in which more than one drug (e.g., heroin AND cocaine, heroin AND fentanyl, etc.) are involved in death.

Select Drug to See Data Interpretation

All Drugs | Cocaine | Heroin
Other Psychostimulants | Poly-Drug | Synthetic Opioids

In Michigan, all drug overdose deaths are stable.

In 2023 in Michigan, there were 2,916 drug overdose deaths. All drug overdose deaths decreased 2.5% (-75) in Michigan from 2022 to 2023.

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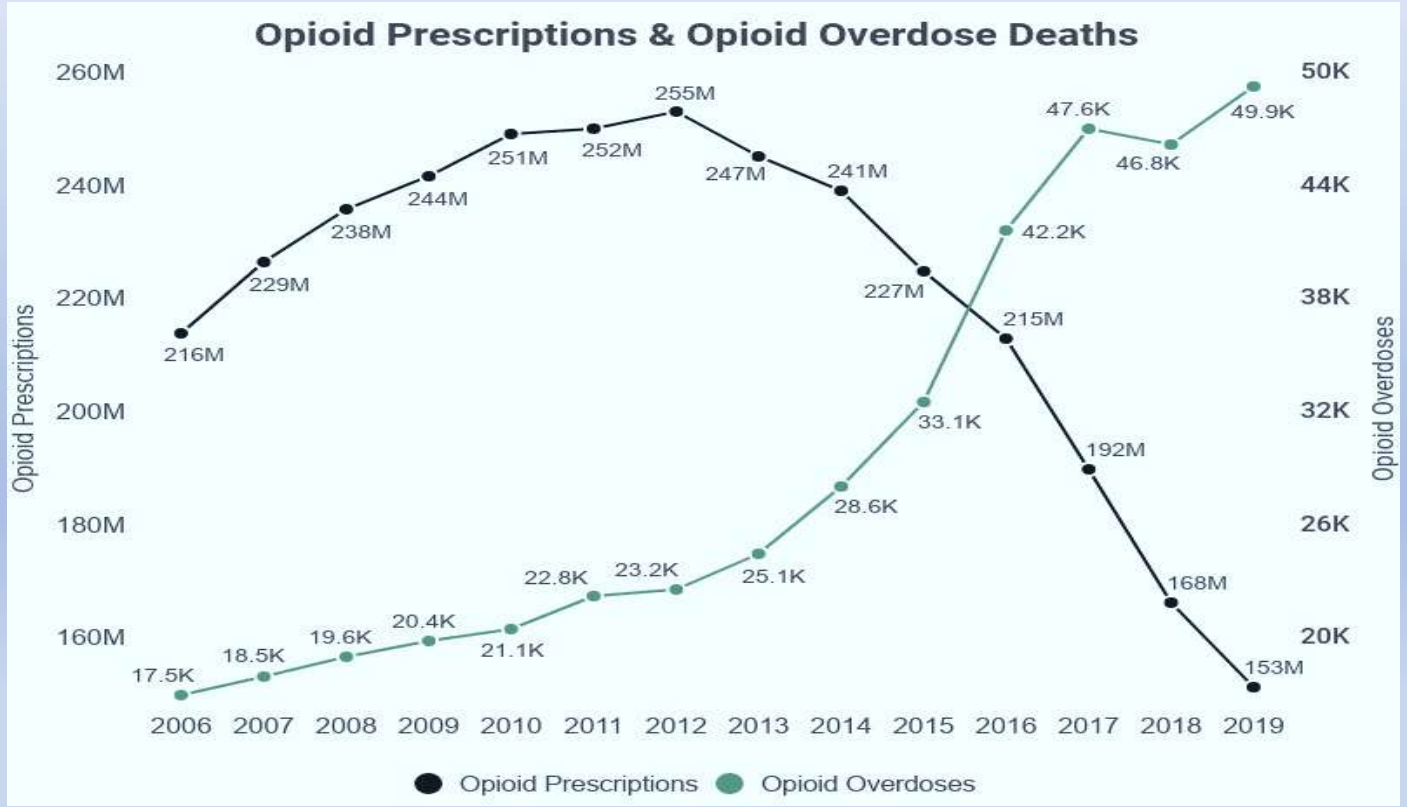
“Fourth Wave” of the Opioid Epidemic

Overdose mortality has continued to increase despite steady reductions in opioid prescribing.



Source: National Center for Drug Abuse Statistics
https://drugabusestatistics.org/opioid-epidemic/

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"Fourth Wave" of the opioid epidemic

CDC guidelines and subsequent regulatory atmosphere leading to aggressive tapering and stopping of opioid prescriptions

Forced tapering was linked to an increase of 69% for overdoses and 130% for mental crises

CDC guidelines, COVID-19 pandemic, increased availability of illicits and reduction of access to interventional techniques

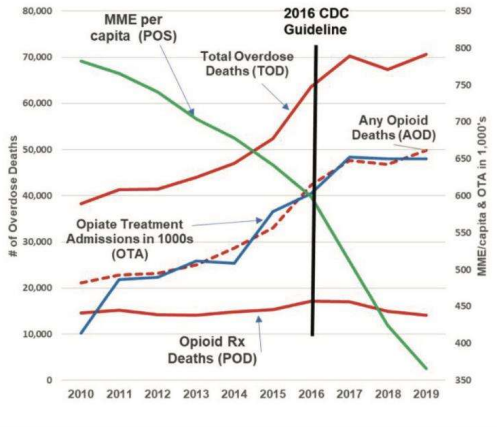

Fig. 3. *2010–2019 update. The green line represents opioid prescribing (POS, MME/capita); the red lines are opioid deaths (POD, AOD, and TOD); the blue line represents opioid addiction (OTA) (20).*

Over the past decade, as the green line (prescription opioids) declined by +50%, prescription opioid deaths remained flat while opioid addiction, any opioid and total overdose deaths continued increasing "exponentially (20)".
Source: Aubry L, Carr BT. Overdose, opioid treatment admissions and prescription opioid pain reliever relationships: United States, 2010-2019. *Front Pain Res (Lausanne)* 2022; 3:884674 (7).

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So…Should we still prescribe opioids?

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Should we still prescribe?

- Treatment of chronic pain a very significant contributor to overall medical expenditure
- In many instances can compare quite favorably to nonopioids in effectiveness
- In many circumstances, opioids remain best available option
  - Lack of other therapy availability
  - Lack of coverage of other therapies
  - Poor candidacy of patient for above

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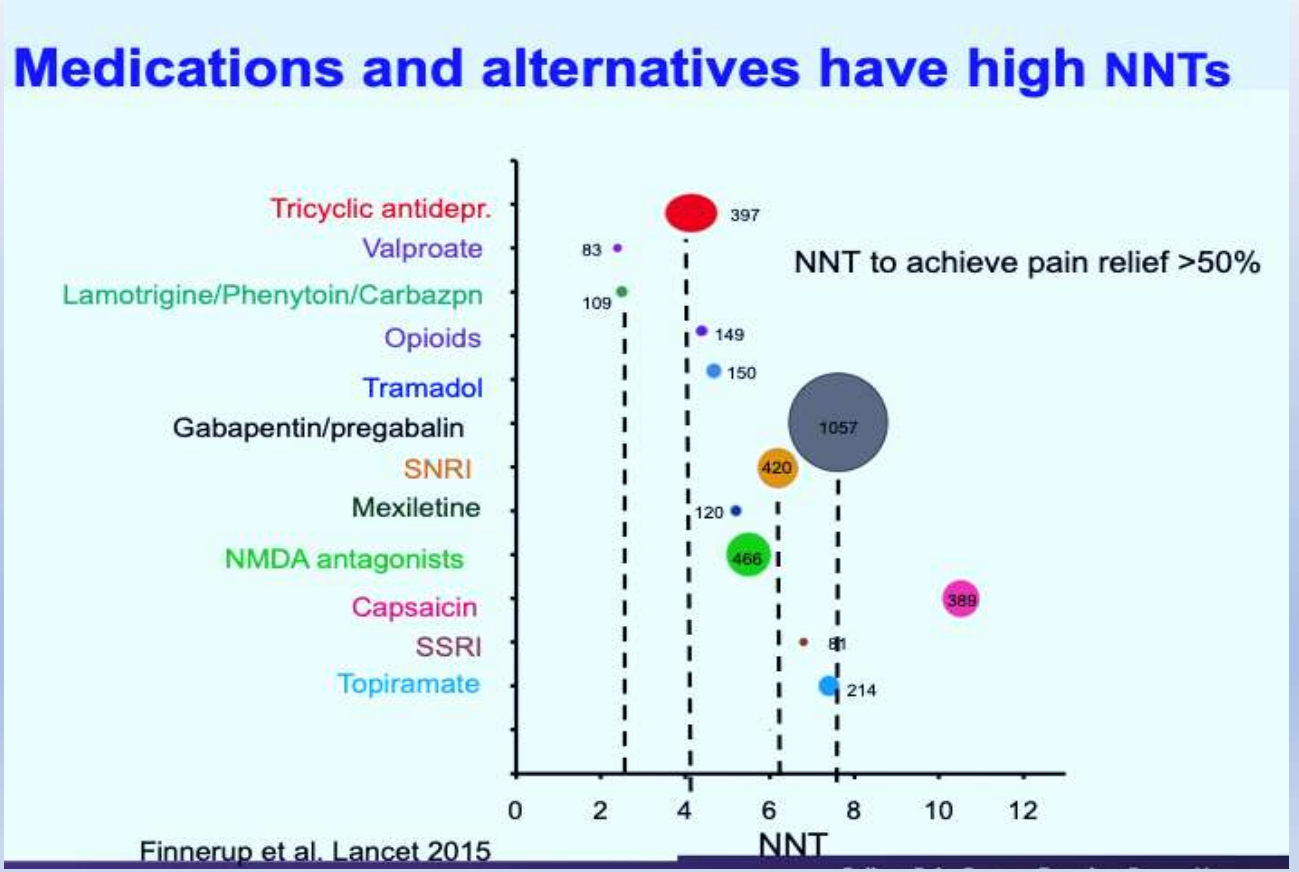
Effectiveness of Opioids vs. Nonopioids



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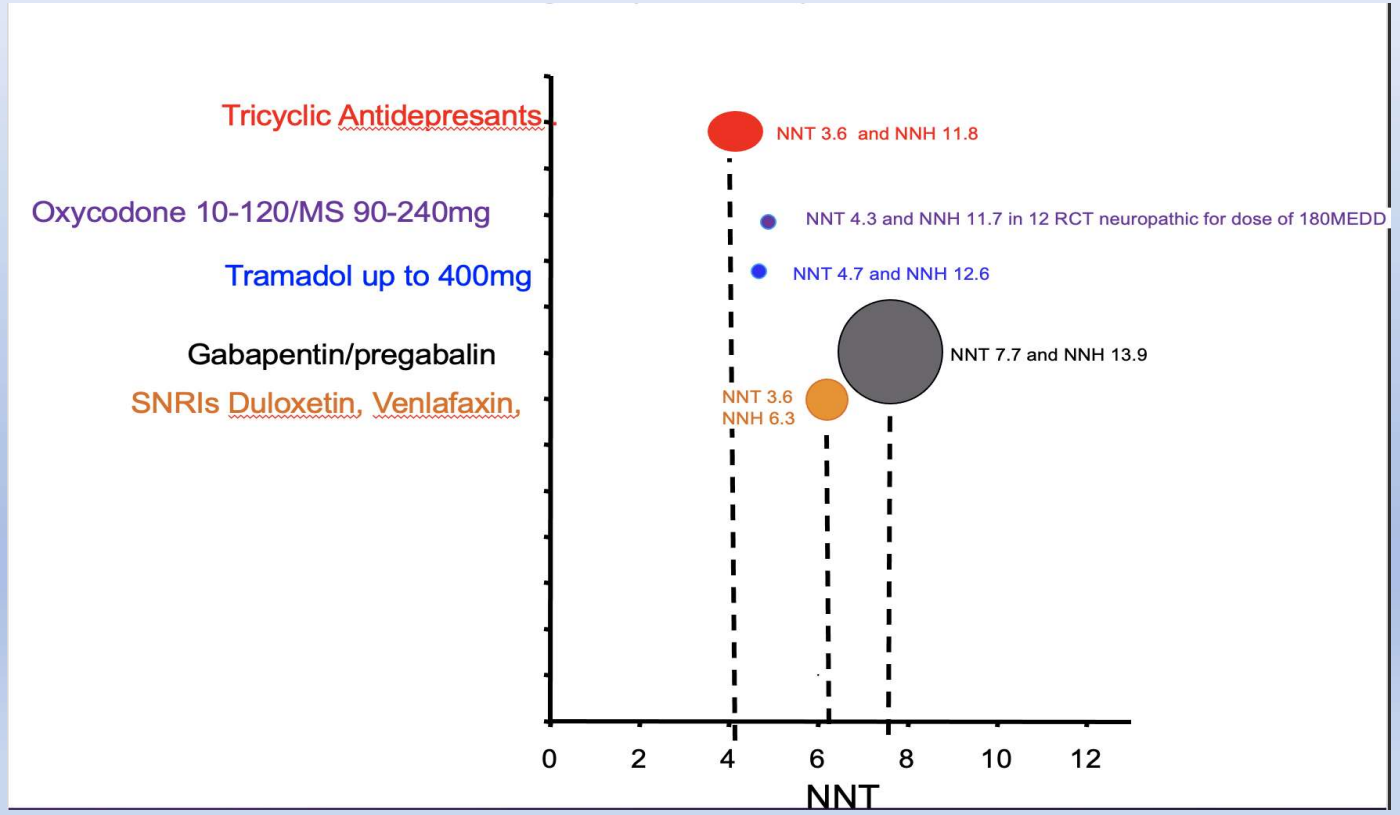
Effectiveness of Opioids vs Nonopioids



Finnerup et al. Lancet 2015

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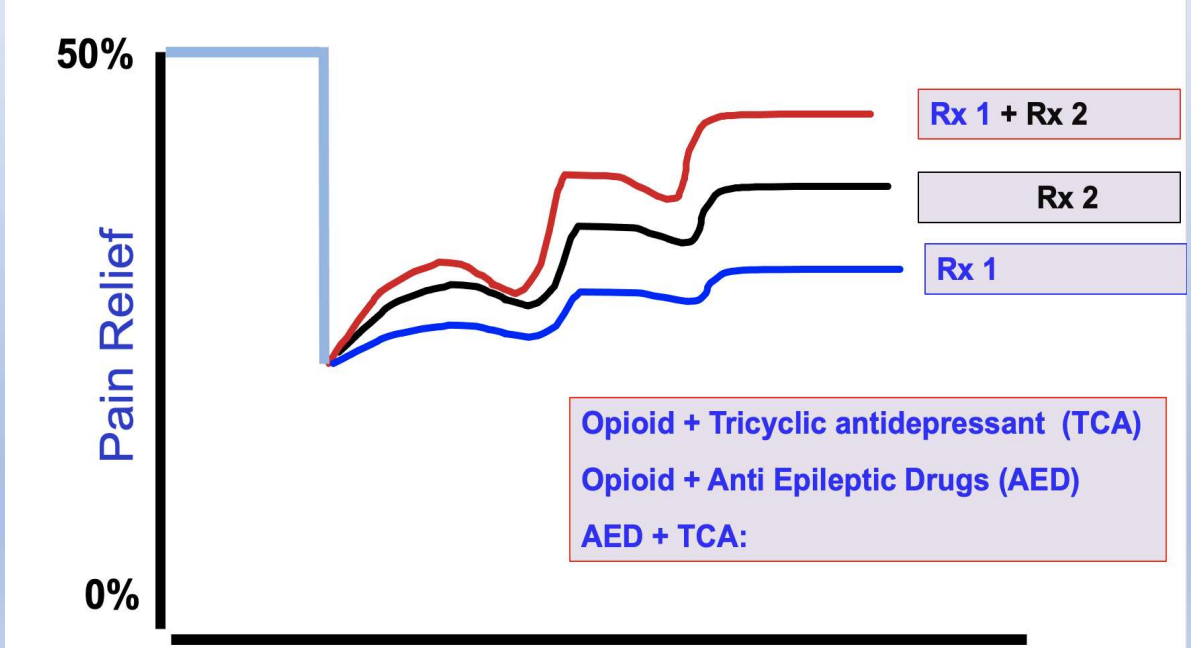
Combination Therapy – Opioids and Non-Opioids



Cochrane Database 2012. Combination pharmacotherapy for the treatment of neuropathic pain in adults.

ttp://onlinelibrary.wiley.com/doi/10.1002/14651858.CD008943.pub2/abstract;jsessionid=3C710E6B636E8E4C2569572E18449875.f03t01?systemMessage=Please+be+advised+that+we+experience

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Alternatives To Opioids For Chronic Pain

- Non-Opioid Medications such as NSAIDS, acetaminophen, certain antidepressants and anticonvulsants, etc.
- Physical Therapies – OMT, PT, Chiropractic, Acupuncture, Tens, Massage, etc.
- Psychological Care - CBT, Mindfulness, Biofeedback, stress reduction, etc.
- Interventional Procedures – Nerve/joint injection, ablation, neuromodulation, etc.

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Medication Options For Chronic Pain

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Atypical Opioids
Mechanism of Action and Metabolism

Atypical Opioids Include Tramadol, Tapentadol, and Buprenorphine

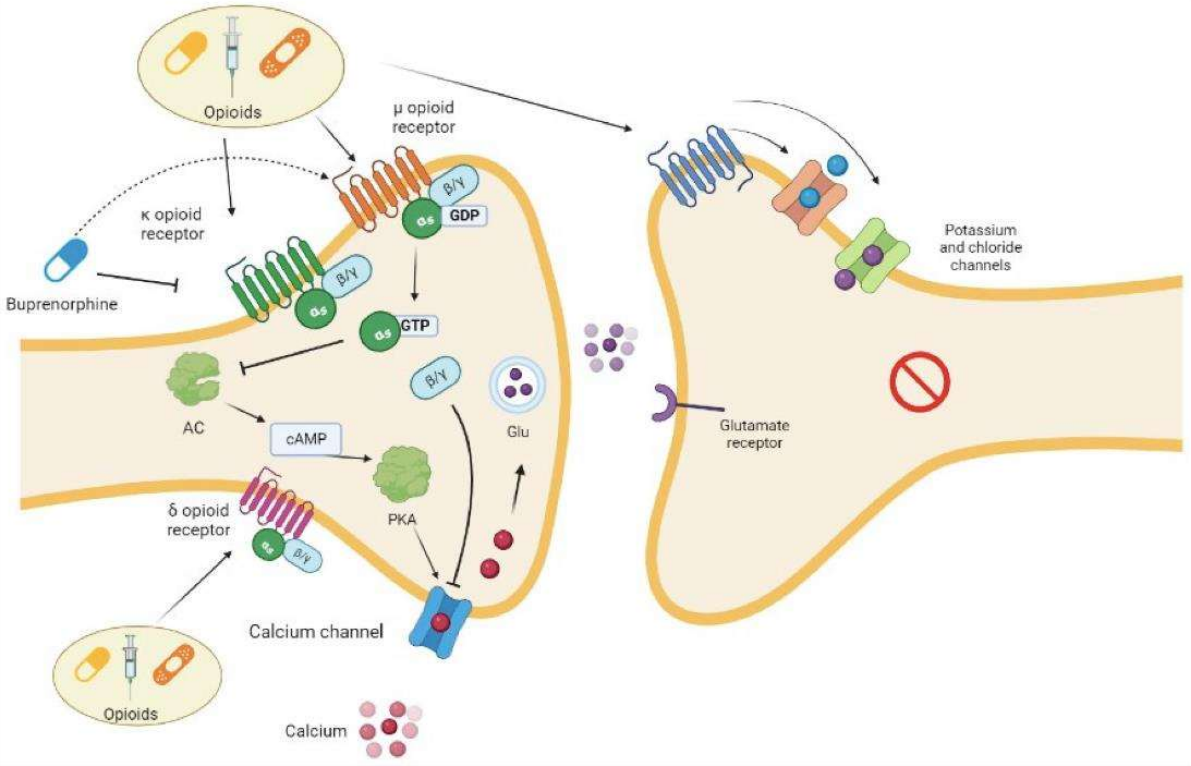
Table 1. Mechanisms of action and metabolism of the atypical opioids

	Tramadol	Tapentadol	Buprenorphine
μ-Opioid receptor	Agonist*	Agonist	Partial agonist
κ-Opioid receptor	N/A	N/A	Antagonist
δ-Opioid receptor	N/A	N/A	Antagonist
Nociceptin opioid receptor	N/A	N/A	Agonist
Norepinephrine reuptake inhibitor	Yes	Yes	N/A
Serotonin reuptake inhibitor	Yes	N/A	N/A
Metabolism	CYP2D6 (*O*-demethylation)	Glucuronidation	CYP3A4 (*N*-dealkylation, glucuronidation)

*Although considered a full agonist, tramadol's affinity for the μ-opioid receptor is substantially lower compared with other full agonists.[72]
CYP2D6: cytochrome P450 2D6; CYP3A4: cytochrome P450 3A4; N/A: not applicable.

Webster L, et al. J Opioid Manag. 2021;17:109-118.

Figure 1. Opioid mechanism of action. Opioids bind to their μ, κ, and δ receptors at presynaptic level, carrying out different actions. After the interaction with a receptor, the α subunit of protein G inhibits the pathway of AC, resulting in a reduction in calcium channel activity and then the release of glutamate. The same channel is inhibited via the βγ subunit. Buprenorphine is a particular drug since it has partial agonist activity on μ receptor and antagonist activity on κ receptors. Opioids also exert stimulating activity on calcium and chloride channels, resulting in hyperpolarization at postsynaptic level. AC, adenylate cyclase; cAMP, cyclic adenosine monophosphate; GDP, guanosine diphosphate; Glu, glutamate; GTP, Guanosine-5′-triphosphate; PKA, protein kinase A.



OPIOID MOA

- Marcianò G, Vocca C, Evangelista M, Palleria C, Muraca L, Galati C, Monea F, Sportiello L, De Sarro G, Capuano A, et al. The Pharmacological Treatment of Chronic Pain: From Guidelines to Daily Clinical Practice. *Pharmaceutics*. 2023; 15(4):1165. https://doi.org/10.3390/pharmaceutics15041165

Tramadol

- Central mu-agonist
- Reuptake inhibitor of serotonin and norepinephrine
- Schedule IV
- .1 x Morphine equivalency
- Decreased risk OIRD, Abuse
- Toxicity – Serotonergic Syndrome
  - CYP2D6 metabolism

SEROTONERGIC SYNDROME

Altered Mental Status

Neuromuscular Abnormalities

Autonomic Hyperactivity

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Tramadol

- Can be life threatening
- Discontinuation of contributing agents
- Thorough review of medication history

Table 3. *Classic Hunter serotonin toxicity criteria: decision rules.*

In the presence of a serotonergic agent PLUS one of the following groups:

- Spontaneous clonus
- Inducible clonus with agitation or diaphoresis
- Ocular clonus with agitation or diaphoresis
- Tremor and hyperreflexia
- Hypertonia, temperature above 100.4 (38 °C), and ocular or inducible clonus

Volpi-Abadie J, Kaye AM, Kaye AD.. Serotonin syndrome. The Ochsner Journal 2013; 13:533-540.

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Tapentadol

- Central mu agonist
- Norepinephrine reuptake inhibition
- Schedule 2
- 0.4 x Morphine equivalency
- Can lower seizure threshold

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Tapentadol
Effects on Respiratory Depression

Clinical evidence regarding tapentadol and OIRD is limited

- Small clinical trial comparing tapentadol and tramadol showed no clinic difference in respiratory depression[a]
- Stollenwerk et al found that reporting of expected side effects (respirat depression and convulsion) was low[b]
  - No major risks were identified

a. Iyer SK, et al. Ann Card Anaesth. 2015;18:352-360; b. Stollenwerk A, et al. Adv Ther. 2018;35:1-30.

Tapentadol
Safety Analysis

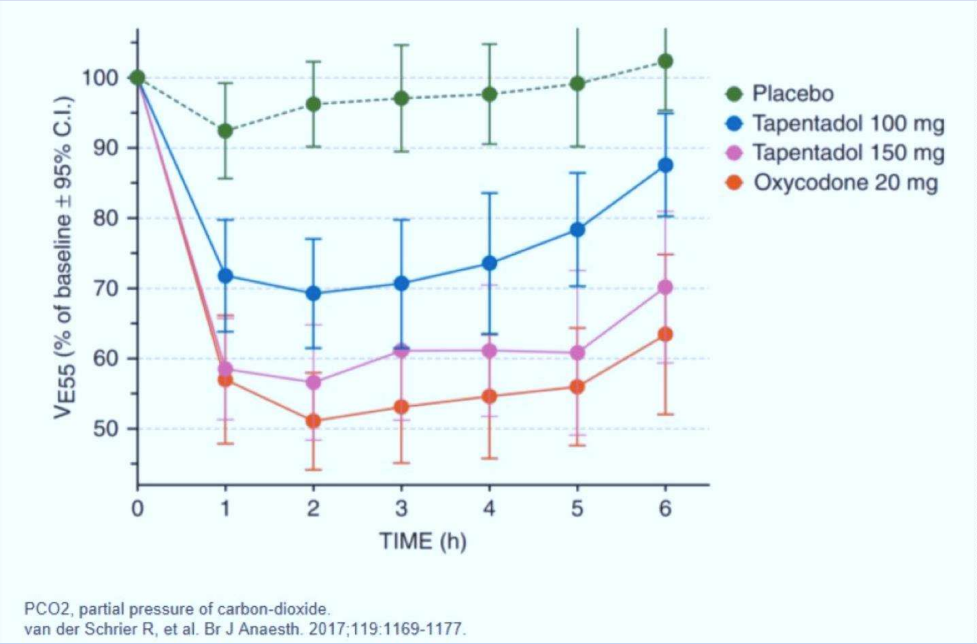
Post-marketing safety data are available

- One study investigated tapentadol use data reported to the NPDS[a]
  - Found significantly greater risk for OIRD with tapentadol (relative risk ratio = 5.56, $P < .001$) compared with tramadol
- Similarly, an analysis of OIRD AEs in Japan found a greater reporting odds ratio for tapentadol compared with tramadol[b]
- A retrospective US NDPS toxicity study of children taking tapentadol reported that 2 children out of 104 experienced OIRD[c]

NPDS, National Poison Data System.
a. Tsutaoka BT, et al. Ann Pharmacother. 2015;49:1311-1316; b. Sugawara H, et al. Biol Pharm Bull. 2019;42:1185-1191; c. Borys D, et al. Pediatrics. 2015;135:e392-e396.

Tapentadol Considerations Cont'd

- Compared to placebo Tapentadol decreased resting ventilation and increased end tidal C02, though less than oxycodone



PCO2, partial pressure of carbon-dioxide.
van der Schrier R, et al. Br J Anaesth. 2017;119:1169-1177.

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Buprenorphine

- "Partial Agonist" of mu receptors
  - Preferential activation of G protein signaling – greater efficacy of activation and decreased mu agonism side effects
  - Preferential spinal mu receptor activation
  - Slower dissociation, higher affinity -> competitive inhibition of pure mu agonists (Use in OUD)
- Antagonist of delta and kappa receptors
  - Decreased respiratory depression, constipation, etc
  - Possible potentiation of anti-depressant/anxiolytic effects
- Agonist at Opioid Receptor-Like 1 (ORL-1)
  - Can contribute to analgesic efficiency
  - Block reward system, potentially slowing tolerance

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Buprenorphine

- Schedule 3
- 1.8 x Morphine Equivalency
- Available as transmucosal, transdermal preparations for use in chronic pain
  - Poor oral bioavailability due to extensive first pass metabolism
- Sublingual – OUD and pain management
- "Think of dopamine" when comparing dosing

- OUD and MAT
  - Elimination of x waiver
- Medication Access and Training Expansion Act
  - New and renewing DEA registrations to complete 8 hour training on OUD/SUD

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ASAM National Practice Guideline for Treatment of OUD

- Discontinuation of methadone or buprenorphine before surgery is NOT required; higher potency IV full agonists can be used perioperatively

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Buprenorphine and Availability of Mu Receptors

- With no buprenorphine, 100% of m-opioid receptors are available.
- At 2 mg of buprenorphine (mean 24-hour area under the curve [AUC] of 6.5 ng/mL* h), 59% of m-opioid receptors are available.
- At 16 mg of buprenorphine (mean 24-hour AUC of 48.6 ng/mL * h), 20% of m-opioid receptors are available.
- At 32 mg of buprenorphine (mean 24-hour AUC of 96.0 ng/mL * h), 16% of m-opioid receptors are available

Greenwald MK, Johanson CE, Moody DE, et al. Effects of buprenorphine maintenance dose on mu-opioid receptor avail- ability, plasma concentrations, and antagonist blockade in heroin-dependent volunteers. Neuropsychopharmacology 2003; 28(11):2000–9.

Buprenorphine
Different Formulations

- Early clinical studies reported OIRD with intravenous buprenorphine[a,b]
  - One study reported epidural buprenorphine caused a prolonged, biphasic respiratory depression[c]
- Phase 3 clinical trials of the safety and efficacy of BBF or transdermal buprenorphine found no episodes of respiratory depression[d-f]
  - A randomized, double-blind, placebo-controlled study of sublingual buprenorphine (0.4 mg) vs intramuscular morphine (10 mg) found no buprenorphine effect on respiration, but found mild effects by morphine on partial pressure of CO_2[g]

	Buprenorphine Transdermal[h]	BBF[h]
Bioavailability	~15%	46% to 65%
Efficacy, opioid-naive trial data/opioid-experienced trial data		
≥ 30% response rate	53%/49%	62%/64%
≥ 50% response rate	43%/35%	41%/40%

BBF, buprenorphine buccal film; MOR, μ-opioid receptor. a. de Klerk G, et al. Acta Anaesthesiol Belg. 1981;32:131-139; b. Downing JW, et al. S Afr Med J. 1979;55:1023-1027; c. Jensen FM, et al. Anaesthesia. 1987;42:470-475; d. Gimbel J, et al. Pain. 2016;157:2517-2526; e. Hale M, et al. J Pain Res. 2017;10:233-240; f. Rauck RL, et al. Postgrad Med. 2016;128:1-11; g. Tantucci C, et al. Int J Clin Pharmacol Ther Toxicol. 1992;30:202-207; h. Hale M, et al. Pain Manag. 2020;10:213-223.

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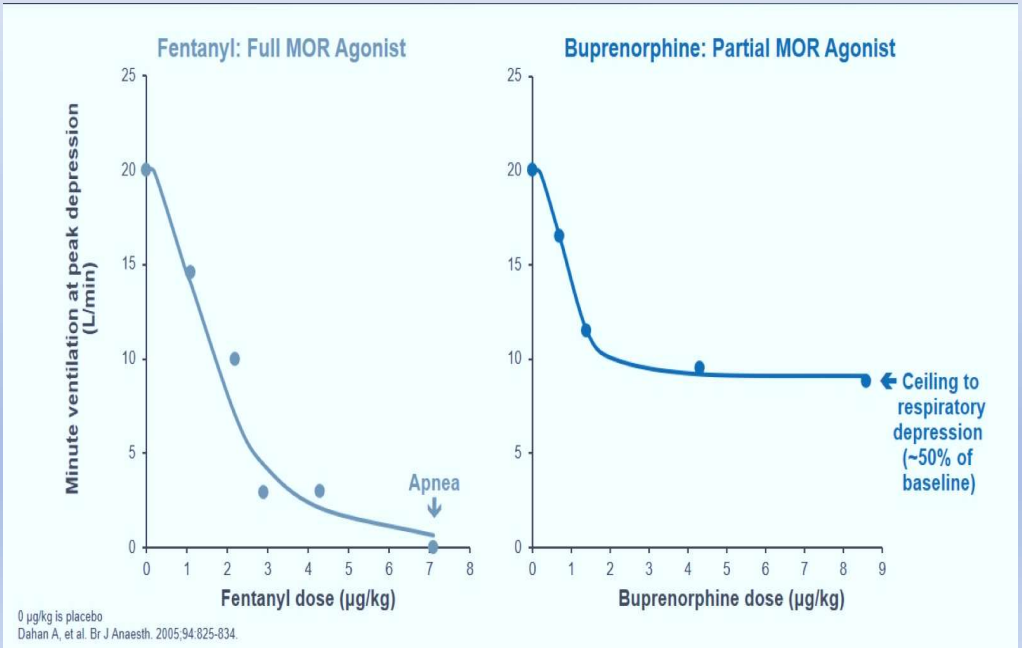
Respiratory Effects of IV Fentanyl vs IV Buprenorphine



- Buprenorphine has higher binding affinity but lower intrinsic activity at the m-opioid receptor than full mu-opioid receptor agonists with a unique mechanism of action at other receptors (e.g., d- and j-opioid receptors and ORL1) that may contribute to analgesia and other favorable clinical properties

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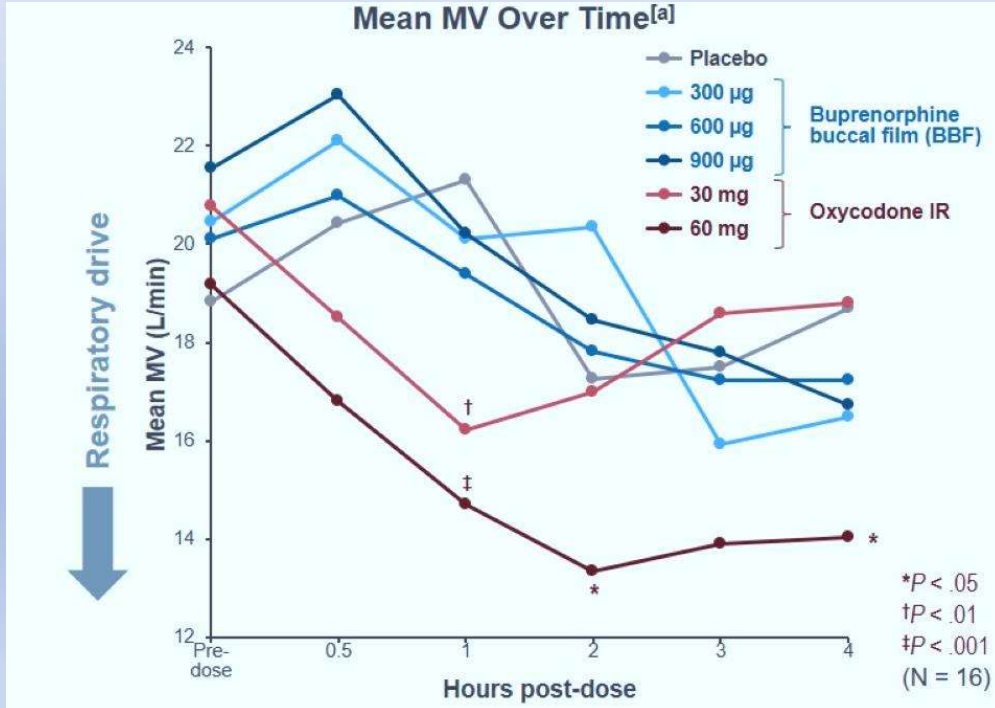
Effects of BFF VS Oral IR Oxycodone on Respiratory Drive



- IR oxycodone caused dose-dependent ↓ respiratory drive[a]
  - 60 mg: significant at 1 h, 2 h, and 4 h
  - 30 mg: significant at 1 h
- No BBF dose significantly ↓ respiratory drive[a]
- BBF clinical studies:
  - No reported cases of respiratory depression[a-d]
  - Comparable analgesic efficacy to full MOR agonists[b-d]
    - BBF may be a safer option for patients with chronic pain[a,c]

a. Webster LR, et al. Adv Ther. 2020;37:4685-4696; b. Gudin J, et al. Pain Ther 2020;9:41-54; c. Pergolizzi JV, et al. J Pain Res. 2019;12:3299-3317; d. Hale M, et al. Pain Manag. 2020;10:213-223.

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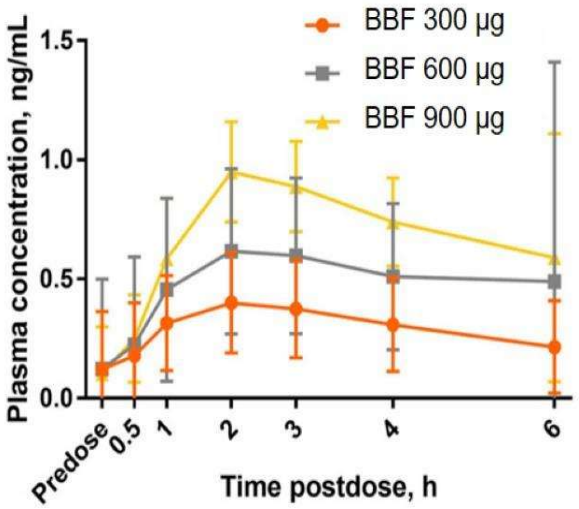
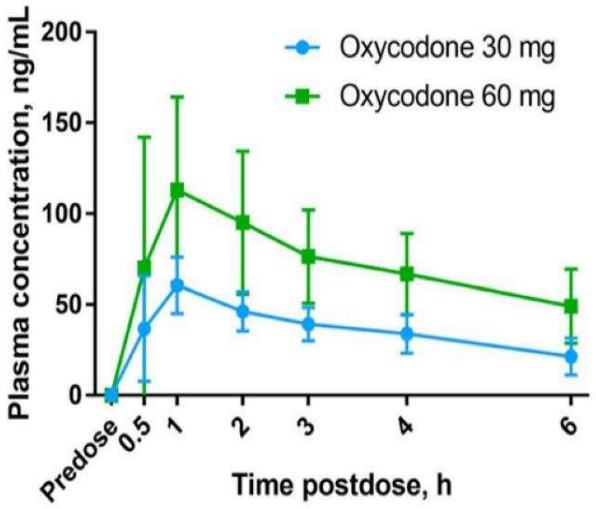
Risk of Abuse vs IR Oxycodone

BBF May Have a ↓ Risk of Abuse vs IR Oxycodone





- Individuals who abuse opioids typically prefer a ↑ Cmax and ↓ Tmax
- ↑ Tmax with BBF may make it less appealing for abuse than IR oxycodone

Cmax; maximum (or peak) serum concentration that a drug achieves in a specified compartment; Tmax, time to maximum plasma concentration. Webster LR, et al. Pain Ther. 2022;817-825.

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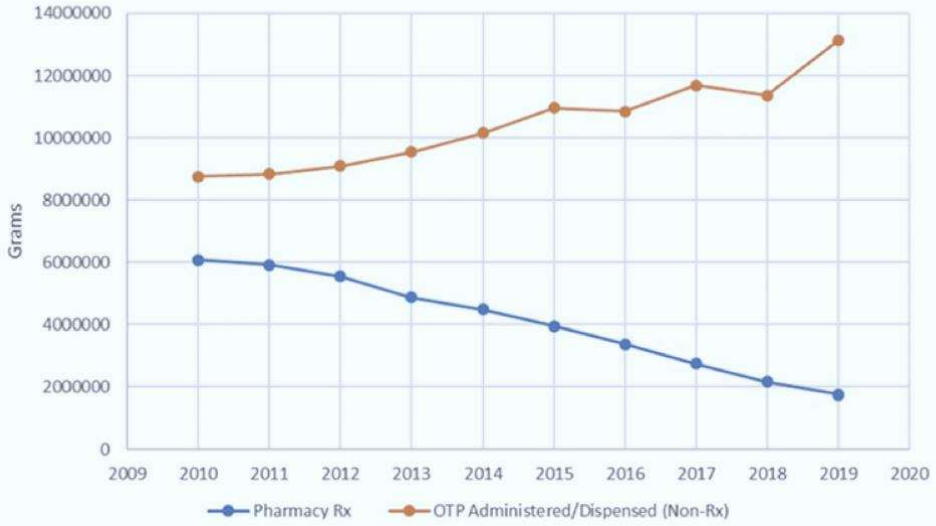
Methadone Considerations

"The preponderance of methadone-associated morbidity and mortality likely arises from its use for pain"[a]



Methadone

- 2009 – 2% Rx → 30% opioid overdoses[a]
- 2014 – 1% Rx → 23% opioid overdoses[a]
- 2019 – 7 times more methadone dispensed from OTP vs Rx[a]

- Methadone prescribing for pain[a]
  - Decreased by 71.2% between 2010 – 2019
- Methadone dispensing from OTP[a]
  - Increased by 49.9% between 2010 – 2019
- Methadone overdose deaths[b]
  - 2019 = ~3000
  - 2020 = ~3600

OTP, opioid treatment plan; Rx, medical prescription.
a. Peppin JF, et al. Pain Ther. 2019;10:25-38; b. Jones C, et al. JAMA Psych. 2022;79:932-934.

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Methadone Considerations

Nonlinear dosage equivalency

PDMP reporting

Calculating morphine milligram equivalents (MME)

OPIOID (doses in mg/day except where noted)	**CONVERSION FACTOR**
Codeine	0.15
Fentanyl transdermal (in mcg/hr)	2.4
Hydrocodone	1
Hydromorphone	4
Methadone	
1-20 mg/day	4
21-40 mg/day	8
41-60 mg/day	10
≥ 61-80 mg/day	12
Morphine	1
Oxycodone	1.5
Oxymorphone	3

These dose conversions are estimated and cannot account for all individual differences in genetics and pharmacokinetics.

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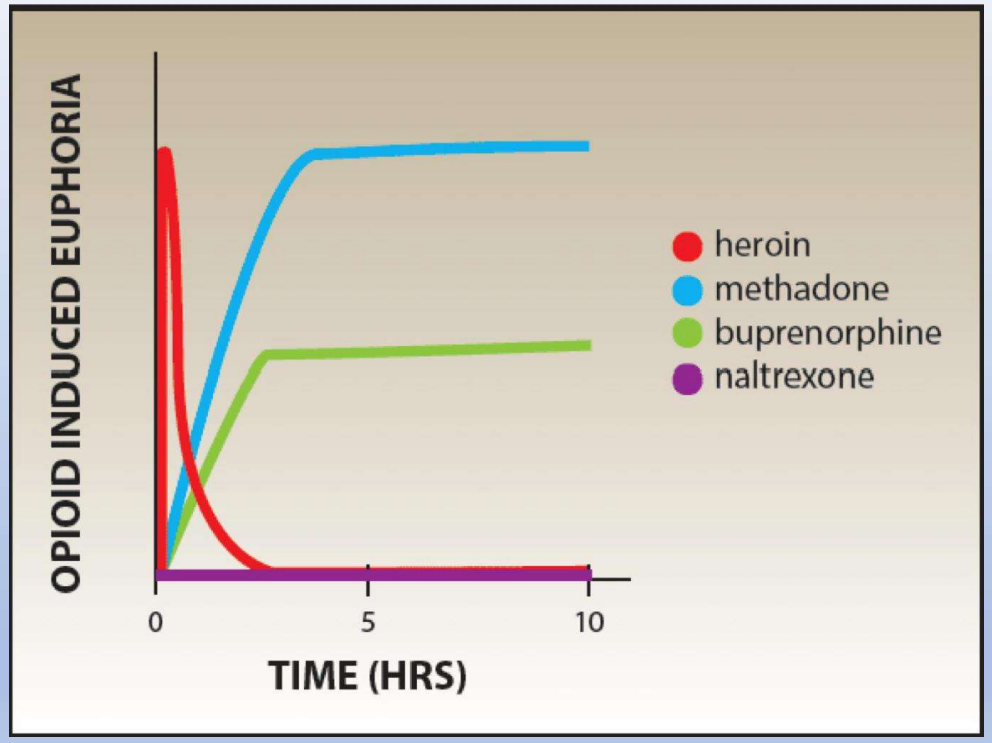

OUD Treatment Characteristics

- Heroin – rapid receptor activation
- Methadone – full agonist, slower rate and prolonged activation
- Buprenorphine – partial agonist, similar profile to methadone in rate/duration
- Naltrexone – antagonist, prevents activation

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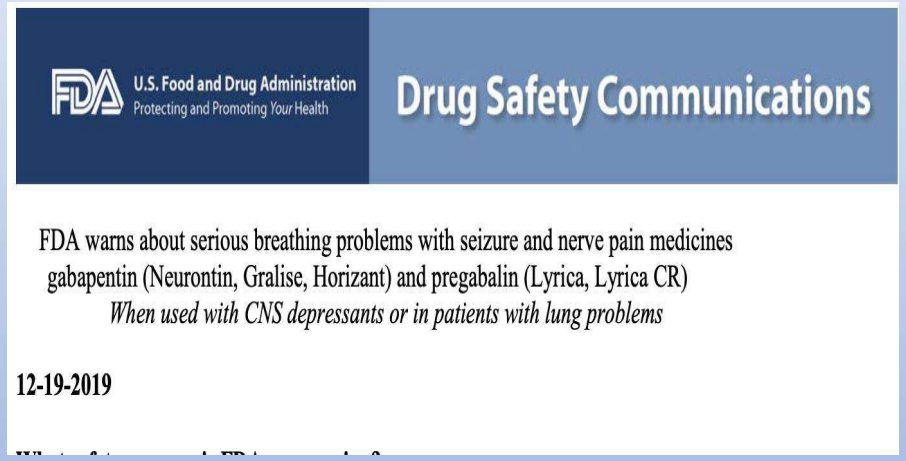
Naltrexone

- Low Dose Naltrexone (LDN)
- 0.1mg-8mg oral
- Analgesic effects at mu receptors
- Antagonism at toll-like receptor 4 leading to anti-inflammatory effects
- Chronic Pain: Fibromyalgia, Rheumatic Disease...
- Competitive antagonism at mu receptors
- Opioid antagonism at 50-100mg
- Active metabolite ½ life 14h

PRO SPINE & PAIN

Gabapentinoids


U.S. Food and Drug Administration
Protecting and Promoting *Your* Health

Drug Safety Communications

FDA warns about serious breathing problems with seizure and nerve pain medicines gabapentin (Neurontin, Gralise, Horizant) and pregabalin (Lyrica, Lyrica CR)

When used with CNS depressants or in patients with lung problems

12-19-2019

- Still useful as primary therapy or as adjunctive
- PDMP – identified as possible abusable
- Respiratory depression both independently and synergistically

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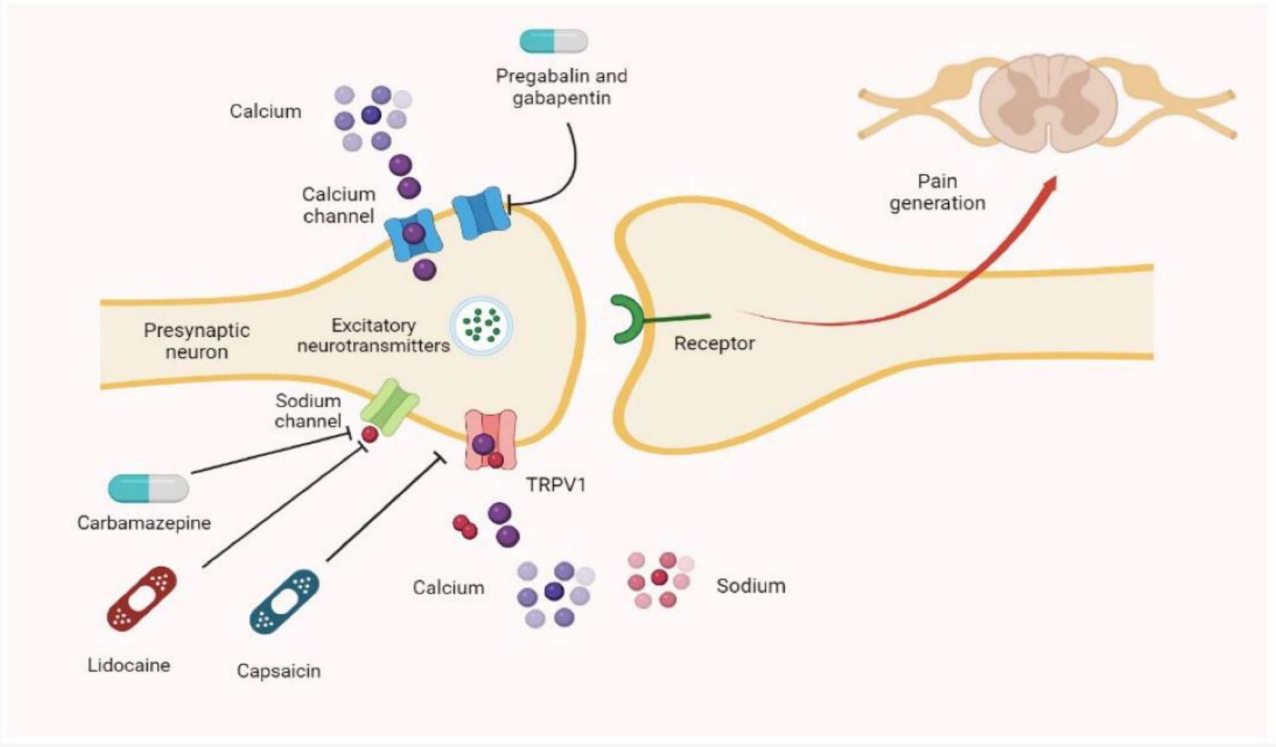
Figure 3. Other neuropathic pain drugs' mechanisms of action. The main principle of counteracting neuropathic pain is reducing the release of excitatory neurotransmitters in the synaptic cleft. Carbamazepine and lidocaine inhibit sodium channels, whereas capsaicin exerts its activity on TRPV1. Pregabalin and gabapentin block calcium channels in their α2δ subunit. TRPV1—transient receptor potential cation channel subfamily V member 1.



Gabapentinoids etc. MOA

- Marcianò G, Vocca C, Evangelista M, Palleria C, Muraca L, Galati C, Monea F, Sportiello L, De Sarro G, Capuano A, et al. The Pharmacological Treatment of Chronic Pain: From Guidelines to Daily Clinical Practice. *Pharmaceutics*. 2023; 15(4):1165. https://doi.org/10.3390/pharmaceutics15041165

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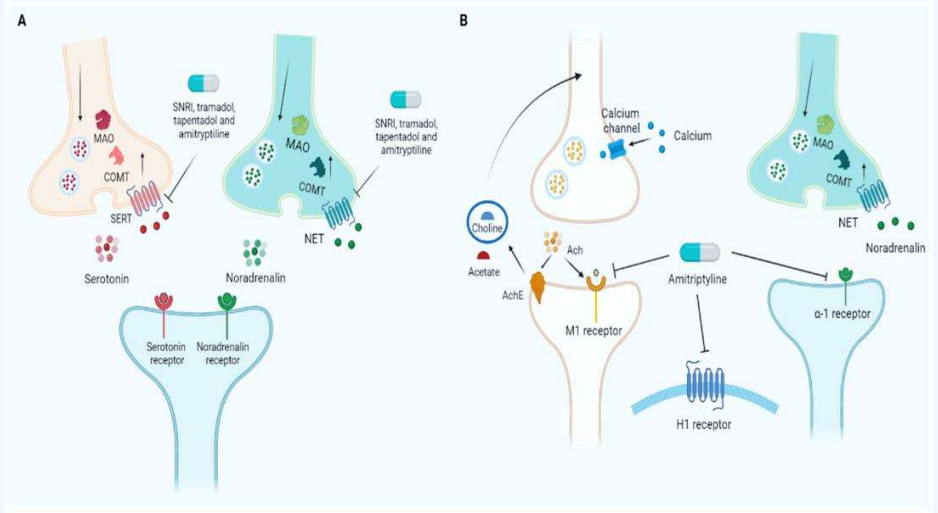
Antidepressants MOA

Marcianò G, Vocca C, Evangelista M, Palleria C, Muraca L, Galati C, Monea F, Sportiello L, De Sarro G, Capuano A, et al. The Pharmacological Treatment of Chronic Pain: From Guidelines to Daily Clinical Practice. *Pharmaceutics*. 2023; 15(4):1165. https://doi.org/10.3390/pharmaceutics15041165

Figure 2. Antidepressants used for pain management. (**A**) Amitriptyline and SNRIs inhibit SERT and NET, blocking serotonin and noradrenaline reuptake and increasing the availability of the two neurotransmitters in synaptic cleft. The same action is shared by two opioids, non-antidepressant drugs, namely, tramadol and tapentadol. (**B**) Nevertheless, amitriptyline is associated with several side effects according to its inhibitory action on cholinergic, adrenergic, and histaminergic pathways. Ach, acetylcholine; AchE, acetylcholinesterase; COMT, catechol-O-methyltransferase; MAO, monoamine oxidase; NET, norepinephrine transporter; SERT, serotonin transporter; SNRI, serotonin and norepinephrine reuptake inhibitors.



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Happy Now?

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Branded Slide Alert!

- Samidorphan- Opioid antagonist
- Can precipitate withdrawal

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Nonpharmacologic Treatment

- Mind-body practices (e.g., yoga, tai chi, qigong)
- Weight loss
- Psychological therapy (e.g., cognitive behavioral therapy)
- OMT, Chiropractic, Physical Therapy
- Mindfulness-based stress reduction
- Low-level laser therapy
- Acupuncture
- Massage
- Exercise therapy (a prominent modality in physical therapy)

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Types of Pain

Neuropathic Pain	Mixed Pain	Nociceptive Pain
• Peripheral neuropathies (diabetes, HIV)	• Migraine and chronic daily headache	• Mechanical low back pain
• Postherpetic neuralgia	• Fibromyalgia	• Rheumatoid arthritis
• Trigeminal neuralgia	• Phantom limb pain	• Osteoarthritis
• Central post-stroke pain	• Complex regional pain syndrome	• Chronic inflammatory conditions
• Spinal cord injury	• Multiple sclerosis	• Somatoform pain disorder
• Neuropathic low back pain	• Low back pain	• Postoperative pain
	• Myofascial pain syndrome	• Sickle cell crisis
	• Skeletal muscle pain	• Sports/exercise injury

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Non-Opioid Medications

Nonopioid Medications for Subacute and Chronic Pain

Several nonopioid pharmacologic therapies can be used for chronic pain conditions. Some examples include:

- Topical NSAIDs
- Oral NSAIDs
- Acetaminophen
- Tricyclic and antidepressants
- Serotonin and norepinephrine reuptake inhibitor (SNRI) antidepressants
- Anticonvulsants (e.g., pregabalin/gabapentin)
- Capsaicin and lidocaine patches

Nonopioid medications are associated with certain risks, particularly in older adults, pregnant patients, and patients with certain comorbidities such as cardiovascular, renal, gastrointestinal, and liver disease.

For more detailed guidance on the use of nonopioid medications to treat acute, subacute, and chronic pain, please refer to the 2022 Clinical Practice Guideline.

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Source: CDC

Voltage Gated Na Channel Blockers

- First new pain medication class in decades
- Journavx (suzetrigine)
- Indication for moderate to severe acute pain

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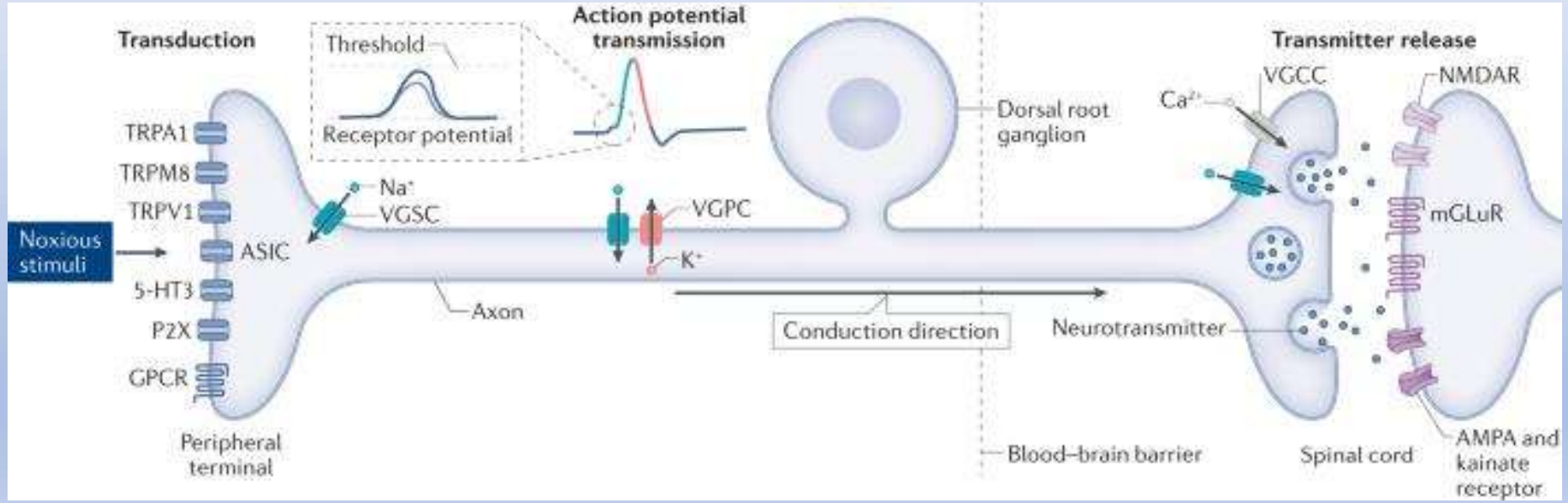
Role of Na Channel in the Transmission of Pain



Goodwin, G., McMahon, S.B. The physiological function of different voltage-gated sodium channels in pain. Nat Rev Neurosci 22, 263–274 (2021). https://doi.org/10.1038/s41583-021-00444-w

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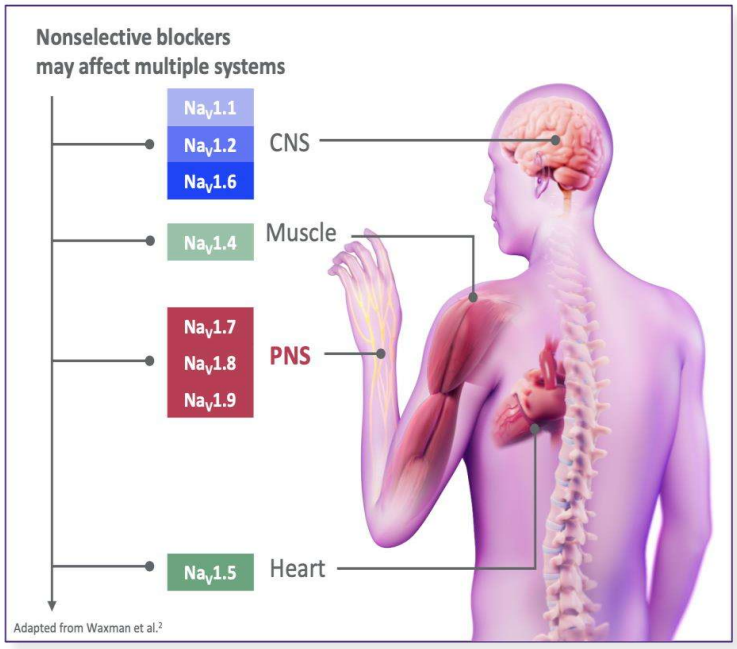
Na Channels and Pain Transmission

OF THE NINE VOLTAGE-GATED SODIUM CHANNELS, $NA_V1.7$, $NA_V1.8$, AND $NA_V1.9$ ARE EXPRESSED IN THE PNS

- There are nine voltage-gated sodium channel subtypes ($Na_V1.1$-$Na_V1.9$), each with a unique cell type–specific expression pattern and function[1,a]
- $Na_V1.7$, $Na_V1.8$, and $Na_V1.9$ are selectively expressed in peripheral sensory neurons[1]
  - These channels are essential for the initiation and propagation of pain signals in peripheral nociceptive neurons[1]
- Within the PNS, $Na_V1.8$ and $Na_V1.9$ are selectively expressed in nociceptive neurons[2]
  - $Na_V1.8$ does not have a functional role in the CNS[1]



[a]$Na_V1.3$ is primarily expressed in the CNS during embryonic and early prenatal life.[3]

CNS, central nervous system; PNS, peripheral nervous system.

1. Osteen JD, et al. [published online ahead of print Jan 8, 2025]. *Pain Ther*. doi: 10.1007/s40122-024-00697-0. 2. Waxman SG. *N Engl J Med*. 2023;389:466-469. 3. Catterall WA, et al. *Pharmacol Rev*. 2005;57(4):397-409.

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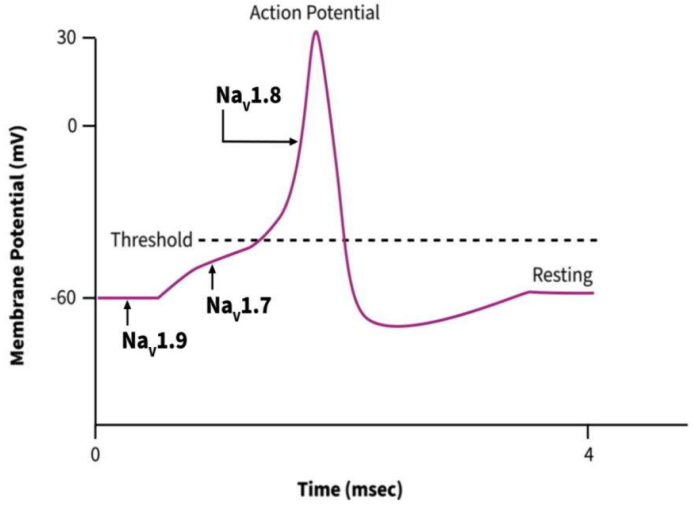
Na Channels and Pain Transmission

$NA_V1.7$, $NA_V1.8$, AND $NA_V1.9$ ARE ESSENTIAL FOR THE INITIATION AND PROPAGATION OF PAIN SIGNALS IN PERIPHERAL NOCICEPTIVE NEURONS[1]

- Noxious stimuli causes peripheral nociceptive neurons to depolarize and fire action potentials[2]
  - Excessive firing of these neurons leads to pain[1]
- $Na_V1.7$ amplifies small stimuli to bring the cell membrane to threshold to activate $Na_V1.8$ channels[1]
- Activated $Na_V1.8$ provides **more than 70%** of the Na^+ current needed for sustained firing of action potentials[1]
- $Na_V1.8$, resistant to depolarization, remains functional when other sodium channels are inactivated **and drives repetitive firing**[1]
- $Na_V1.9$ modulates resting potential and amplifies response to depolarization[1]



Adapted from Waxman et al.[3]

1. Waxman SG. *N Engl J Med*. 2023;389:466-469. 2. Kendroud S, et al. Physiology, nociceptive pathways. *StatPearls [Internet]*. Treasure Island (FL): StatPearls Publishing; 2023.

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Na Channel Blockers

- First new pain medication class in decades
- Journavx (suzetrigine)
- Indication for moderate to severe acute pain

- Binds voltage-sensing domain of Na 1.8 to inhibit passage of sodium ions
- Keeps nerve cell from reaching threshold of action potential generation

PRO SPINE & PAIN

Suzetrigine: Clinical Evidence

- Evaluated in two randomized double-blind, placebo and active controlled trials for the treatment of acute pain
- Primary endpoint: time weighted reduction in pain vs placebo
- Secondary endpoints: superiority vs HB/APAP, time to reduction ≥ 2 point reduction in NPS

- NAVIGATE 1 (s/p bunionectomy)
- NAVIGATE 2 (s/p abdominoplasty)

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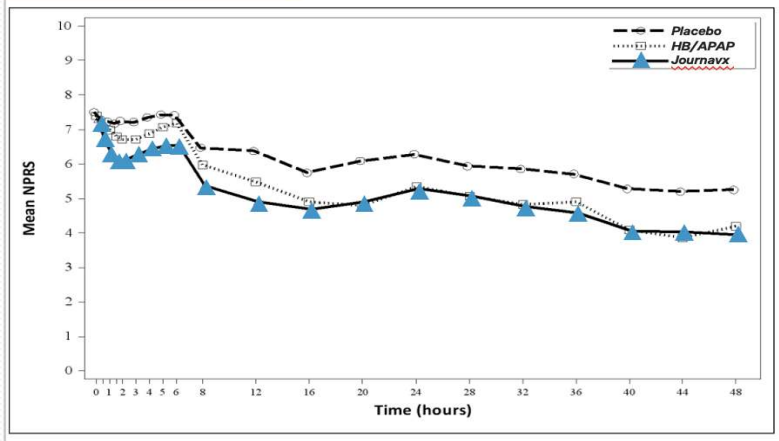
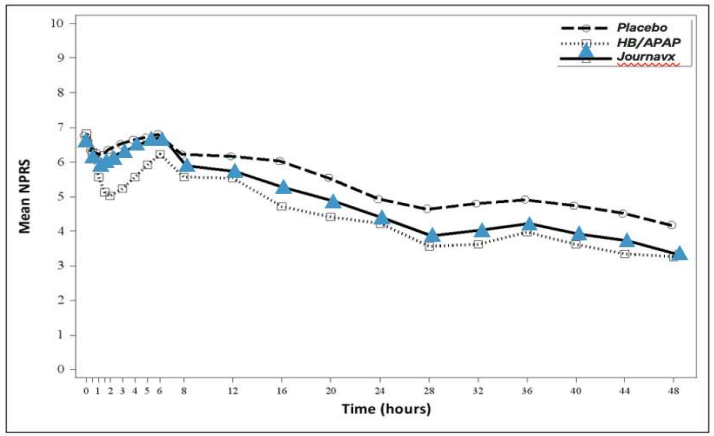
Suzetrigine: Clinical Evidence

Metric		Description					
		Trial 1			Trial 2		
Efficacy	*Least squares mean for time weighted sum of pain intensity difference from 0-24 hours (SPID24)*[1]	**Journavx** *(n=447)*	**Placebo** *(n=223)*	**HB / APAP** *(n=448)*	**Journavx** *(n=426)*	**Placebo** *(n=216)*	**HB / APAP** *(n=431)*
		118.4	70.1	111.8	**99.9**	70.6	120.1
	Median time to meaningful pain relief[2]	**119 mins.**	480 mins.	***N/A***	**240 mins.**	480 mins.	***N/A***
	Least squares mean difference for Journavx (95% CI)	***N/A***	48.4 *(33.6, 63.1)*	6.6 *(-5.4, 18.7)*	***N/A***	29.3 *(14.0, 44.6)*	-20.2 *(-32.7, -7.7)*
	Mean pain intensity over time via NPRS (11-point numeric pain rating scale)[3]						

Source: Simon-Kucher. 1. A larger value of mean of least squares indicates better efficacy measured by SPID48. 2. Defined as greater than or equal to 2-point reduction in NPRS. 3. Lower NPRS ratings correspond to lower pain levels. HB / APAP: Hydrocodone bitartrate / acetaminophen; NPRS: Numeric pain rating scale; SPID: Sum of Pain Intensity Difference.

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Suzetrigine: Clinical Evidence

- “Neither trial achieved the first key secondary endpoint of superiority of suzetrigine compared to hydrocodone bitartrate/acetaminophen…on SPID48, the efficacy of orally administered suzetrigine is in the range seen with opioids (e.g., morphine, tramadol, oliceridine) administered intravenously that have been studied in both abdominoplasty and bunionectomy …post hoc analyses without imputation also provided evidence of efficacy in combination with ibuprofen, suggesting suzetrigine is efficacious both as a monotherapy and as the base for a multimodal regimen in the real-world setting”

Bertoch, Todd M.D.1; D’Aunno, Dominick M.D.2; McCoun, Jessica M.D.3; Solanki, Daneshvari M.D.4; Taber, Louise M.D.5; Urban, Joshua M.D.6; Oswald, Jessica M.D., M.P.H.7; Swisher, Matthew W. M.D.8; Tian, Simon M.D.9; Miao, Xiaopeng Ph.D.10; Correll, Darin J. M.D.11; Negulescu, Paul Ph.D.12; Bozic, Carmen M.D.13; Weiner, Scott G. M.D., M.P.H.14. Suzetrigine, a Nonopioid NaV1.8 Inhibitor for Treatment of Moderate-to-severe Acute Pain: Two Phase 3 Randomized Clinical Trials. Anesthesiology 142(6):p 1085-1099, June 2025. | DOI: 10.1097/ALN.0000000000005460

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Ziconitide

- Nonopioid agent
- Selectively and reversibly binds to N-type voltage sensitive calcium channels
- Blocks pronociceptive neurotransmitter release from afferent nerves in the dorsal horn

- Intrathecal administration only
- Narrow Therapeutic Window
- No respiratory depression or withdrawal
- Contraindicated in history of psychosis
- Risk of neurologic adverse effects

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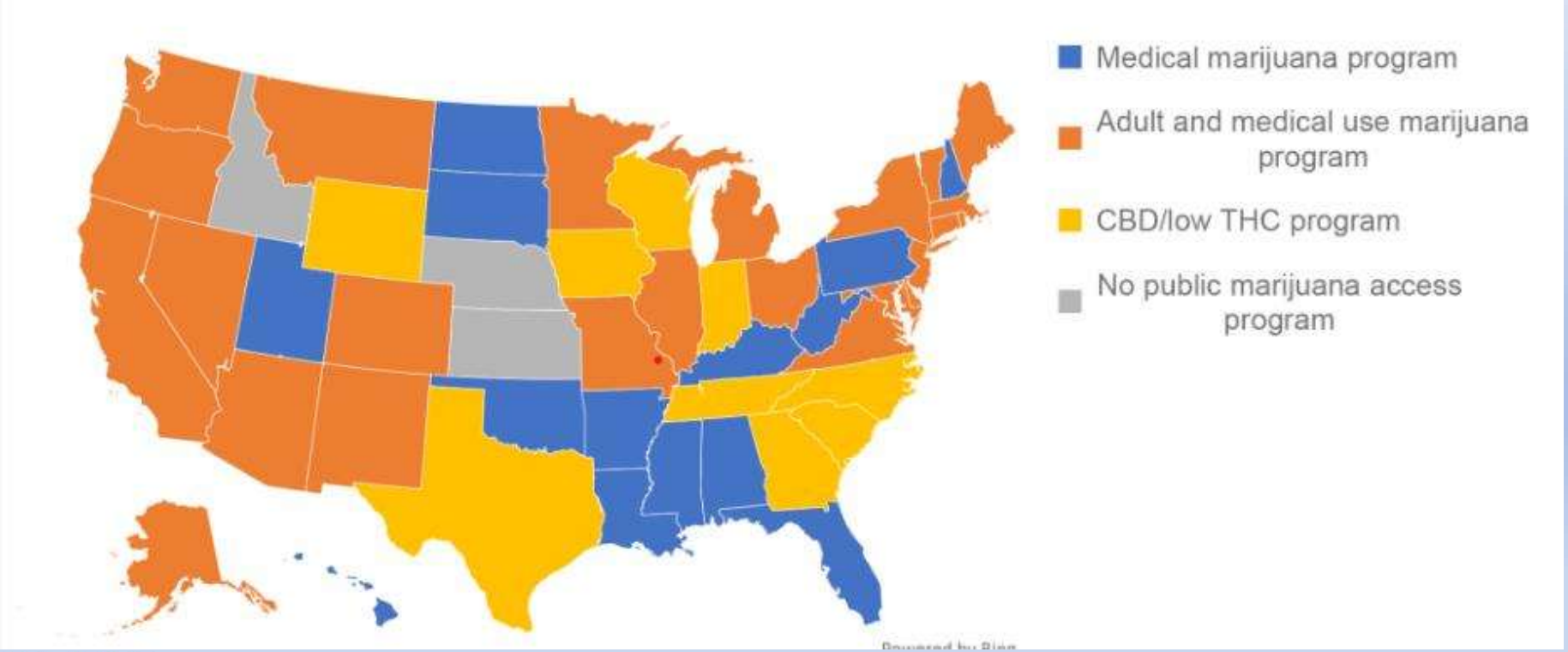
Marijuana Legality by State updated 2024



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Cannabinoids

- 1. MMJ – Federal • Schedule 1 “ Drugs, substances, or chemicals are defined as drugs with no currently accepted medical use and high potential for abuse.” DEA.gov
- 2. MMJ – State
- 3. CBD – Federal • Approved under the 2019 Farm Bill • However, limitations do exist • <0.3% THC • Labelling Restrictions • Food Restrictions • Must be derived from Hemp plants

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Physiologic Effects of Cannabinoids

System	Acute Effects	Chronic Effects
Cardiovascular	Tachycardia Vasodilation Orthostasis	Atheromatous Disease
Pulmonary	Bronchodilation Hyperreactivity Airway Edema	Chronic Bronchitis Emphysema
Central Nervous System	Anxiolysis Anxiety Paranoia/Psychosis Euphoria Dizziness Headache Memory Dysfunction Analgesia	Similar to acute; however, tolerance develops requiring higher doses for similar effects
Gastrointestinal	Anti-nausea Increased Appetite Abdominal Pain	Hyperemesis
Endocrine	–	Gynecomastia Anovulation Galactorrhea

Alexander JC. A Review of the Anesthetic Implications of Marijuana Use. Baylor UMC Proceedings, 32:3 364-371

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Anesthesia Considerations with Cannabis

- Perioperative
- 1. ↑Risk of M.I. within 1hr after use
- 2. Airway hyperactivity
- 3. Anxiety paranoia
- 4. Assess for other drugs

- Intraoperative
- 1. Tolerance to induction agents
- 2. Elevated bispectral index
- 3. Unknown cross-tolerance to other anesthetic agents
- 4. Elevated risk of M.I. within 1hr of use
- 5. Airway hyperreactivity

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Alexander JC. A Review of the Anesthetic Implications of Marijuana Use. Baylor UMC Proceedings, 32:3 364-371

Anesthesia Considerations with Cannabis

Post-Operative

1. Unknown cross-tolerance to analgesics

2. Possible heightened pain perception

3. Withdrawal

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Cannabis Withdrawal Syndrome

- Onset can be less than one day for high dose chronic users, with duration for several weeks

- Irritability, Anger, Anxiety, Depressed Mood, Insomnia
- Anorexia, Abdominal Cramping
- Headaches, Tremors
- Fevers, Chills

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Alexander JC. A Review of the Anesthetic Implications of Marijuana Use. Baylor UMC Proceedings, 32:3 364-371

Kratom

- M. Speciosa, found in SE Asia
- Utilized in diarrhea treatment
- Increased use in Western countries as analgesic
- Not currently scheduled by DEA
  - Available via multiple avenues
- Oral, rapid onset

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Kratom

- Side Effects include weight loss, xerostomia, nausea, vomiting, hepatic damage
- Higher doses – drowsiness, delusion, respiratory impairment
- Withdrawal symptoms similar to opioids

- Mitragynine
  - Mu and sigma receptor agonism
  - Activation of Alpha 2 adrenergic receptors – analgesia via descending pathways
- 7-OH mitragynine
  - Mu and kappa receptor agonism
  - 13 x potency of morphine

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Naltrexone

- Competitive antagonism at mu receptors
- Opioid antagonism at 50-100mg
- Active metabolite ½ life 14h

- Low Dose Naltrexone (LDN)
  - 0.1mg-8mg oral
  - Analgesic effects at mu receptors
  - Antagonism at toll-like receptor 4 leading to anti-inflammatory effects
  - Chronic Pain: Fibromyalgia, Rheumatic Disease...

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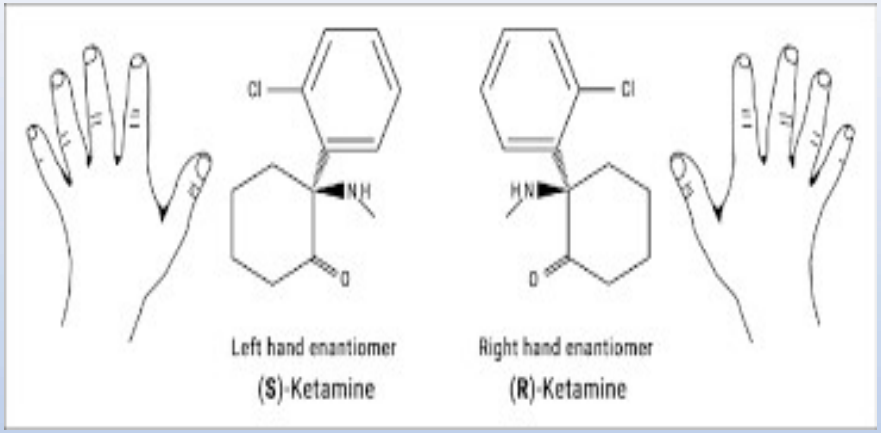
Ketamine

- IV, SL, Nasal (esketamine)
- CSA Class III
- blocks glutamatergic neurons via its antagonistic effect on NMDA receptors
- Dopaminergic, adrenergic, serotoninergic, opioid, muscarinic receptor effects
- modulates the reuptake of serotonin, dopamine, and norepinephrine and causes a paradoxical increase in glutamate with stimulation of the descending inhibitory pathways



- IV anesthetic: 1-1.5 mg/kg max
- SL for chronic pain: 150mg/day
- Abuse potential
- Multiple chronic pain applications
  - Multiple dosage regimens

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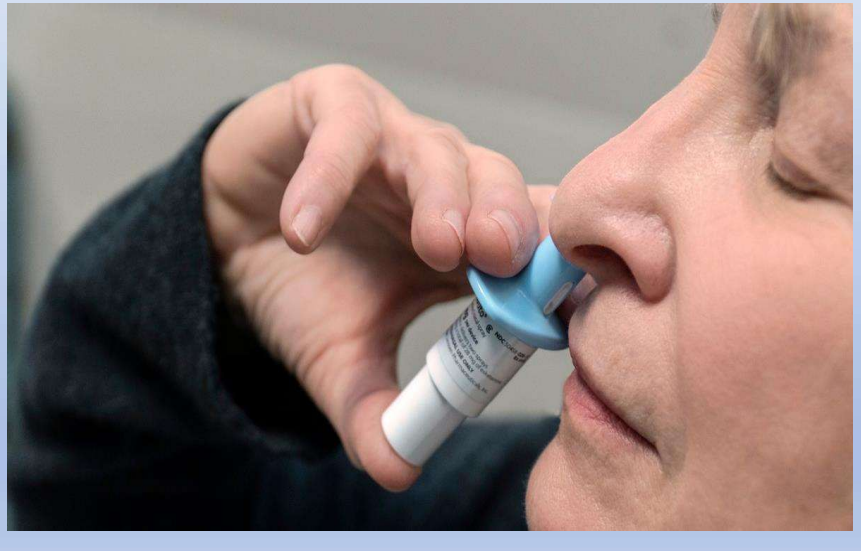
https://pmc.ncbi.nlm.nih.gov/articles/PMC10179418/

Ketamine

- (*S*)-ketamine more directly affecting mechanistic target of rapamycin complex 1(mTORC1) signaling
- FDA indication for treatment resistant depression in adults (monotherapy or in combination)
- Not indicated for pain, *but…*



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Interventional Pain Procedures

- Trigger Point Injections
- Joint Injections
- Peripheral Nerve Injection
- Soft Tissue Injection
- PRP Therapy
- Stem Cell Therapy
- Nerve Blocks
- Occipital Nerve Block

- Facet Joint Nerve Block
- Epidural Steroid Injection
- Radiofrequency Ablation
- Regenerative/Adult Autologous Stem Cell Therapy
- Celiac Plexus Block
- Nucleoplasty
- ReActiv8
- Epidual Adhesiolysis

- Spinal Cord Stimulator
- Peripheral Nerve Stimulator
- Intrathecal Drug Delivery (Pain Pump)
- Kyphoplasty/Vertebral Augmentation
- Interspinous Spacer (Vertiflex)
- Posterior Interspinous Fusion (Minute Man)
- Sacroiliac Joint Fusion
- Facet Fusion
- Percutaneous Discectomy
- Lumbar Decompression
- MILD Procedure
- Laminectomy
- Intracept Procedure

Degree of Complexity

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Interventional Procedure Considerations and Options

- Consider Conservative Therapy First: OMT, PT, Chiropractic, Acupuncture
- Evaluate Medication Options
- When conservative measures don't yield satisfactory results consider:
  - Epidural Steroid Injection (ESI)
  - Joint Interventions
  - Nerve Blocks
  - Vertebral Augmentation Procedure
  - Minimally Invasive Fusion
  - Intrathecal Drug Delivery System
  - Neuromodulation (Spinal Cord Stimulation, Peripheral Nerve Stimulation)

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Why Interventional Pain Procedures?

- Improve function and quality of life
- Limit exposure and or duration to other therapies
- Hopefully reduce seeking of illicit/dangerous alternatives
- Work together with physical medicine, cognitive-behavioral approaches

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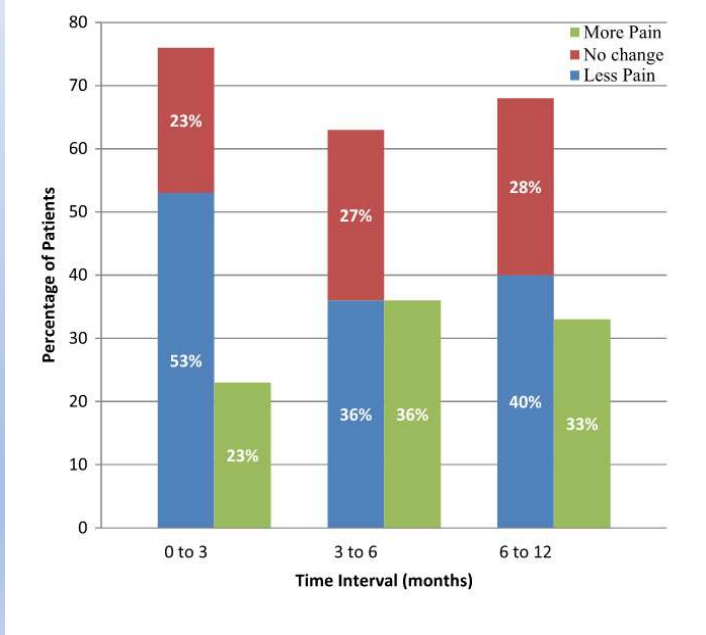
Interventions and non-opioid treatments actually decrease pain in most



"The average percent reduction of opioid doses was 46% over a 12-month period."

Harden P et al. **Clinical Implications of Tapering Chronic Opioids in a Veteran Population** Pain Medicine 2015

Clinical Implications of Tapering Chronic Opioids

Table 3 Opioid regimen in patients successfully and unsuccessfully tapered

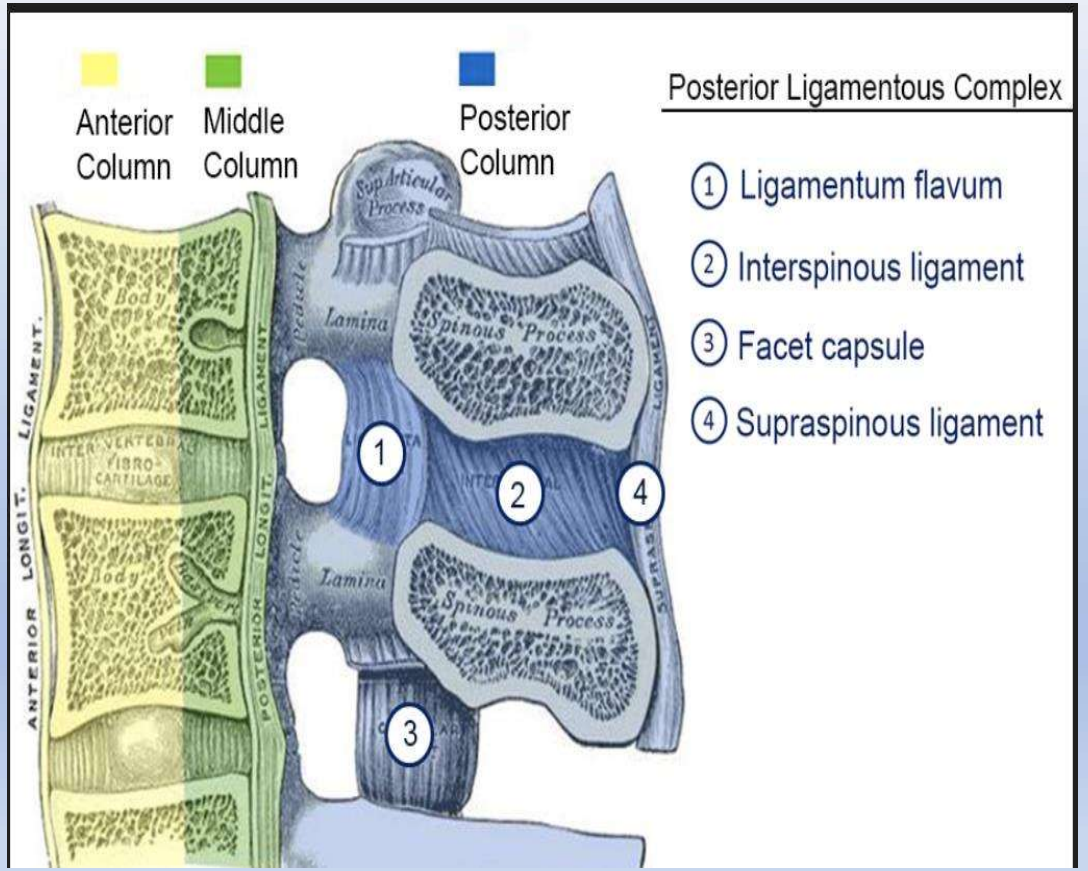
Opioid Regimen	Successful Taper	Unsuccessful Taper
Fentanyl Transdermal + Oxycodone IR	1	1
Methadone	4	
Methadone + Morphine IR	2	
Methadone + Oxycodone IR	10	
Morphine SA + Morphine IR	7	2
Morphine SA + Oxycodone IR	15	
Oxycodone IR	5	
Oxycodone SA	1	
Oxycodone SA + Morphine IR	1	
Oxycodone SA + Oxycodone IR	1	
	47	**3**

IR = Immediate Release; SA = Sustained-Acting.

3 Column Spine Model

Anterior, Middle, Posterior

Allows Correlation of Symptoms, Physical Examination and Treatment options



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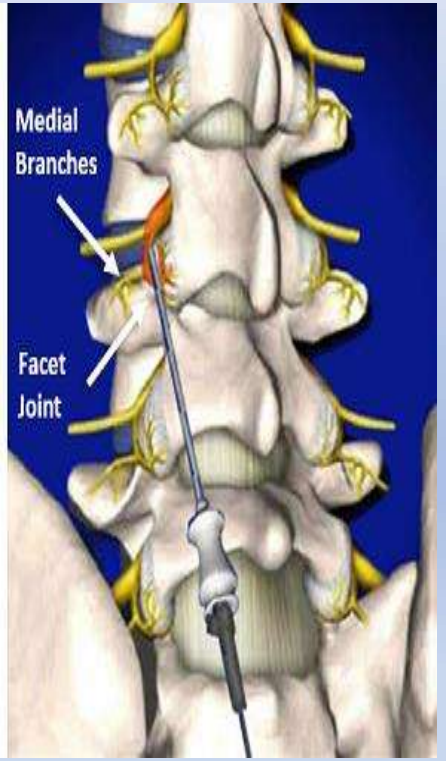
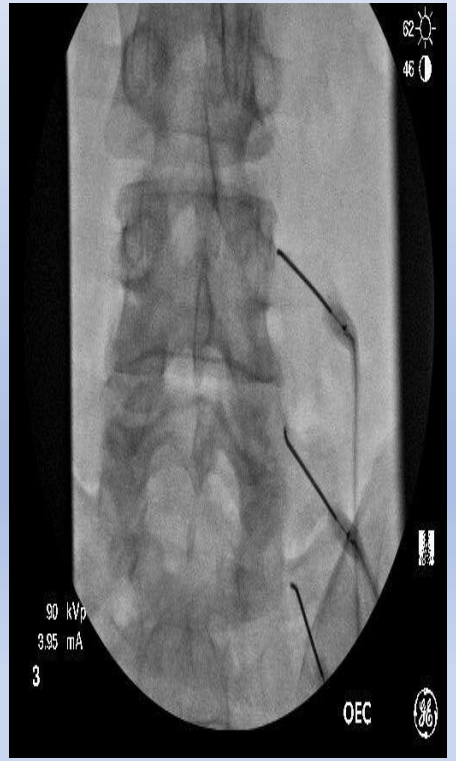
https://www.orthobullets.com/spine/2003/spine-biomechanics

Radiofrequency Ablation/Rhizotomy





- Prolonged relief from axial spine pain secondary to facet degenerative disease/spondylosis
- Cervical, Thoracic, Lumbar
- Medial branch blocks/facet joint blocks confirm candidacy for RFA

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Radiofrequency Ablation

- use of high-frequency alternating current (300 000–500 000 Hz), which results in ionic agitation and friction generating focal heating in tissue (ie, the tissue surrounding the electrode becomes the primary source of the heat). Irreversible cellular damage can occur from focal temperatures above 42°C, although for most mammalian tissues damage occurs between 46°C and 49°C.
- Such temperatures applied to a nerve result in local destruction and Wallerian degeneration of nerve axons.
- Axonal regeneration/ regain of function approximates duration of relief
- Thermal, cooled, pulsed, bipolar

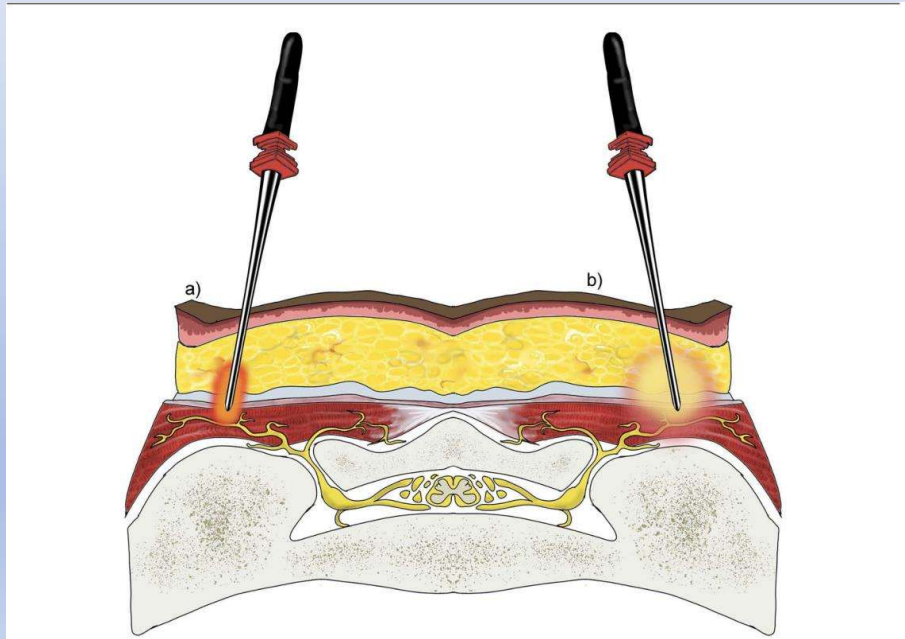

Figure 3 Conventional versus Cooled Radiofrequency Ablation. (**a**) Conventional RFA requires precise placement of the RFA probe within 1–2 mm of the intended target. Conventional RFA probes can reach temperatures of 100°C and insulating properties prevent heat radiofrequency waves from reaching further target tissue. (**b**) Cooled RFA needles utilize continuously circulating coolant within a hollow exterior shell to modulate temperature at the tip of the probe to around 60°C. This cooling mechanism avoids charring surrounding tissue, allowing for more effective heat transfer beyond the immediate proximity of the probe tip. The result is a significant difference in the overall size, shape, and area of effect of the ablated lesion, as compared to conventional RFA. Original medical illustration by Kamil Sochacki, DO.

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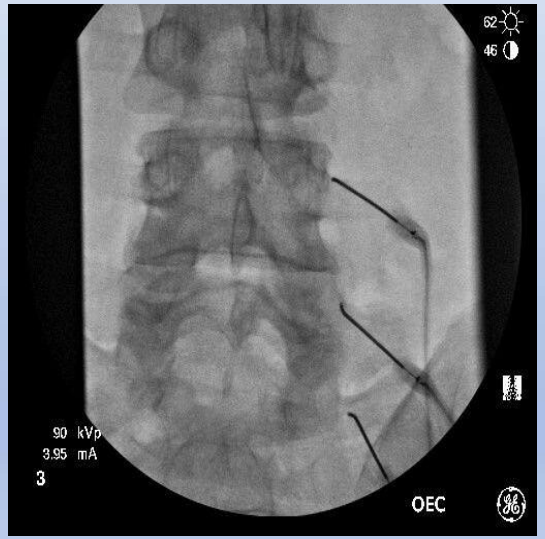
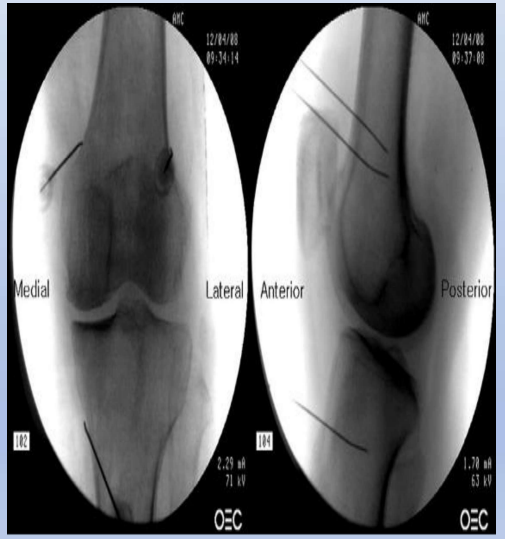
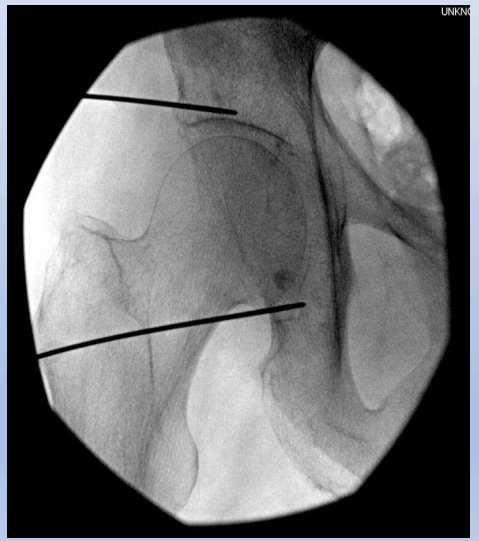
Radiofrequency Ablation/Rhizotomy: Other Applications







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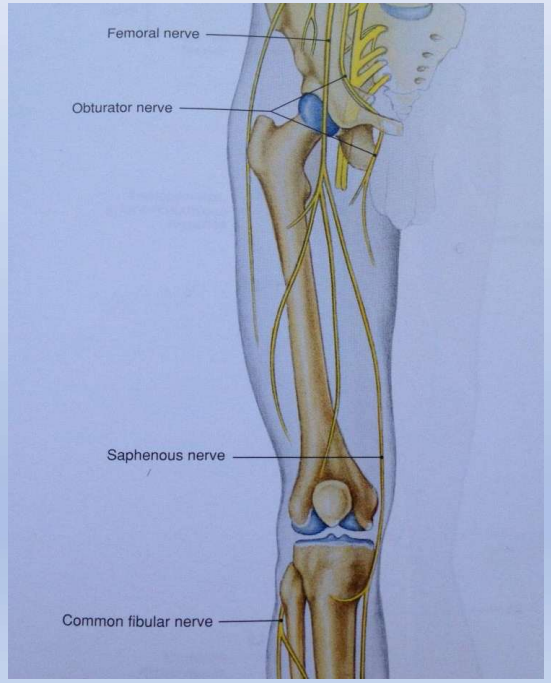
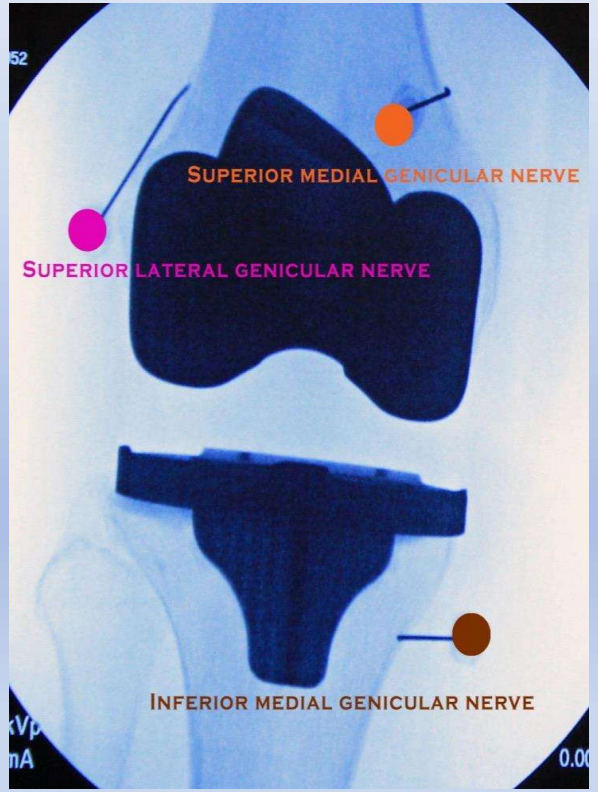
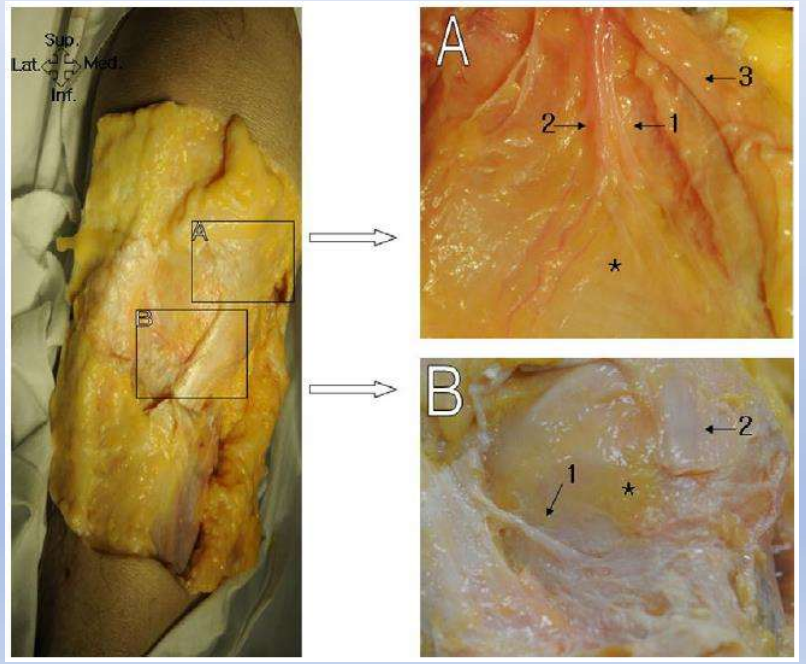
Genicular Nerve Radiofrequency Ablation







Masahiko Ikeuchi, Percutaneous Radiofrequency Treatment for Refractory Anteromedial Pain of Osteoarthritic Knees. Pain Medicine 2011; 12: 546–551
N=35, RF(N=18), Nerve block(N=17). Age 69-85 4, 8, 12 week follow up
Outcome measures: VAS, Western Ontario McMaster Universities(WOMAC) Osteoarthritis Index Score
Statistically significant pain relief (VAS) for the radiofrequency group at 4, 8, and 12 weeks
Woo-Jong Choi, Radiofrequency treatment relieves chronic knee osteoarthritis pain: A double-blind randomized controlled trial. (PAIN 2011;152 : 481–487
Genicular neurotomy vs. sham N= 38, RF(N=19), sham(N=19), 61-75yo 1, 4, and 12 week follow up Outcome measures: VAS, Oxford Knee Score
In the RF group 10/17(59%), 11/17(65%), and 10/17(59%) achieved at least 50% knee pain relief at 1, 4, and 12 weeks respectively

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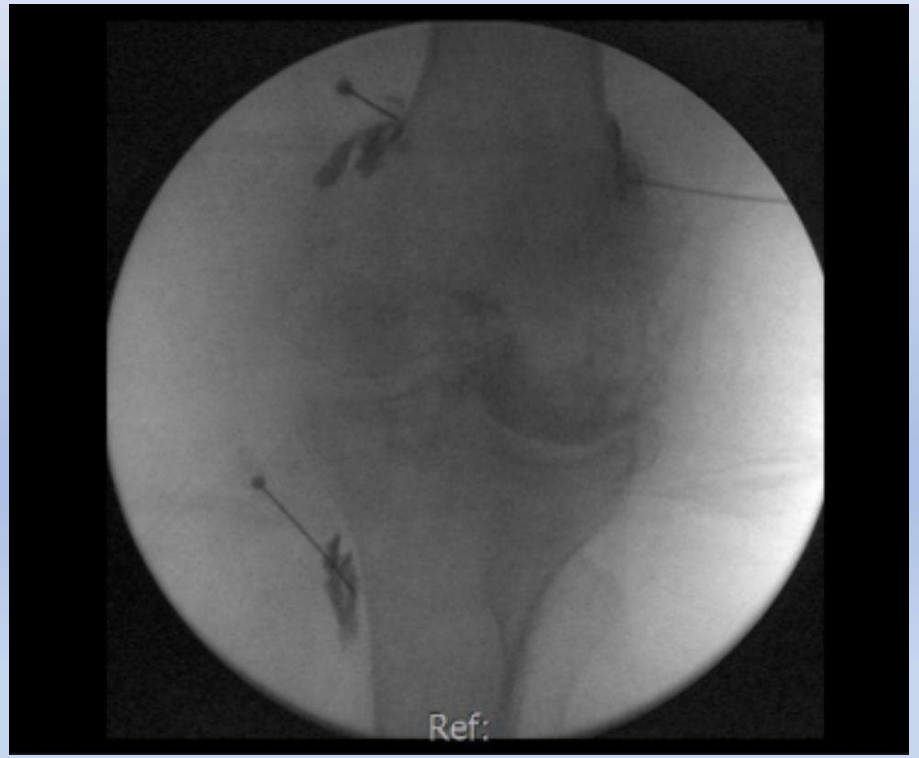
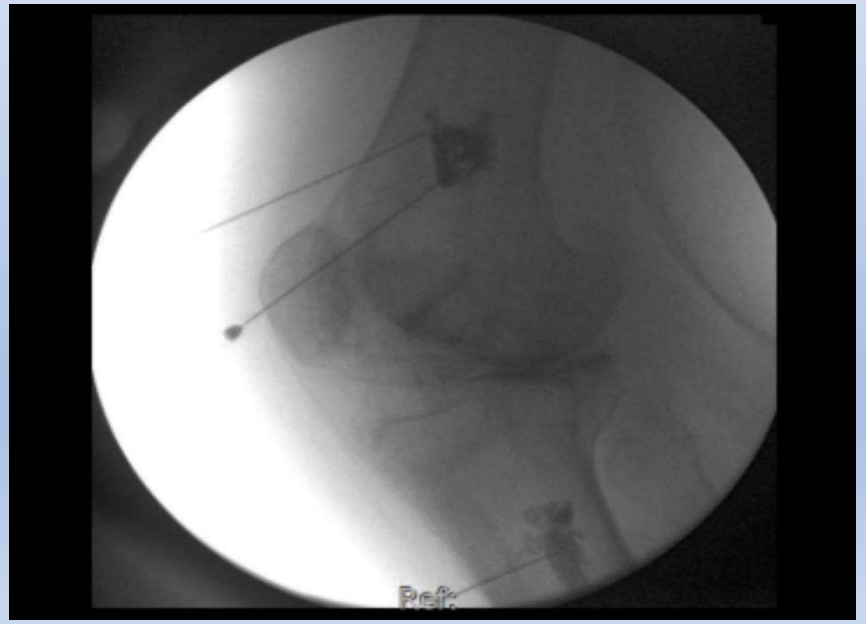
Genicular Nerve Blocks





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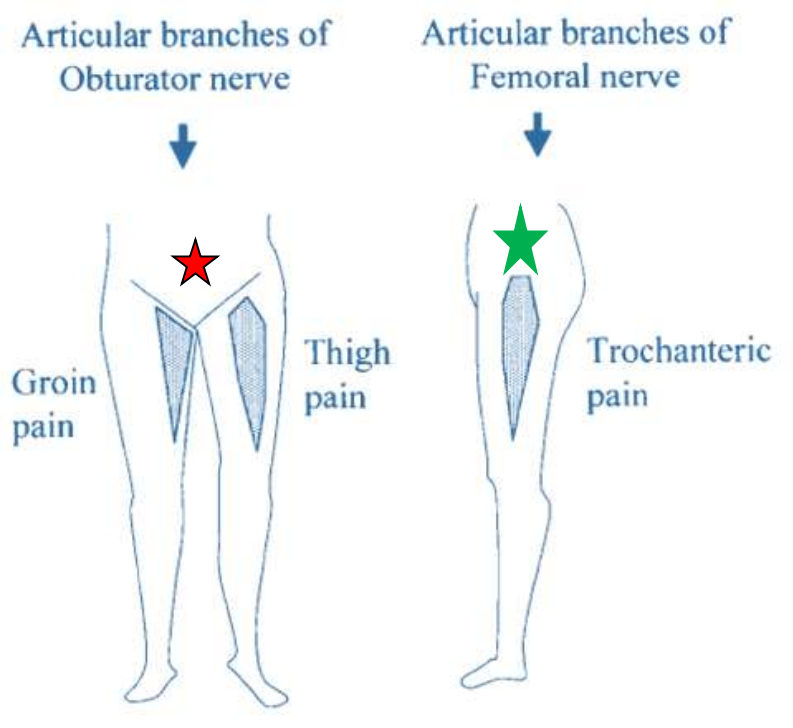
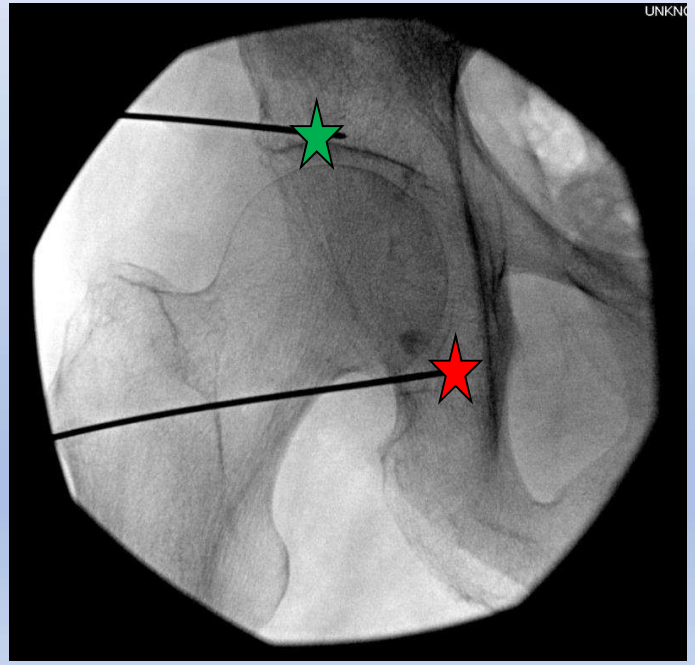
Hip Joint RFA



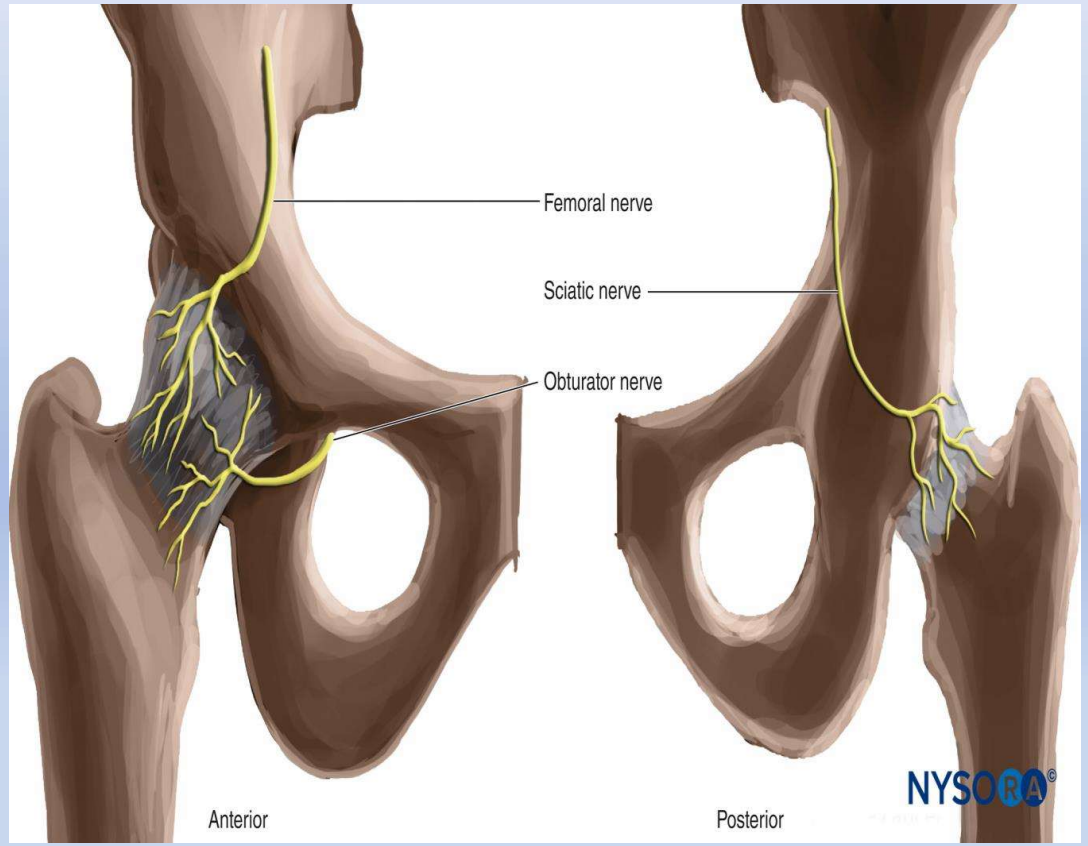


Patients with hip joint pain may suffer from groin, thigh and trochanteric pain. **Groin pain and thigh pain** arise from the articular branches of **obturator** nerves. A trochanteric **(lateral) pain** arises mainly from the articular branches of **femoral nerve**.

PRO SPINE & PAIN

Kawaguchi M, et al. Percutaneous Radiofrequency Lesioning of Sensory Branches of the Obturator and Femoral Nerves for the Treatment of Hip Joint Pain. Reg Anesth and Pain Medicine, 26:6, 2001:576–581

Joint Radiofrequency Rhizotomy -Hip



- Targeting the sensory branches of the femoral and obturator nerves

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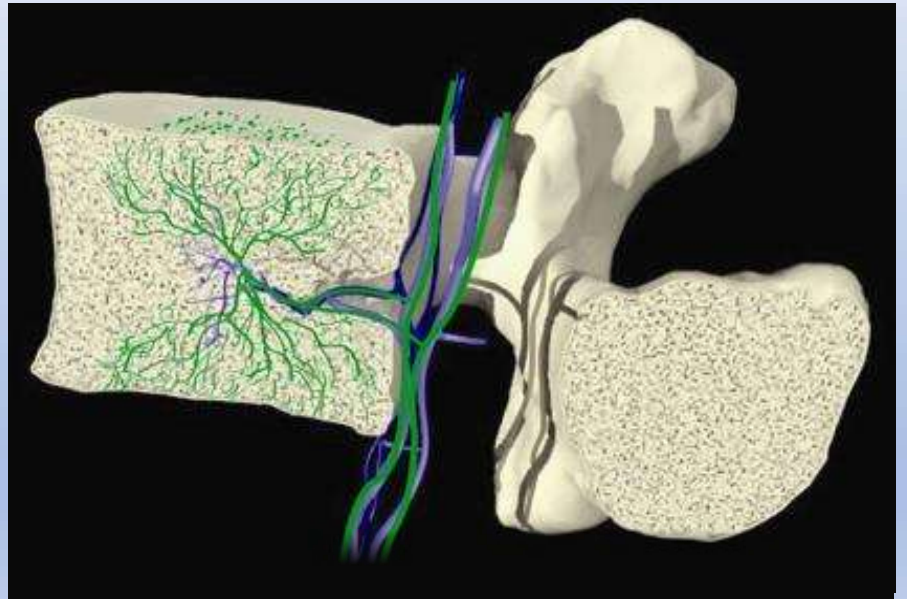
Radiofrequency Basivertebral Nerve

- Discs and vertebral endplates (VEPs) are one functional unit
- Traditionally, discogenic and vertebrogenic pain have been seen as clinically distinct with treatments focused on the disc
- Vertebral endplates are more highly innervated than intervertebral discs[1]
    - 30% of discs show evidence of pathologic innervations compared with 90% of adjacent VEPs.
- Basivertebral nerve (BVN) innervates VEPs[2]



Distribution of the basivertebral nerve

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1. Fields AJ, Liebenberg EC, Lotz JC. The Spine Journal 2014;14(3):513-521
2. Bailey JF, Liebenberg E, Degmetich S, Lotz JC. Innervation patterns of PGP 9.5-positive nerve fibers within the human lumbar vertebra. Journal of Anatomy 2011;218(3):263-70

Degenerative Disc Disease and Modic Changes

- Degenerative disc disease
- Endplate Erosion (Modic Changes)

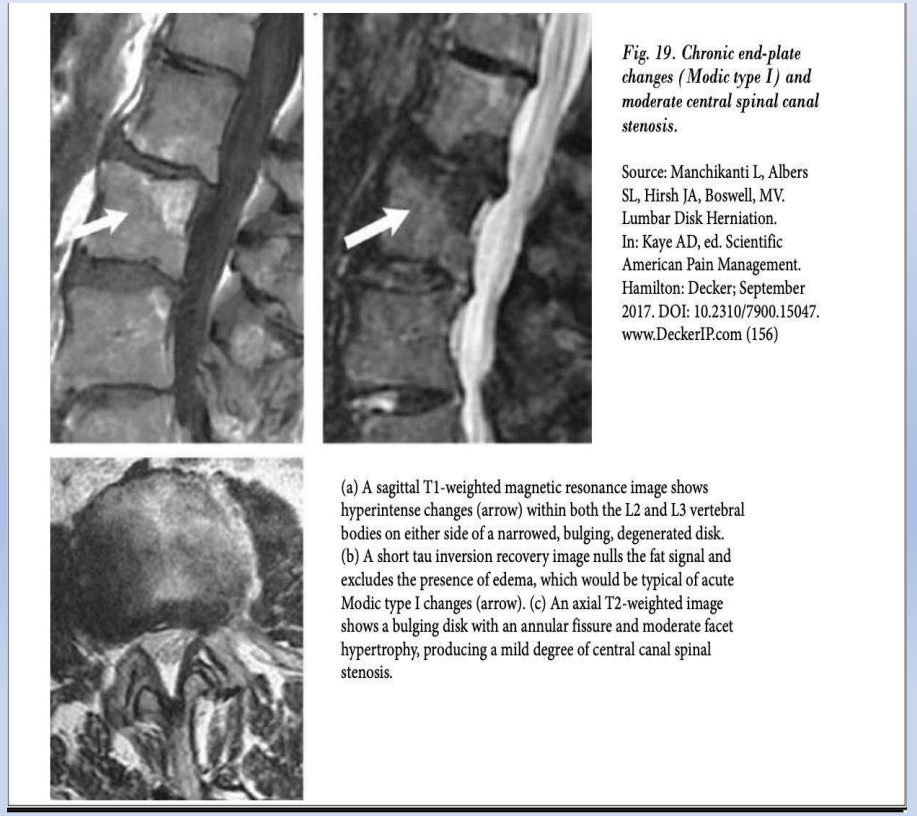

Fig. 19. Chronic end-plate changes (Modic type I) and moderate central spinal canal stenosis.

Source: Manchikanti L, Albers SL, Hirsh JA, Boswell, MV. Lumbar Disk Herniation. In: Kaye AD, ed. Scientific American Pain Management. Hamilton: Decker; September 2017. DOI: 10.2310/7900.15047. www.DeckerIP.com (156)

(a) A sagittal T1-weighted magnetic resonance image shows hyperintense changes (arrow) within both the L2 and L3 vertebral bodies on either side of a narrowed, bulging, degenerated disk. (b) A short tau inversion recovery image nulls the fat signal and excludes the presence of edema, which would be typical of acute Modic type I changes (arrow). (c) An axial T2-weighted image shows a bulging disk with an annular fissure and moderate facet hypertrophy, producing a mild degree of central canal spinal stenosis.

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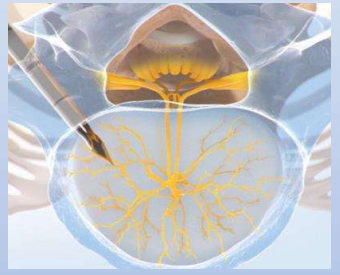
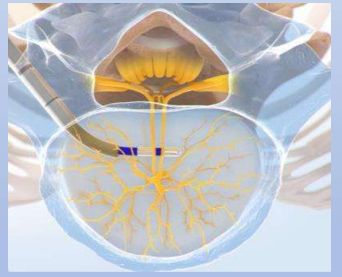
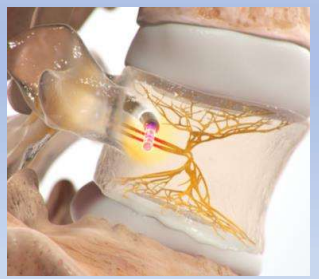
Radiofrequency Ablation Basivertebral Nerve

- Targeting the basivertebral nerve with approach similar to vertebroplasty/kyphoplasty
- Treatment of vertebrogenic back pain –midline, non-radicular, worse with flexion
- • Chronic Low Back Pain of at least 6 months duration;
- Failure to respond to at least 6 months of conservative care; and
- MRI changes consistent with Modic Type 1 or Type 2 at one or more levels







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Regenerative Stimulation

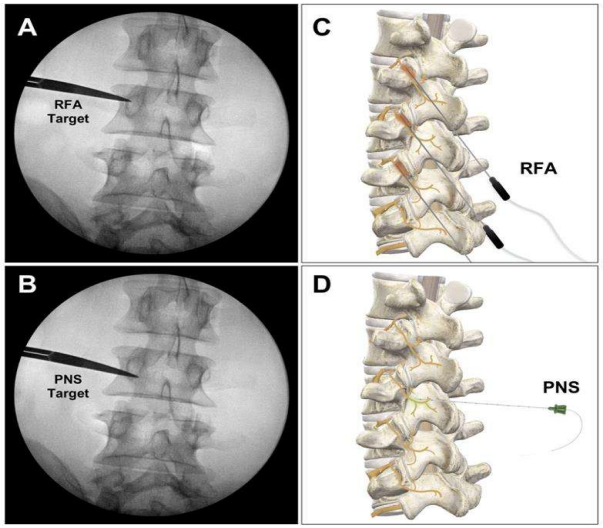
Temporary (30-60 day) stimulation of the multifidus muscle via simulation of medial branches (L2, L3) to treat chronic lower back pain using percutaneous stimulation leads

Unlike traditional SCS/PNS, typically no preprocedural psychological clearance required

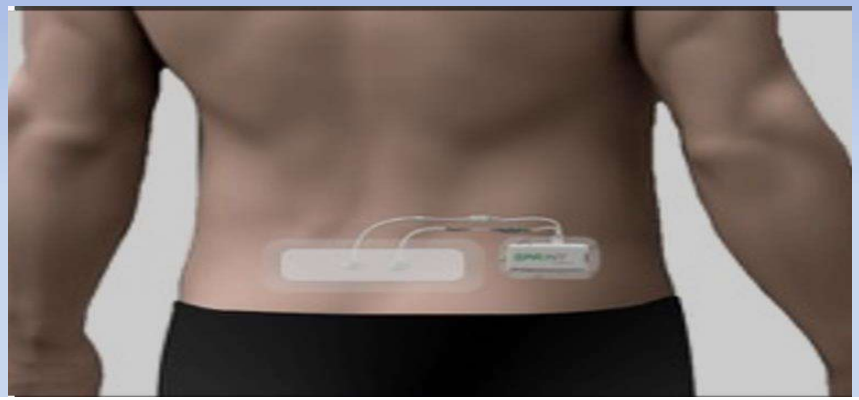
Following removal can progress to other options including RFA or permanent PNS system

Timothy R Deer, Christopher A Gilmore, Mehul J Desai, Sean Li, Michael J DePalma, Thomas J Hopkins, Abram H Burgher, David A Spinner, Steven P Cohen, Meredith J McGee, Joseph W Boggs, Percutaneous Peripheral Nerve Stimulation of the Medial Branch Nerves for the Treatment of Chronic Axial Back Pain in Patients After Radiofrequency Ablation, Pain Medicine, Volume 22, Issue 3, March 2021, Pages 548–560,

Figure 3. Comparison of needle insertion approach for medial-branch PNS and medial-branch RFA. Although the same nerve ...

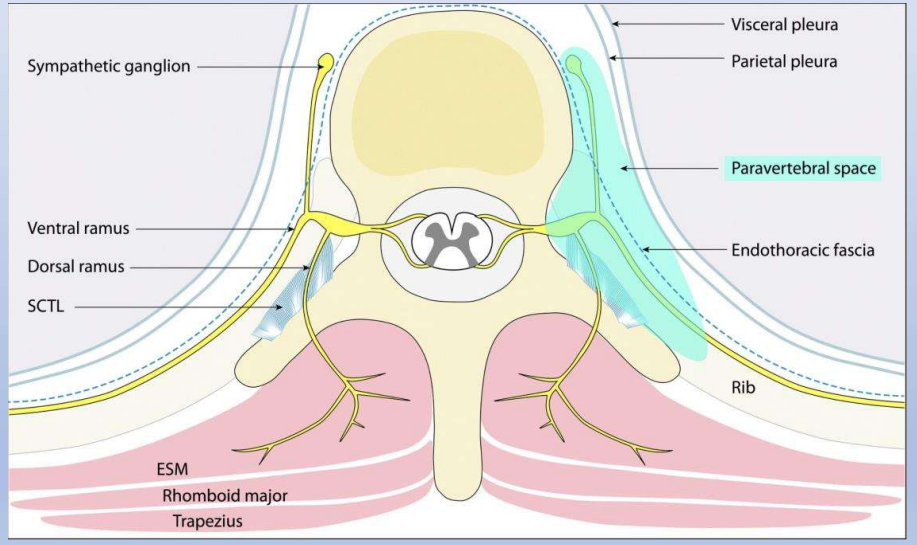


Pain Med, Volume 22, Issue 3, March 2021, Pages 548–560, https://doi.org/10.1093/pm/pnaa432



Erector Spinae Block

- ? Paravertabral spread vs intrafascial spread towards dorsal primary rami
- Akin to transverse abdominal plane block (TAP block) - fascial plane injection
- Acute and chronic thoracic pain applications



Pawa, A., Wojcikiewicz, T., Barron, A. et al. Paravertebral Blocks: Anatomical, Practical, and Future Concepts. Curr Anesthesiol Rep 9, 263–270 (2019). https://doi.org/10.1007/s40140-019-00328-x

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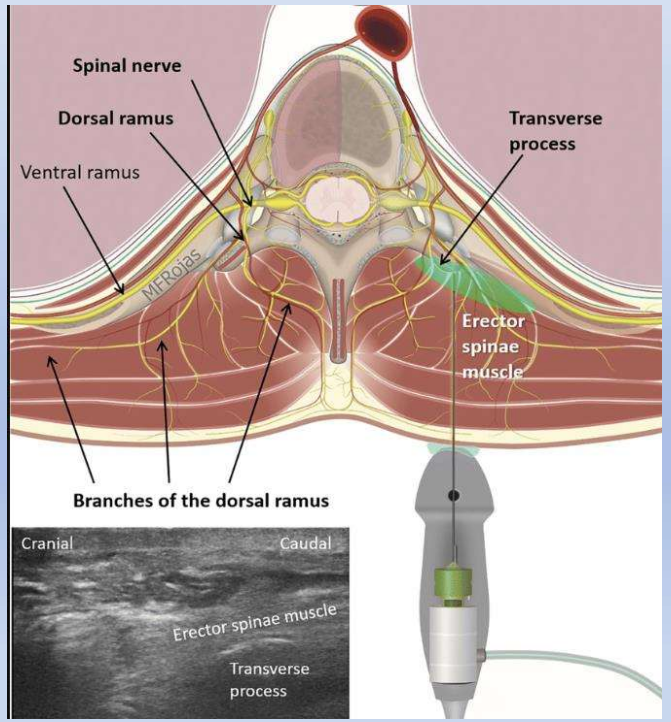
Erector Spinae Block

- Primarily described in regional anesthesia literature for intraoperative/postoperative analgesia
- Also utilized in acute pain presentations (shingles, posterior rib fractures, thoracic wall injury)



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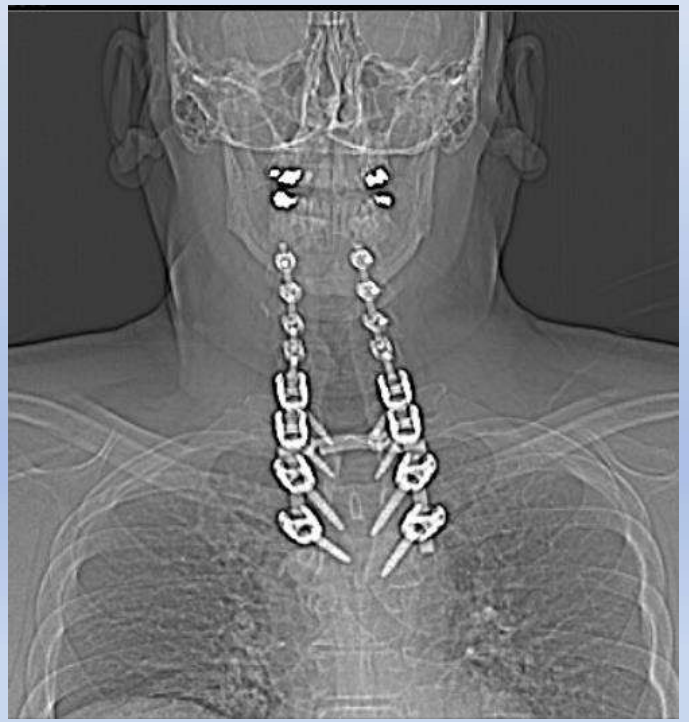
Chin, Ki & Dinsmore, Michael & Lewis, Stephen & Chan, Vincent. (2020). Opioid-sparing multimodal analgesia with bilateral bi-level erector spinae plane blocks in scoliosis surgery: a case report of two patients. European Spine Journal.

Erector Spinae Block: Case Report (GJ)

- 67-year-old man with an extensive history of chronic pain primarily affecting his cervico-thoracic spine. He is status post cervical and thoracic laminectomy and fusions, complicated with infection and subsequent revisions
- Significant cardiovascular history requiring anticoagulation; IDDM, solitary kidney
- Mainly describes cervicothoracic paraspinal pain, no relief from trigger point injections, minimal improvement following cervicothoracic facet joint treatment



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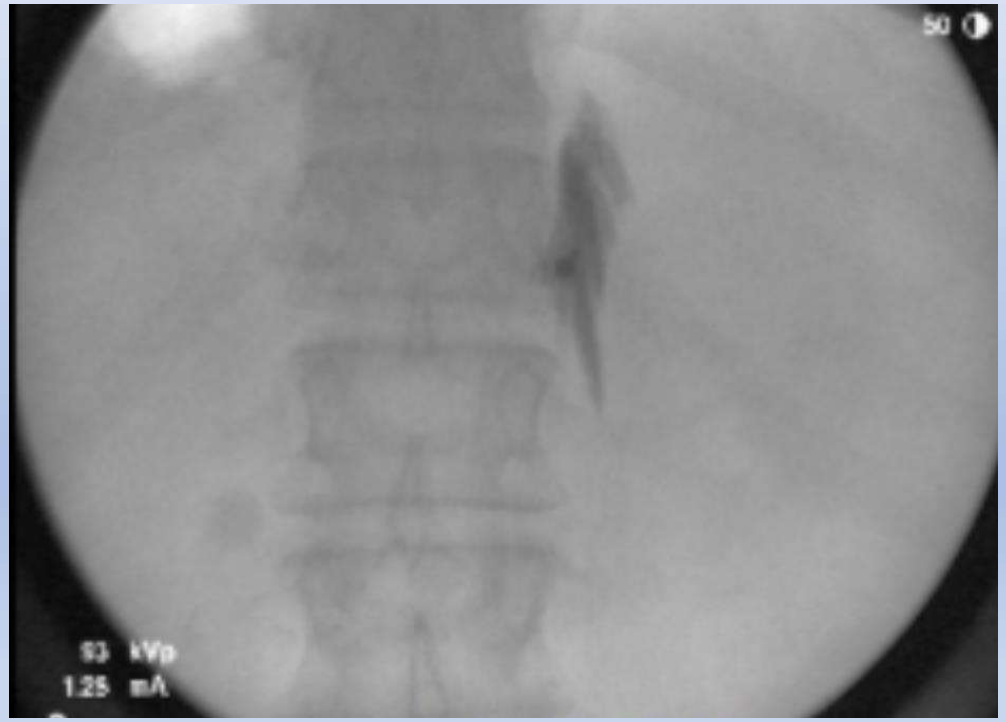
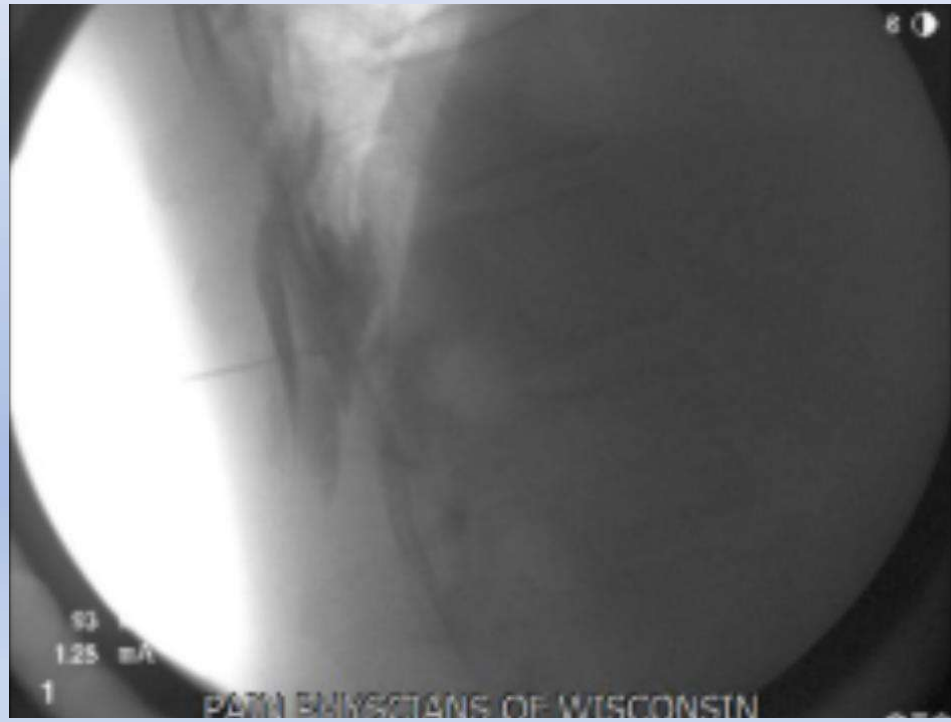
Erector Spinae Block





Spinal Cord Stimulation

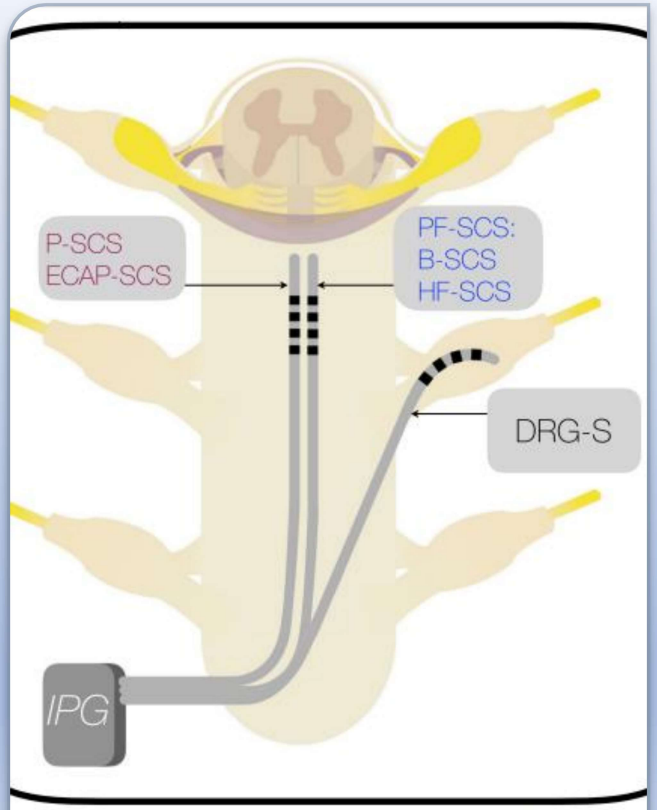
Paresthesia Based SCS (tonic)

Paresthesia-Free

Burst

High Frequency

Dorsal Root Ganglion



PF-SCS: Dorsal column stimulation with traditional P-SCS, B-SCS and HF-
in the targeted foramina overlying the dorsal root ganglion. In all cases
cronyms: IPG (Implantable Pulse Generator)

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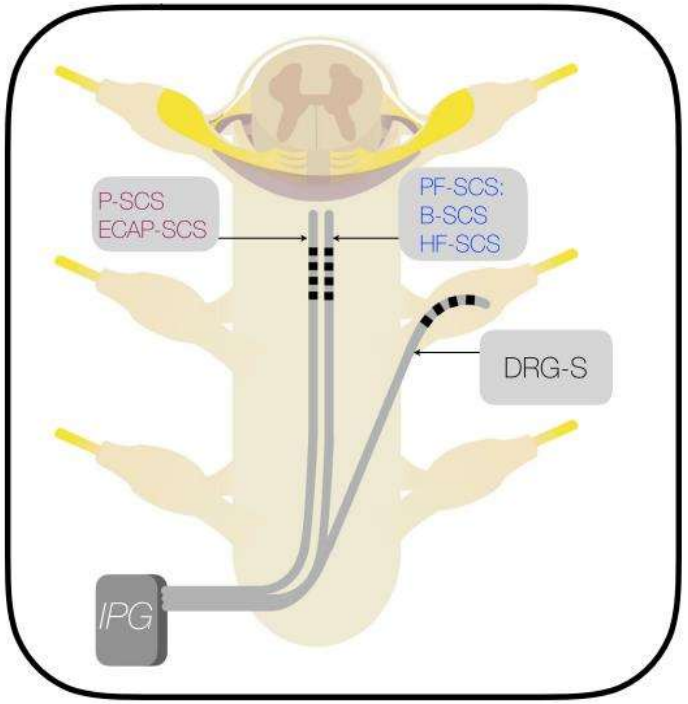
Caylor et al. Bioelectronic Medicine (2019) 5:12
https://doi.org/10.1186/s42234-019-0023-1

Neuromodulation: Spinal Cord Stimulation

- Classic Indications
  - Lumbar Radiculopathy
  - Postlaminectomy Syndrome
  - CRPS
  - Angina (Non US)
- New Indications
  - Painful Diabetic Neuropathy
  - Nonsurgical Back Pain
  - Peripheral Neuropathy
  - Mononeuropathy



ead Placement in P-SCS and PF-SCS: Dorsal column stimulation with traditional P-SCS, B-SCS and HF-SCS are anatomically placed
lumns. DRG-S is placed within the targeted foramina overlying the dorsal root ganglion. In all cases SCS can result in orthodrom
n or antidromic activation. Acronyms: IPG (Implantable Pulse Generator)

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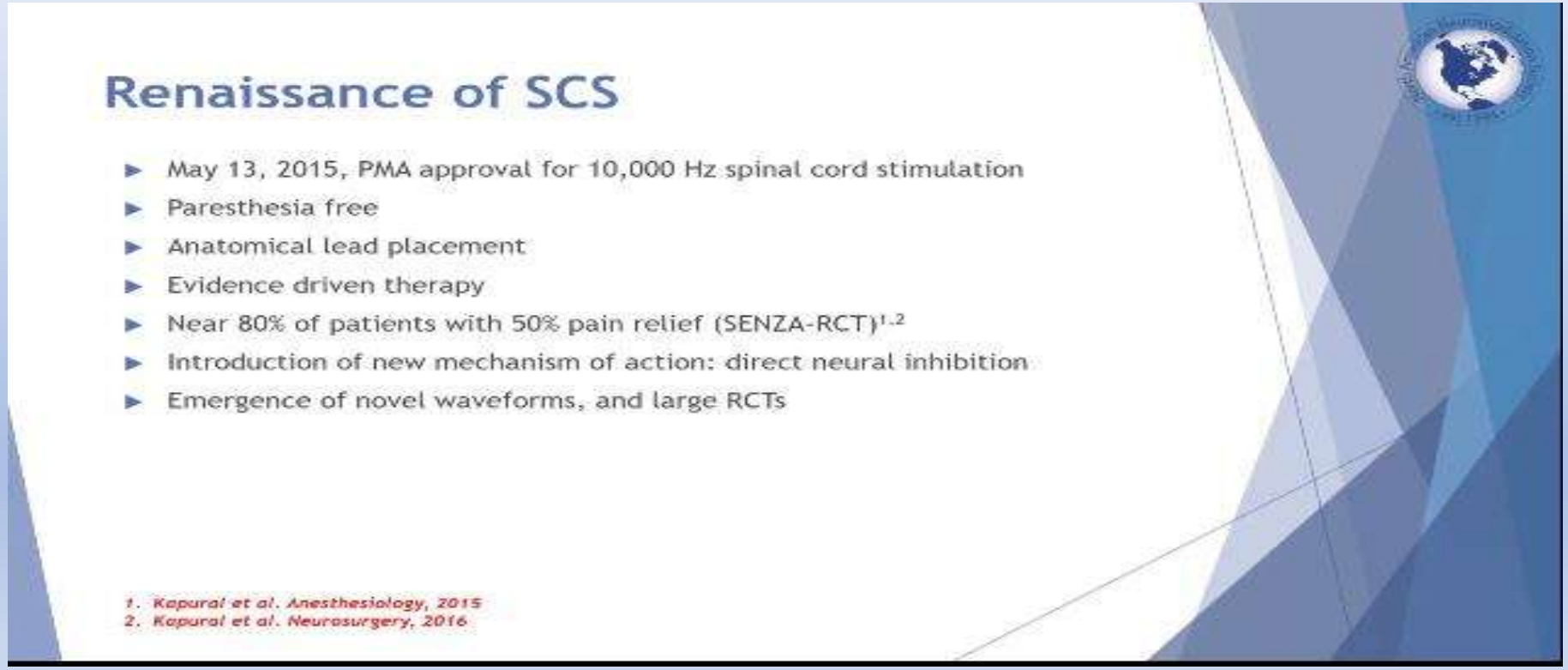
Spinal Cord Stimulation



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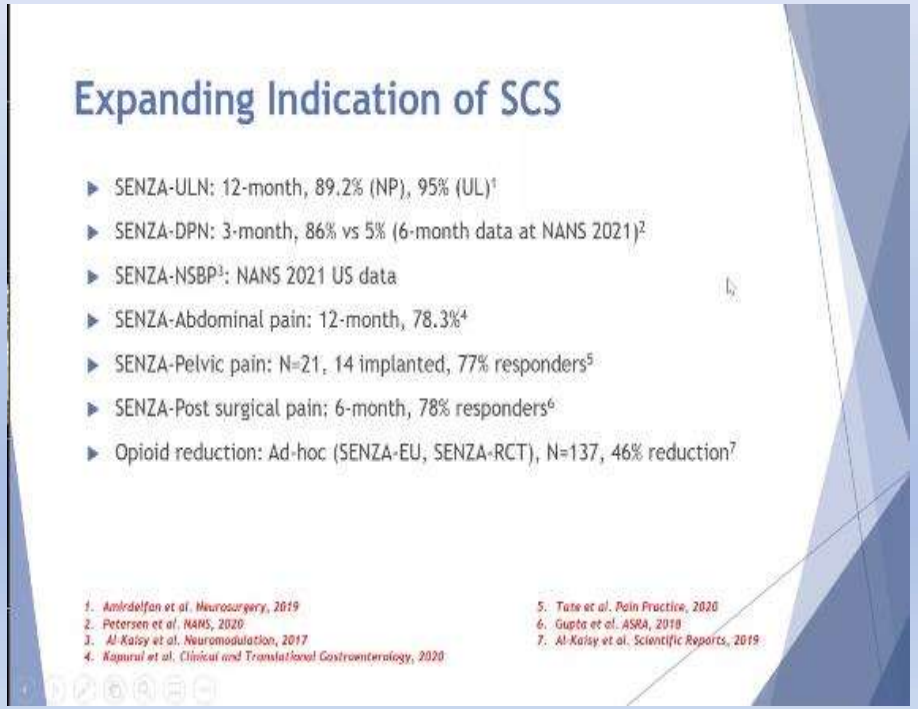
Spinal Cord Stimulation – High Frequency Stimulation



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Superior Alternative Treatments

NNT 1.3 !

ORIGINAL ARTICLE

High-Frequency 10-kHz Spinal Cord Stimulation Improves Health-Related Quality of Life in Patients With Refractory Painful Diabetic Neuropathy: 12-Month Results From a Randomized Controlled Trial

Erika A. Petersen, MD; Thomas G. Stauss, MD; James A. Scowcroft, MD; Elizabeth S. Brooks, PhD; Judith L. White, MD; Shawn M. Sills, MD; Kasra Amirdelfan, MD; Maged N. Guirguis, MD; Jijun Xu, MD, PhD; Cong Yu, MD; Ali Nairizi, MD; Denis G. Patterson, DO; Kostandinos C. Tsoulfas, MD; Michael J. Creamer, DO; Vincent Galan, MD; Richard M. Bundschu, MD; Neel D. Mehta, MD; Diawood Sayed, MD; Shivanand P. Lad, MD, PhD; David J. DiBenedetto, MD; Khalid A. Sethi, MD; Johnathan H. Gores, MD; Matthew T. Bennett, MD; Nathan J. Harrison, MD; Atef F. Israel, MD; Paul Chang, MD; Paul W. Wu, MD; Charles E. Argoff, MD; Christian E. Nasr, MD; Rod S. Taylor, PhD; David L. Caraway, MD, PhD; and Nagy A. Makhail, MD, PhD

Abstract

Objective: To evaluate high-frequency (10-kHz) spinal cord stimulation (SCS) treatment in refractory painful diabetic neuropathy.

Patients and Methods: A prospective, multicenter randomized controlled trial was conducted between Aug 28, 2017 and March 16, 2021, comparing conventional medical management (CMM) with 10-kHz SCS+CMM. The participants had hemoglobin A1c level of less than or equal to 10% and pain greater than or equal to 5 of 10 cm on visual analog scale, with painful diabetic neuropathy symptoms 12 months or more refractory to gabapentinoids and at least 1 other analgesic class. Assessments included measures of pain, neurologic function, and health-related quality of life (HRQoL) over 12 months with optional crossover at 6 months.

Results: The participants were randomized 1:1 to CMM (n=103) or 10-kHz SCS+CMM (n=113). At 6 months, 77 of 95 (81%) CMM group participants opted for crossover, whereas none of the 10-kHz SCS group participants did so. At 12 months, the mean pain relief from baseline among participants implanted with 10-kHz SCS was 74.3% (95% CI, 70.1-78.5), and 121 of 142 (85%) participants were treatment responders (≥50% pain relief). Treatment with 10-kHz SCS improved HRQoL, including a mean improvement in the EuroQol 5-dimensional questionnaire index score of 0.136 (95% CI, 0.104-0.169). The participants also reported significantly less pain interference with sleep, mood, and daily activities. At 12 months, 131 of 142 (92%) participants were "satisfied" or "very satisfied" with the 10-kHz SCS treatment.

Conclusion: The 10-kHz SCS treatment resulted in substantial pain relief and improvement in overall HRQoL 2.5- to 4.5-fold higher than the minimal clinically important difference. The outcomes were durable over 12 months and support 10-kHz SCS treatment in patients with refractory painful diabetic neuropathy.

Trial registration: clinicaltrials.gov Identifier: NCT03228420

12-Month[1]
Mayo Clinic Proceedings
July 2022

TABLE 3. Number Needed to Treat for PDN Treatments

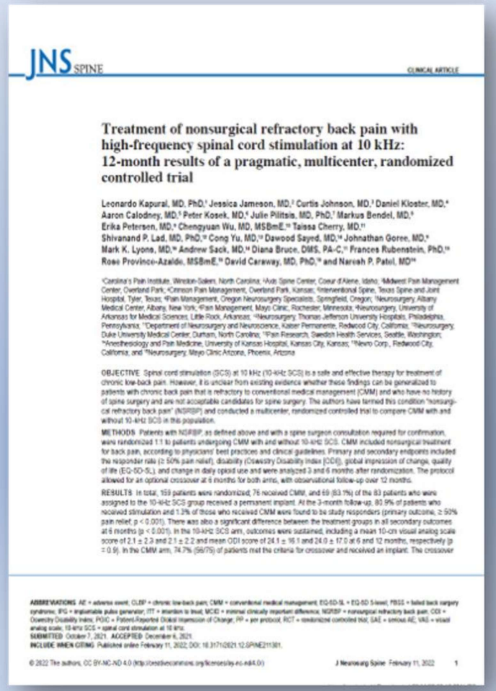
PDN treatment	Number needed to treat[b] (95% CI)
High-concentration (8%) capsaicin patches	10.6 (7.4-19)
Gabapentin, extended-release	8.3 (6.2-13.0)
Pregabalin	7.7 (6.5-9.4)
Serotonin-norepinephrine reuptake inhibitors	6.4 (5.2-8.4)
Gabapentin	6.3 (5.0-8.3)
Weak opioid agonists	4.7 (3.6-6.7)
Strong opioid agonists	4.3 (3.4-5.8)
Tricyclic antidepressants	3.6 (3.0-4.4)
10-kHz SCS[a]	1.3 (1.1-1.4)

[a]SCS, spinal cord stimulation.
[b]The number needed to treat represents the number of patients that need to be treated with an intervention to achieve 1 more responder with at least 50% pain relief compared with the control intervention. Finnerup et al[12] completed a systematic review and meta-analysis of randomized controlled trials for neuropathic pain medications vs placebo. The current study results were used to calculate the number needed to treat for 10-kHz SCS compared with continued conventional medical management.

1. Petersen, E. A., et al. (2022). High-Frequency 10-kHz Spinal Cord Stimulation Improves Health-Related Quality of Life in Patients With Refractory Painful Diabetic Neuropathy: 12-Month Results From a Randomized Controlled Trial. *Mayo Clinic proceedings. Innovations, quality & outcomes, 6*(4), 347–360. https://doi.org/10.1016/j.mayocpiqo.2022.05.003

PRO SPINE & PAIN

SCS: Nonsurgical Refractory Back Pain (Spine 2022)



JNS SPINE

CLINICAL ARTICLE

Treatment of nonsurgical refractory back pain with high-frequency spinal cord stimulation at 10 kHz: 12-month results of a pragmatic, multicenter, randomized controlled trial

- Pain that is refractory to conventional medical management (CMM)
- Patient has not had previous spine surgery
- **Surgical evaluation** indicates the patient is not an acceptable candidate for surgery

The study demonstrated that the addition of 10 kHz SCS to CMM results in profound improvements in pain relief, function, and quality of life, with concurrent reduction in opioid use

PRO SPINE & PAIN

SCS -Closed Loop Stimulation

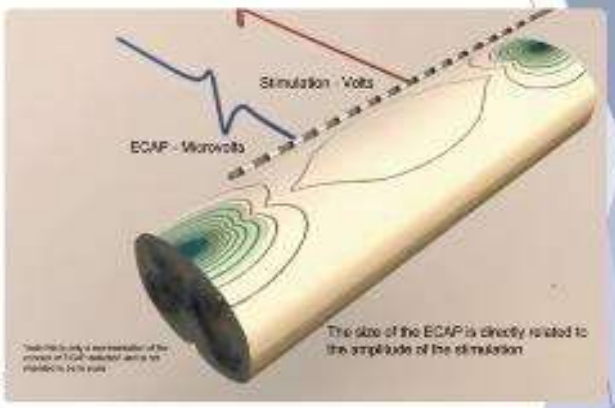
- Utilization of evoked compound action potentials (ECAP) to provide real time data indicating response to stimulation

PRO SPINE & PAIN

SCS – Closed Loop Stimulation

ECAPS are a Measure of DC Response and Reflect the Magnitude of Aβ Fiber Activation

- When the dorsal column is stimulated, ECAPS are evoked from Aβ fiber collaterals and they propagate bi-directionally.
- The ECAP is recorded on the same lead and on non-stimulating electrodes and measured in microvolts.
- The measurements can be taken in real-time millions of times per day.

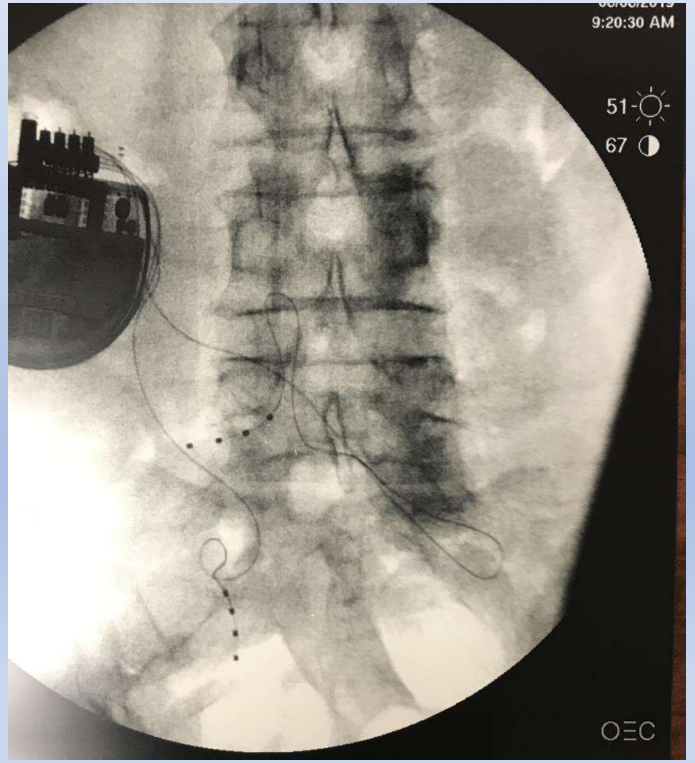


Parker et al., Compound action potentials recorded in the human spinal cord during neurostimulation for pain relief. *PAIN*, 153 (2012), 593-601.

PRO SPINE & PAIN

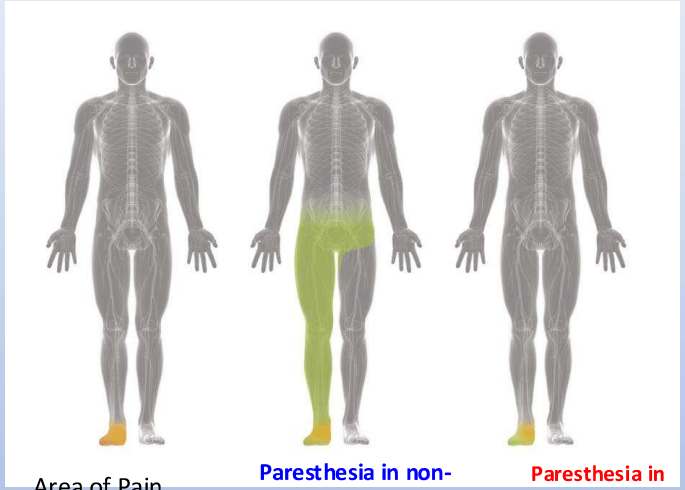
Dorsal Root Ganglion Stimulation (DRG)

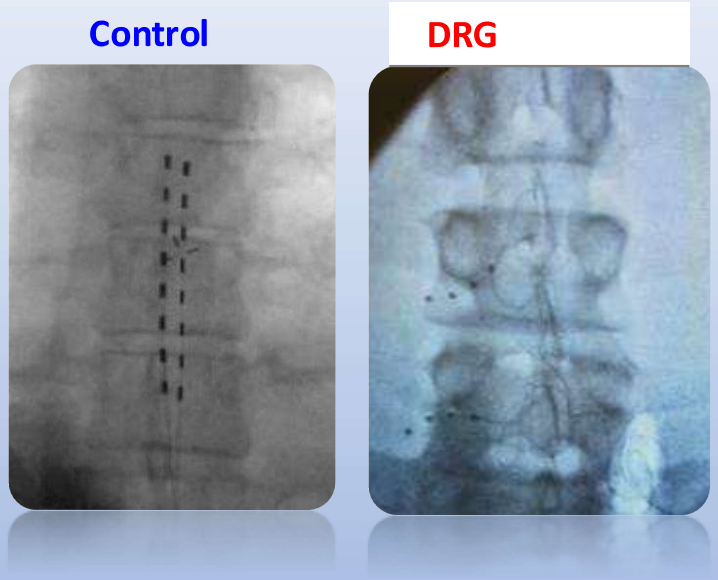
- Placement of leads over dorsal root allows modulation of specific sensory neurons
- Allows stimulation exclusively to specific dermatomes/pathologies



PRO SPINE & PAIN

Accurate study: Therapy Specificity at 12 months



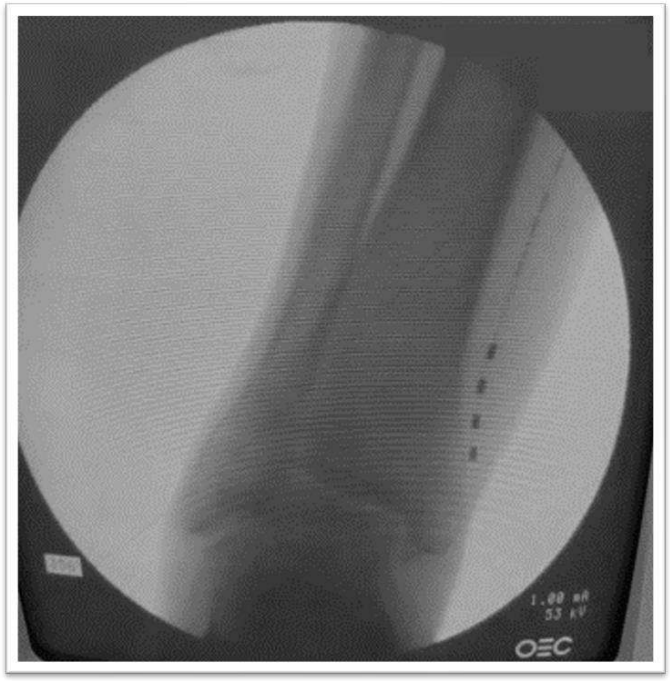


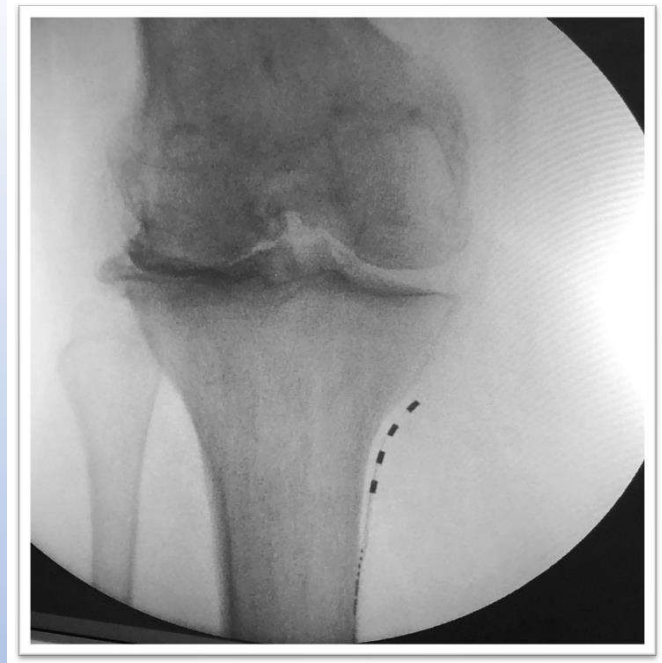
Control	DRG
61.2%	**94.5%**

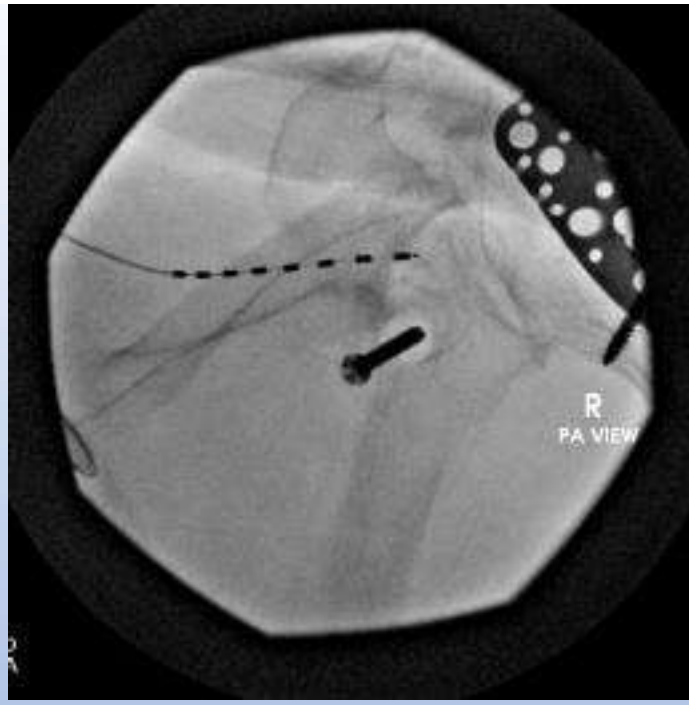
Subjects in the DRG group experienced greater stimulation specificity than subjects in the control group.

Levy R and Deer T. NANS 2015

PRO SPINE & PAIN







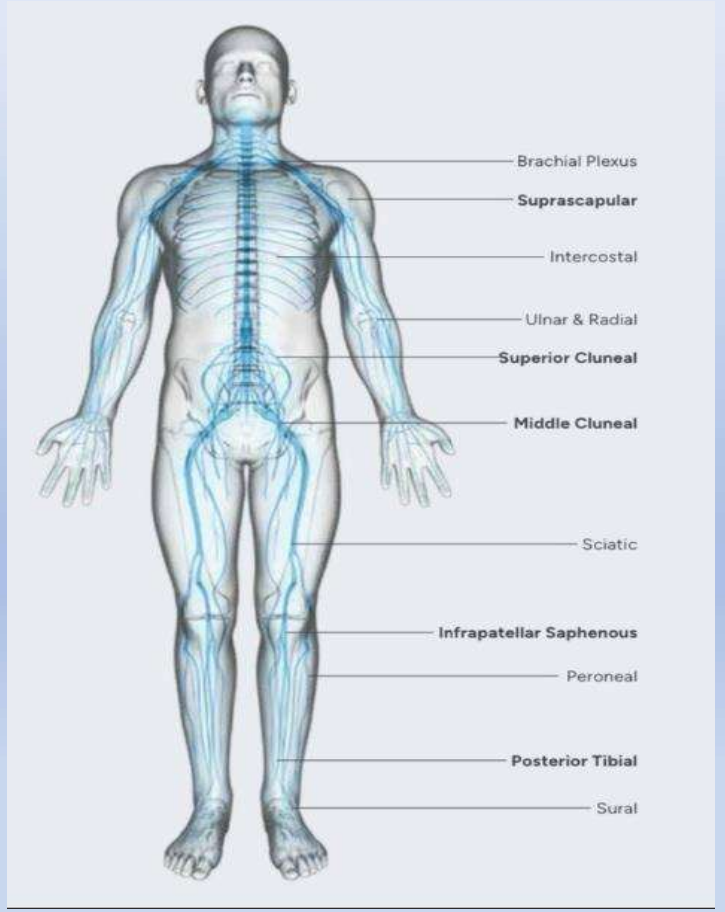
Neuromodulation: Peripheral Nerve Stimulation

- Lower stimulation modes
- Less invasive than spinal cord stimulation

PRO SPINE & PAIN

Peripheral Nerve Stimulation

- Advances in technology and technique allow reliable placement of stimulation leads aimed at treating peripheral neuropathy
- Can also treat nociceptive pain with stimulation of specific innervation



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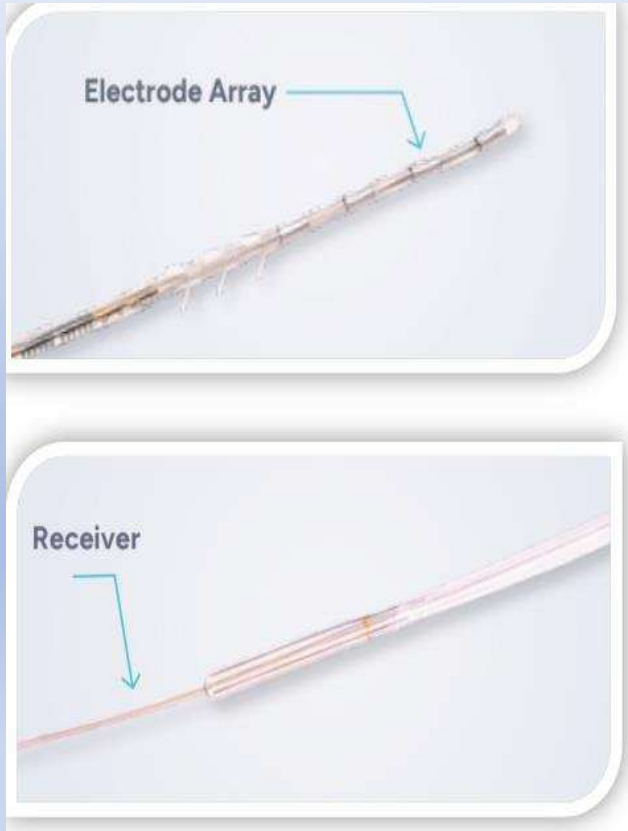
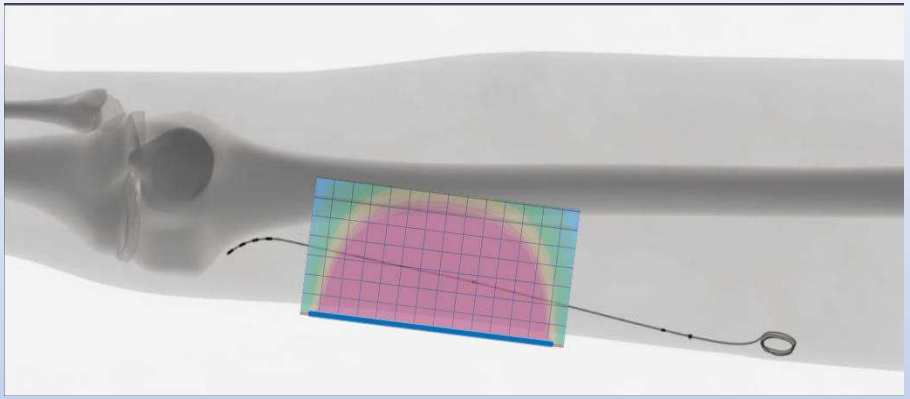
Neuromodulation: Peripheral Nerve Stimulation

- Externalized power source vs implanted battery
- Wearable technology

PRO SPINE & PAIN

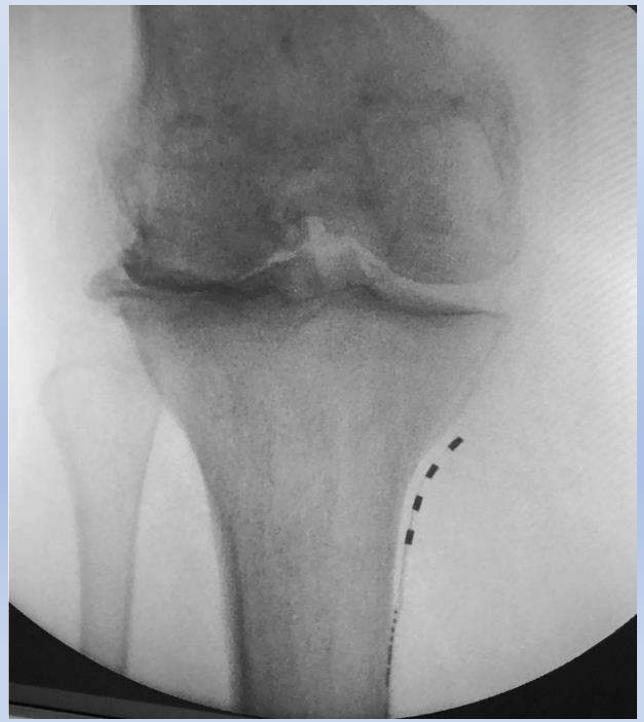
PNS

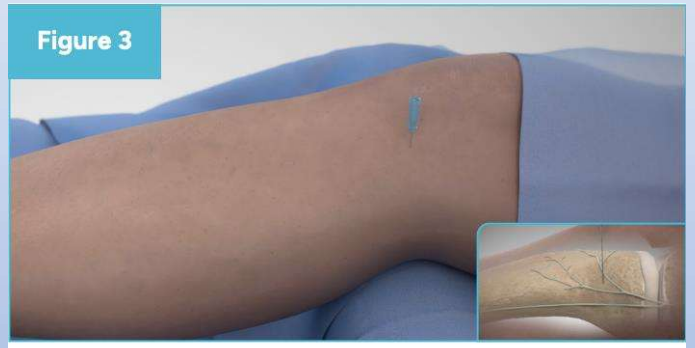


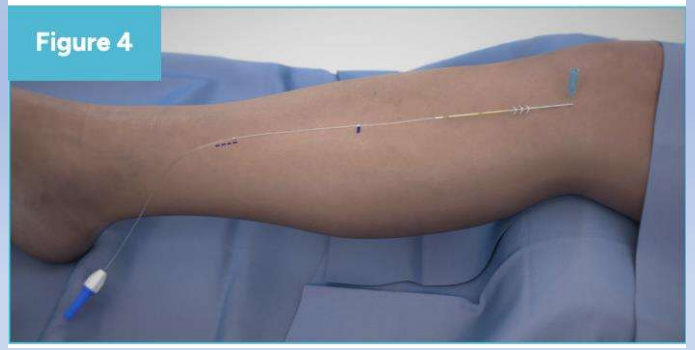


PRO SPINE & PAIN

Neuromodulation: Peripheral Nerve Stimulation

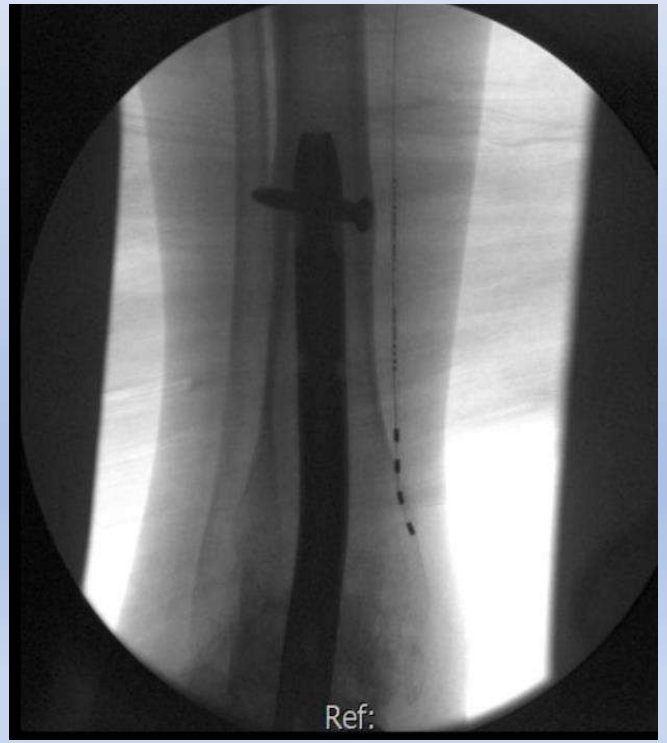






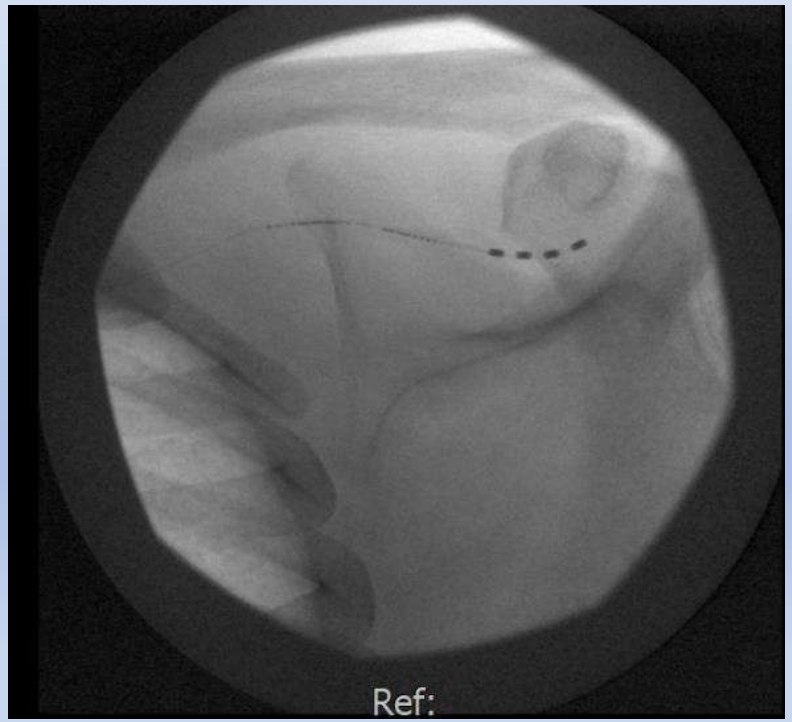
PRO SPINE & PAIN

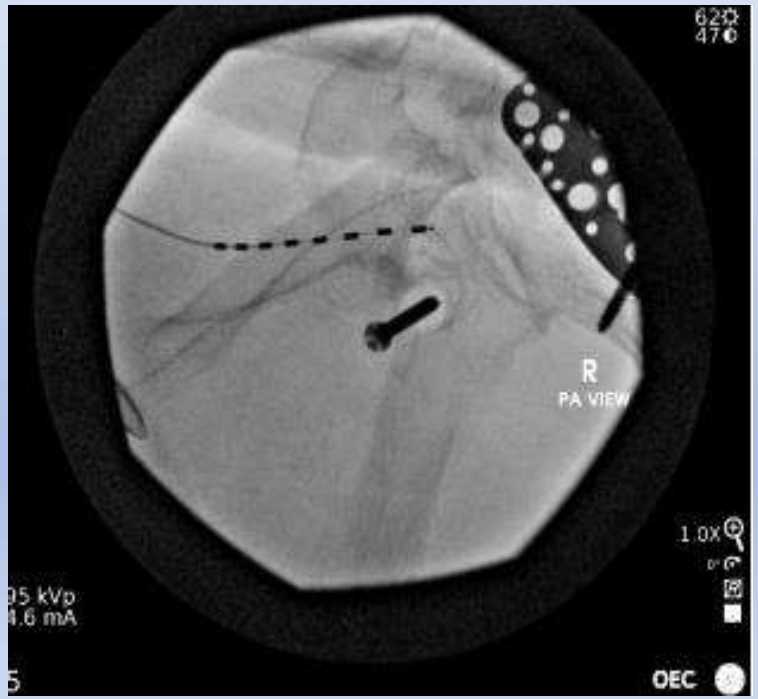
PNS – Lower Extremity



PRO SPINE & PAIN

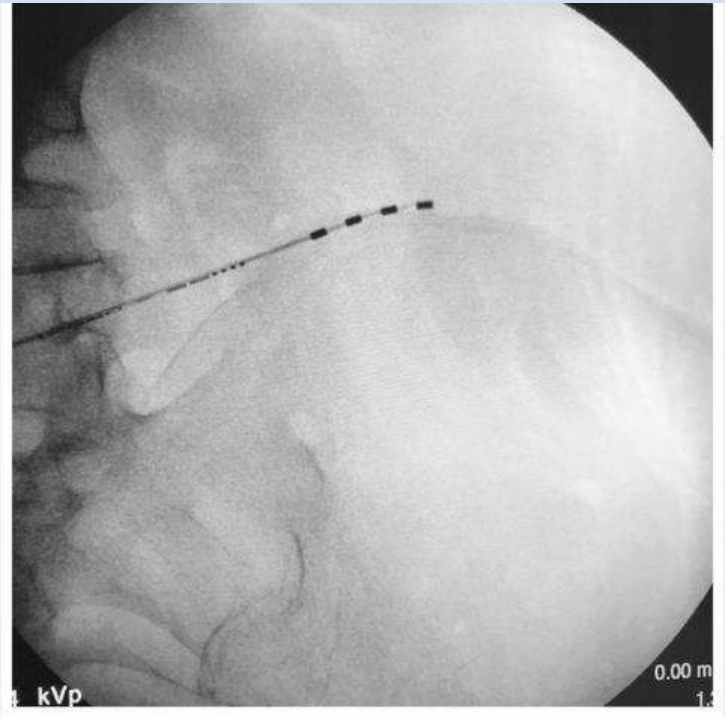
PNS – Upper Extremity





PRO SPINE & PAIN

PNS – Lumbar



- Peripheral Nerve Stimulation of the Cluneal Nerve
- Axial/lateral back pain; suprailiac pain

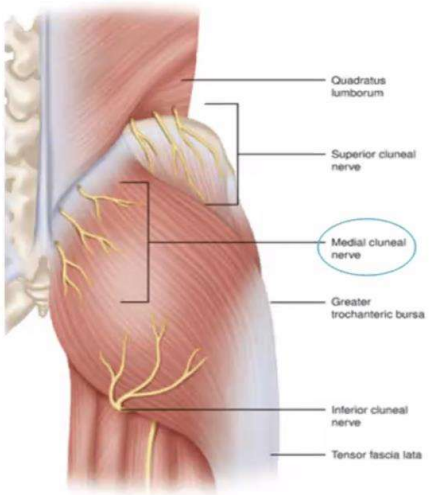
PRO SPINE & PAIN

PNS – Cluneal Nerve Stimulation

Middle Cluneal Nerves

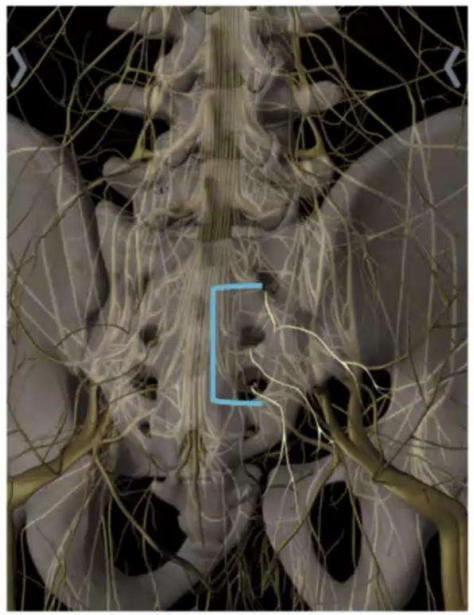
Anatomy

- A branch of the posterior ramus of the sacral nerve roots, arising from the dorsal rami of the S1 to S4 at the corresponding foramina
- The MCN is sensory



Patient Identification

- Persistent SI Joint Pain
- SI Joint Fusion
- SI Joint Stabilization
- Lumbar Fusions



PRO SPINE & PAIN

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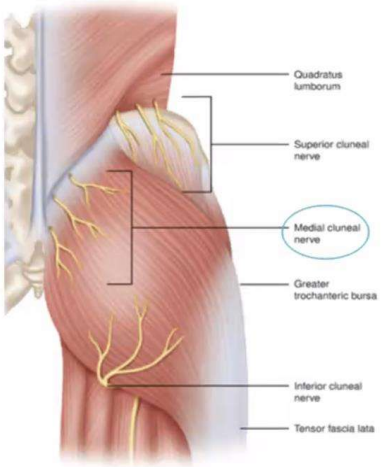

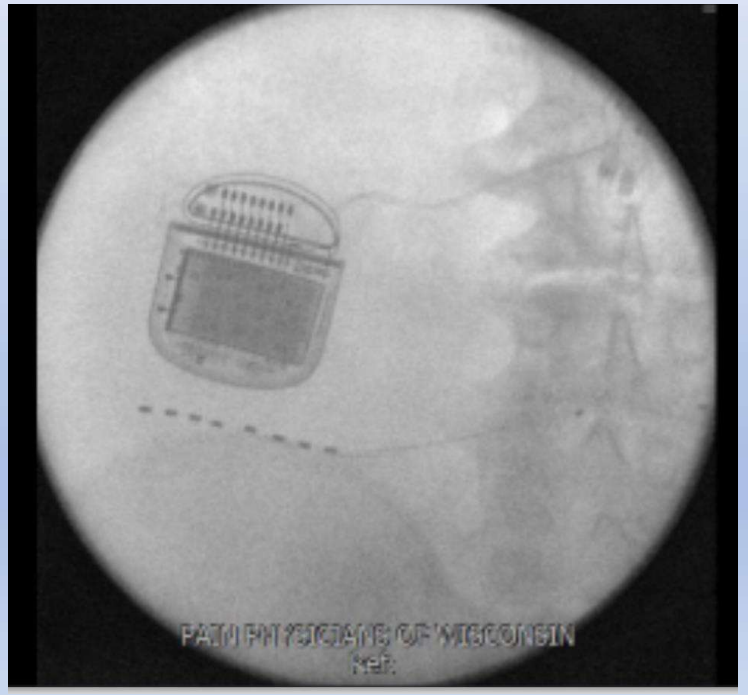

PRO SPINE & PAIN

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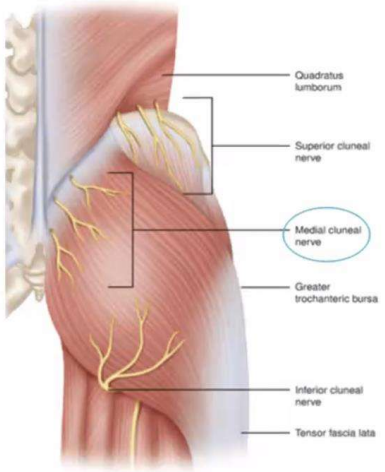
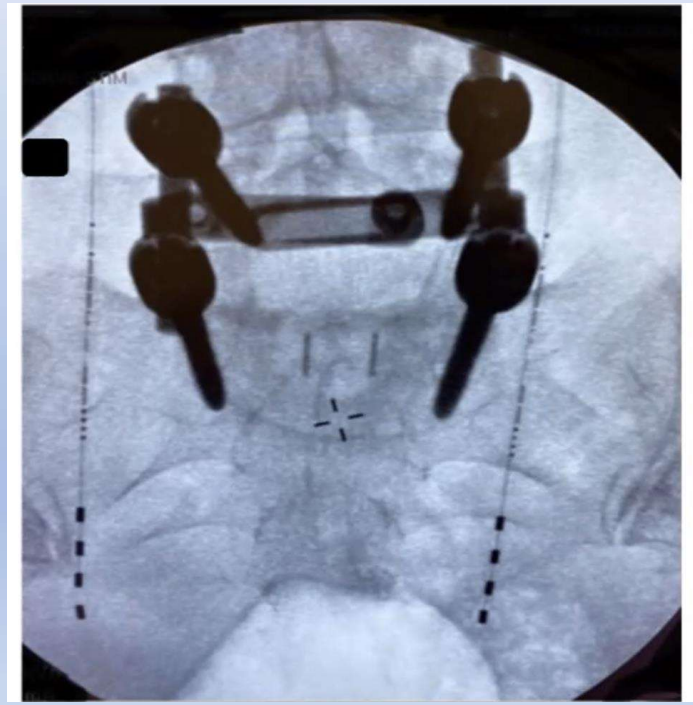
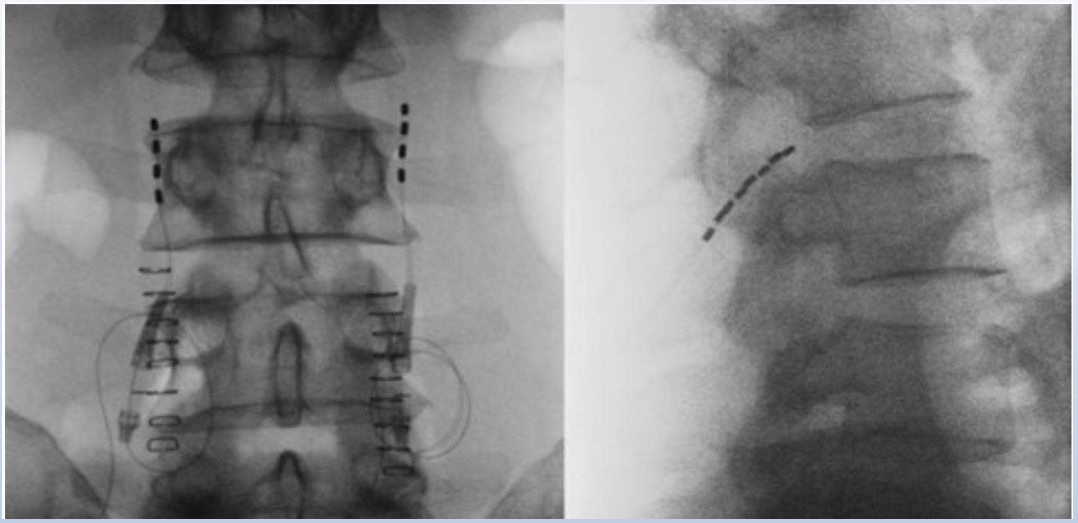


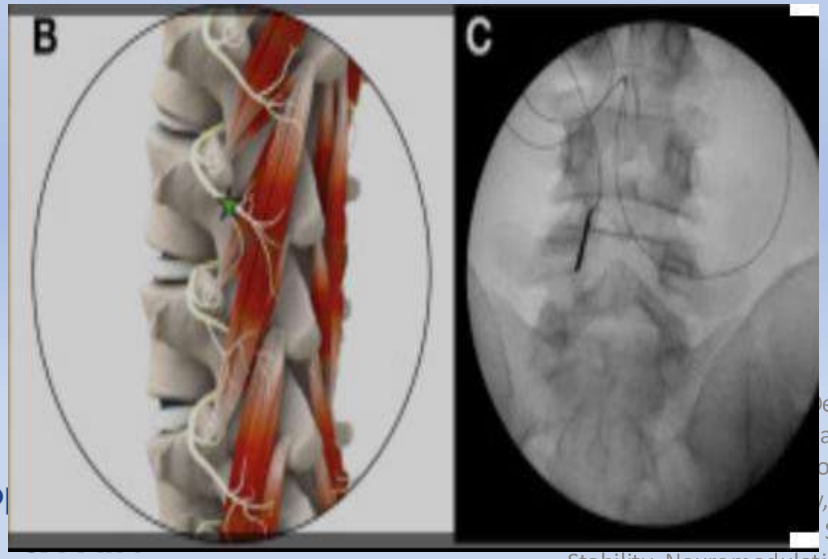


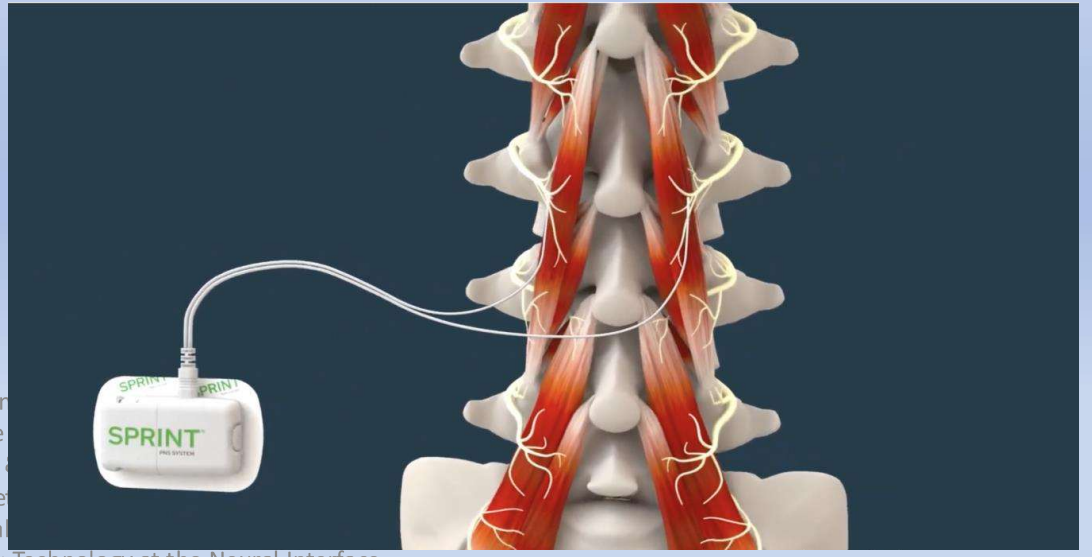
PRO SPINE & PAIN

Regenerative Stimulation

Temporary (30-60 day) stimulation of the multifidus muscle via simulation of medial branches (L2, L3) to treat chronic lower back pain

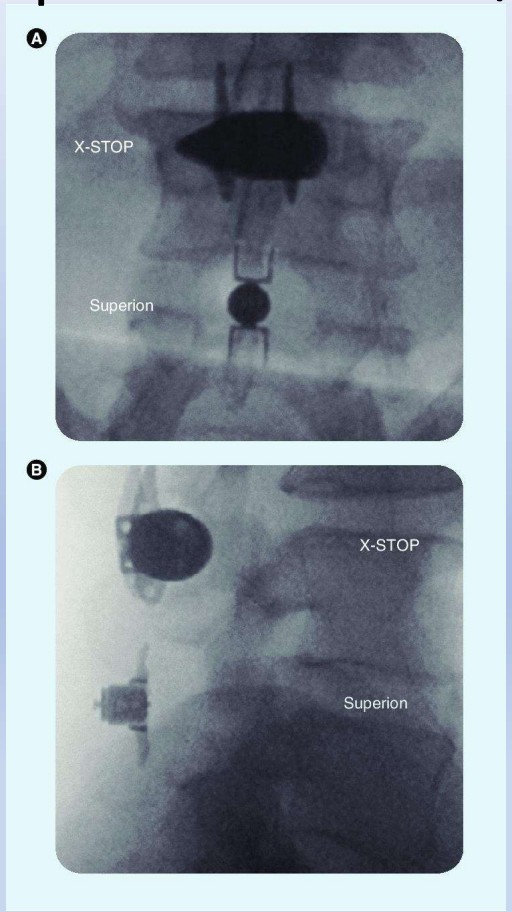


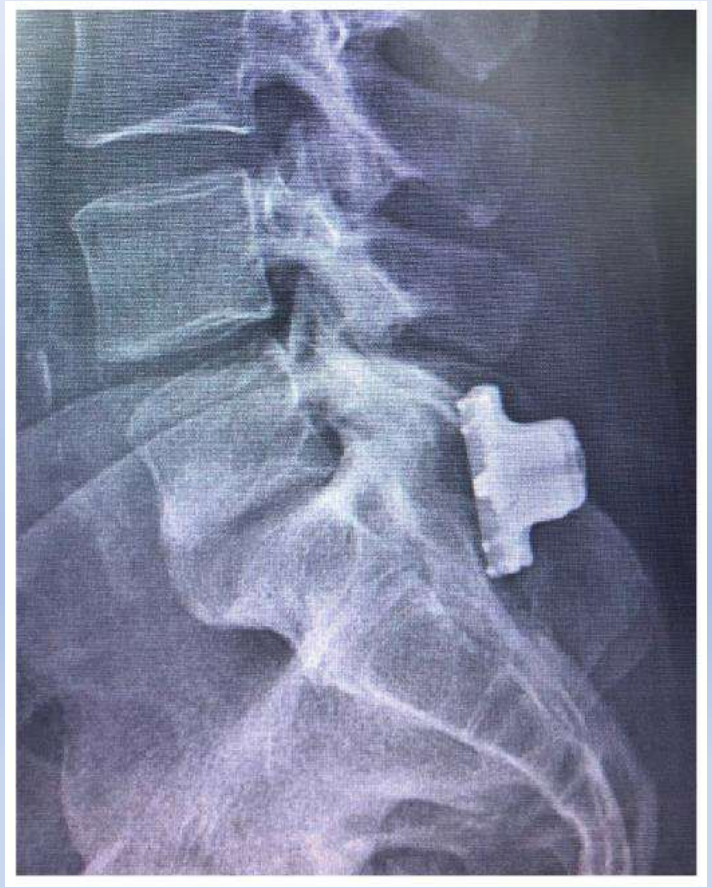




Stability. Neuromodulation: Technology at the Neural Interface. 18. 10.1111/ner.12275.

Interspinal Fusion/Stabilization Devices

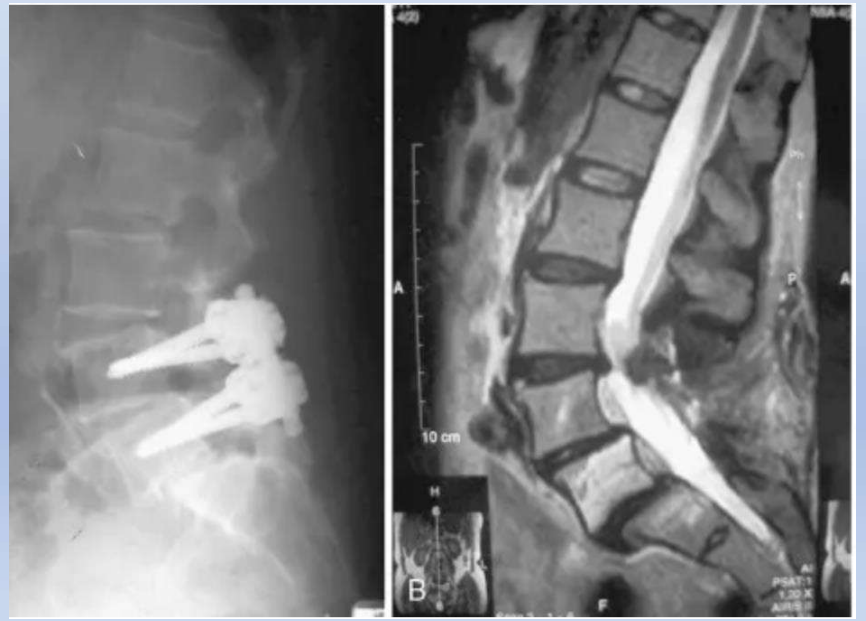




PRO SPINE & PAIN

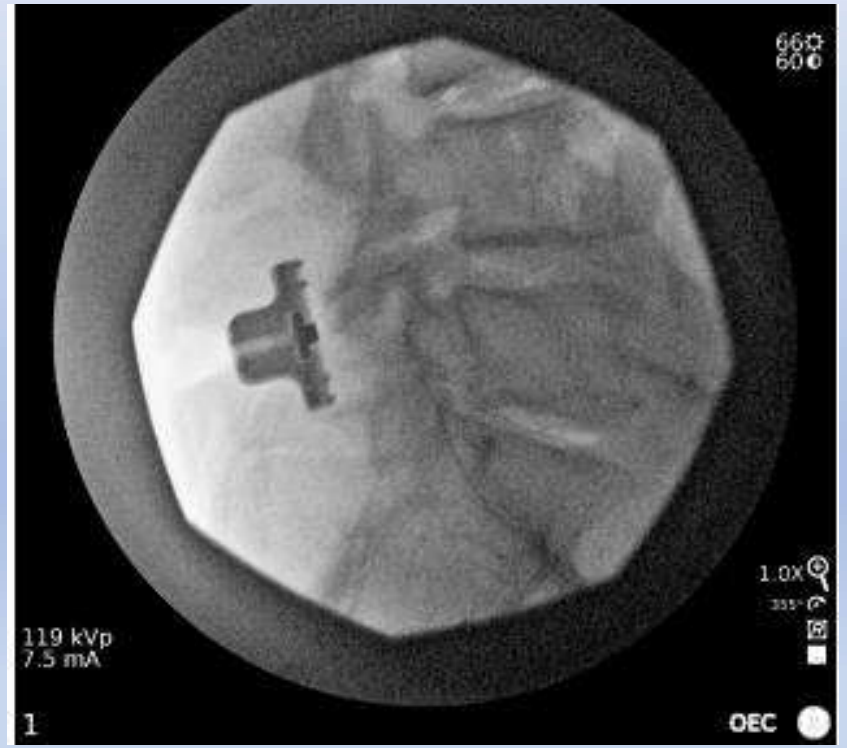
Adjacent Segment Disease

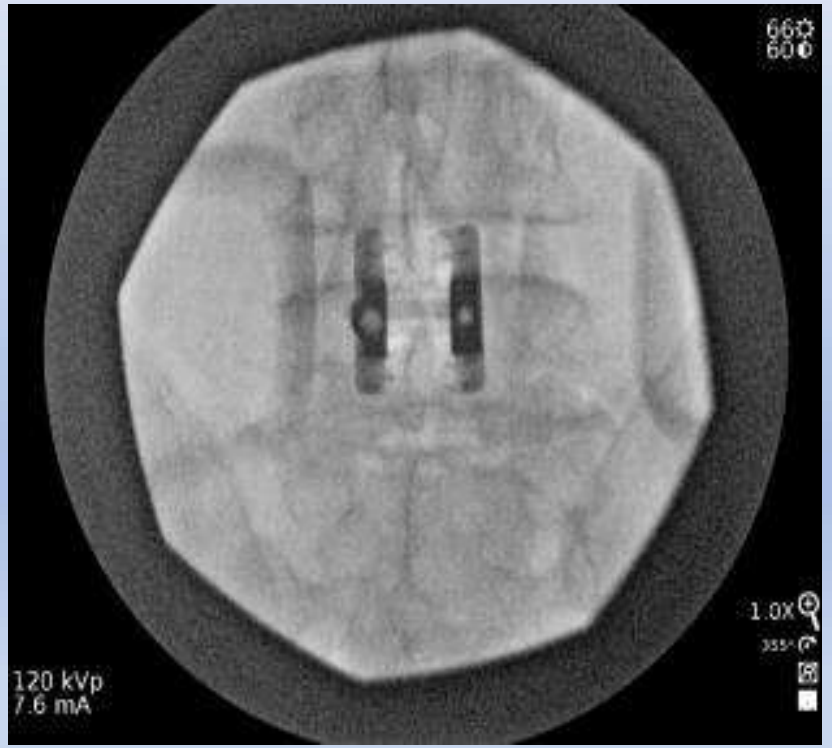
- Development of degenerative changes, disc herniation or spinal stenosis at the next mobile segment after a spinal fusion procedure



PRO SPINE & PAIN

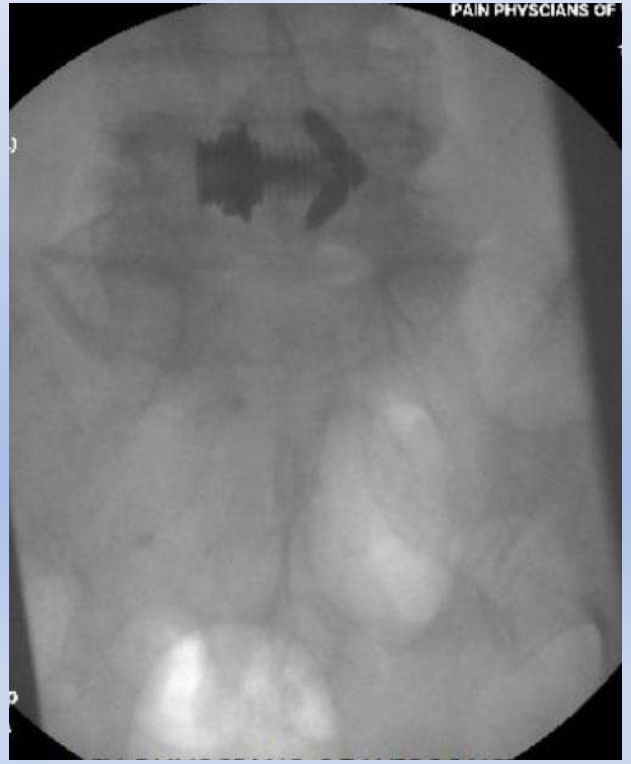
Interspinal Fusion/Stabilization Devices





PRO SPINE
& PAIN

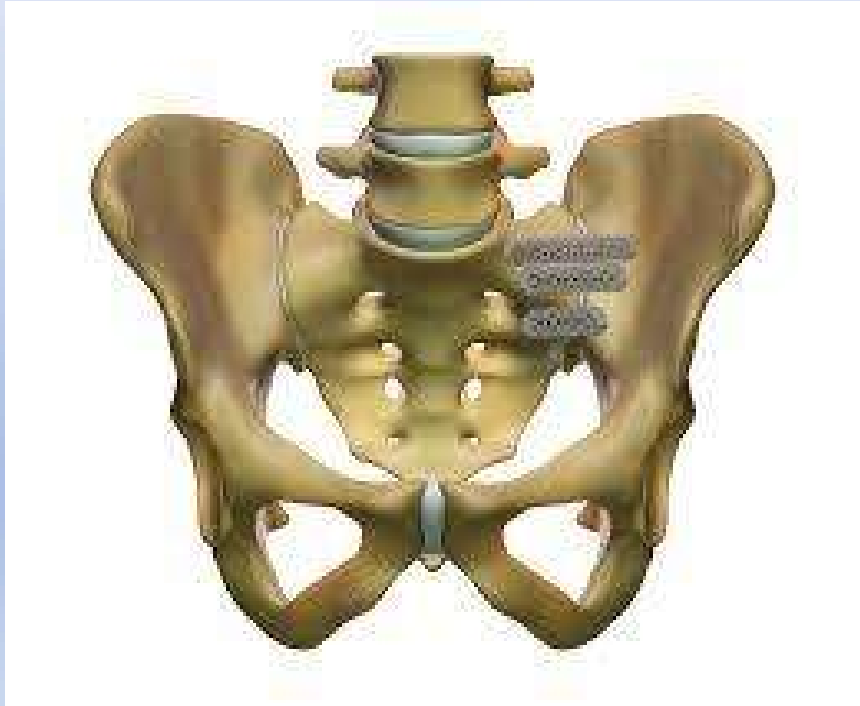
Interspinal Fusion/Stabilization Devices



- Lateral fixation device
- Avoids midline incision/extensive dissection

PRO SPINE & PAIN

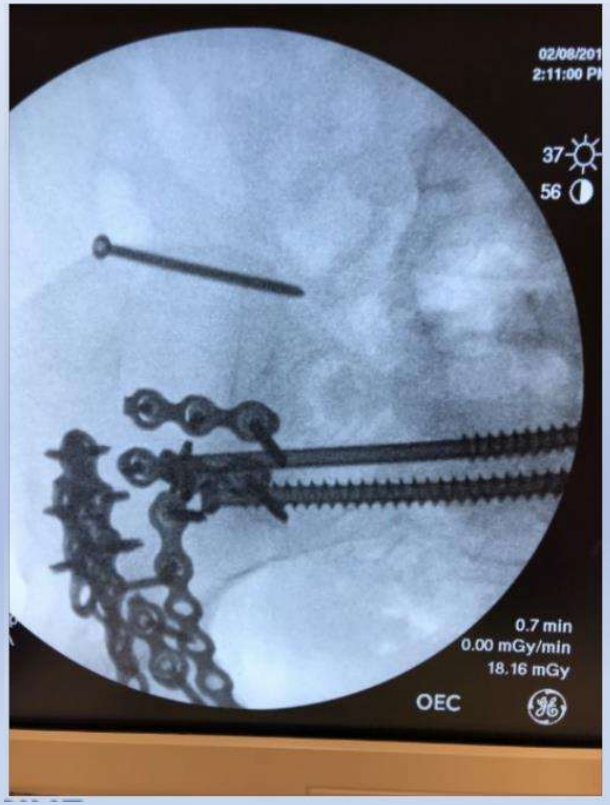
Sacroiliac Joint Fusion

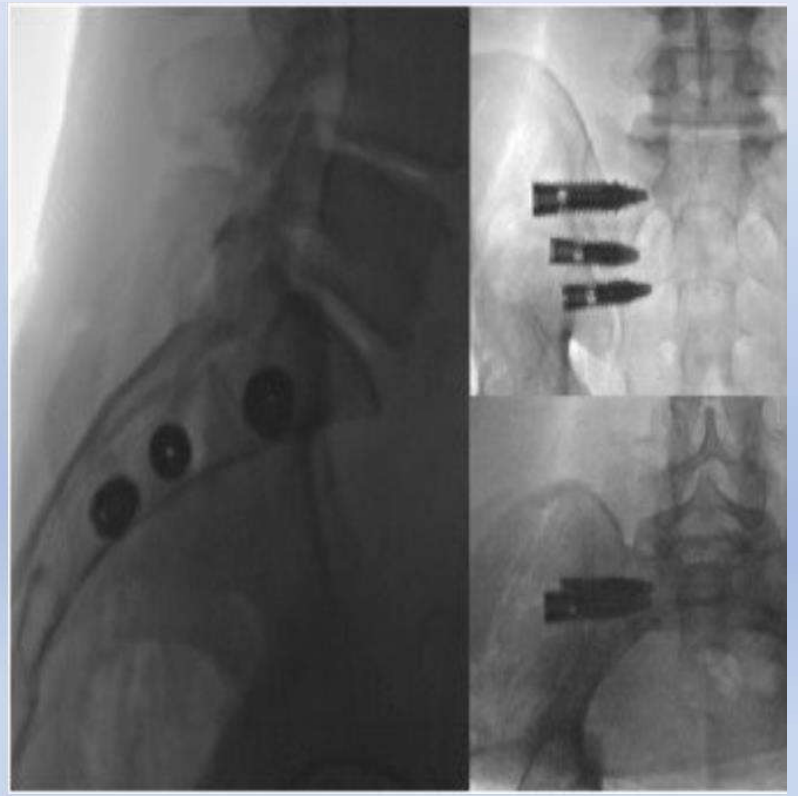


- 75% of lumbar fusions develop significant SI joint degeneration
- Multiple devices/approaches
- Stabilization of the Joint
- RFA SI joint has not been covered by Medicare (variation in innervation, no consensus technique)

PRO SPINE & PAIN

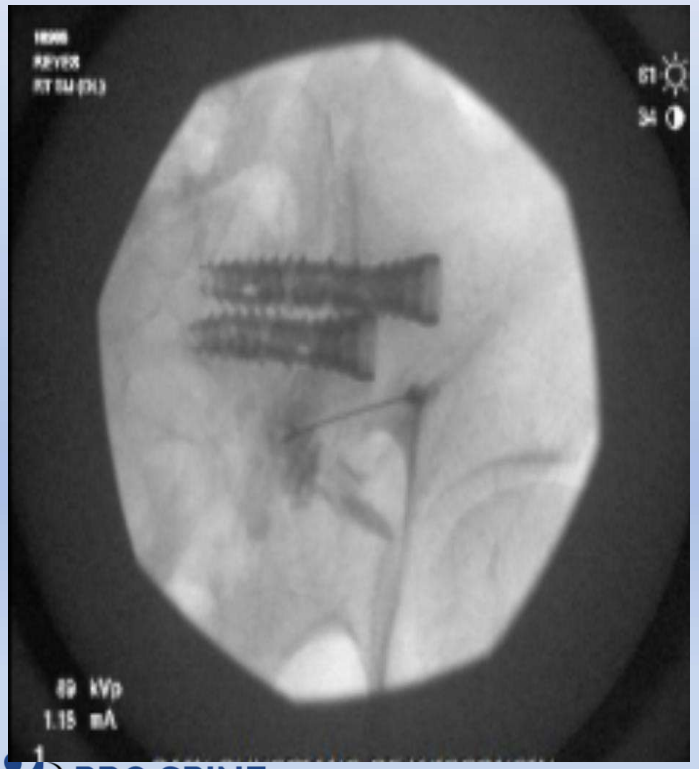
Sacroiliac Joint Fusion

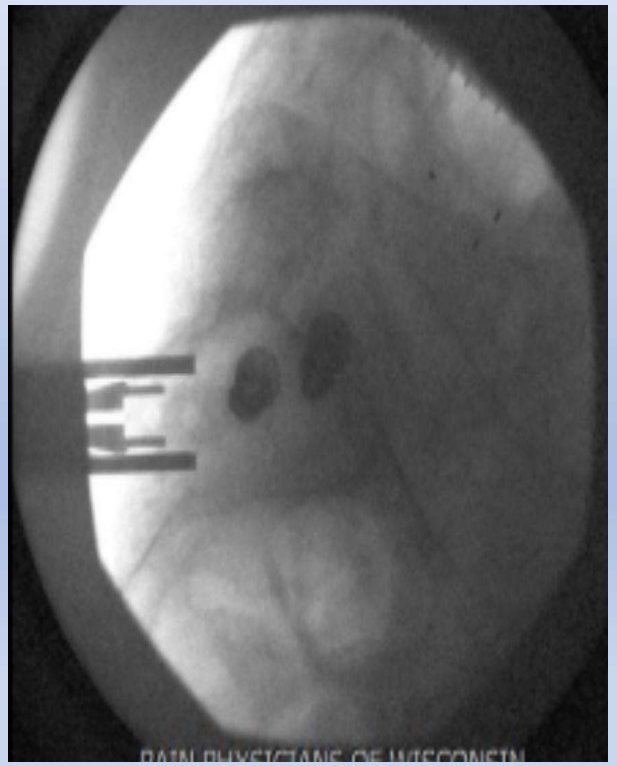


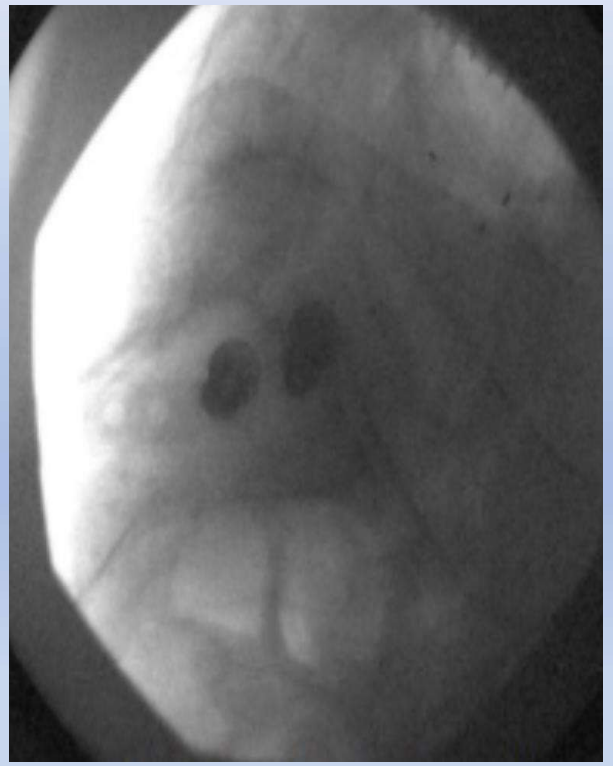


PRO SPINE & PAIN

Sacroiliac Joint Fusion - Salvage

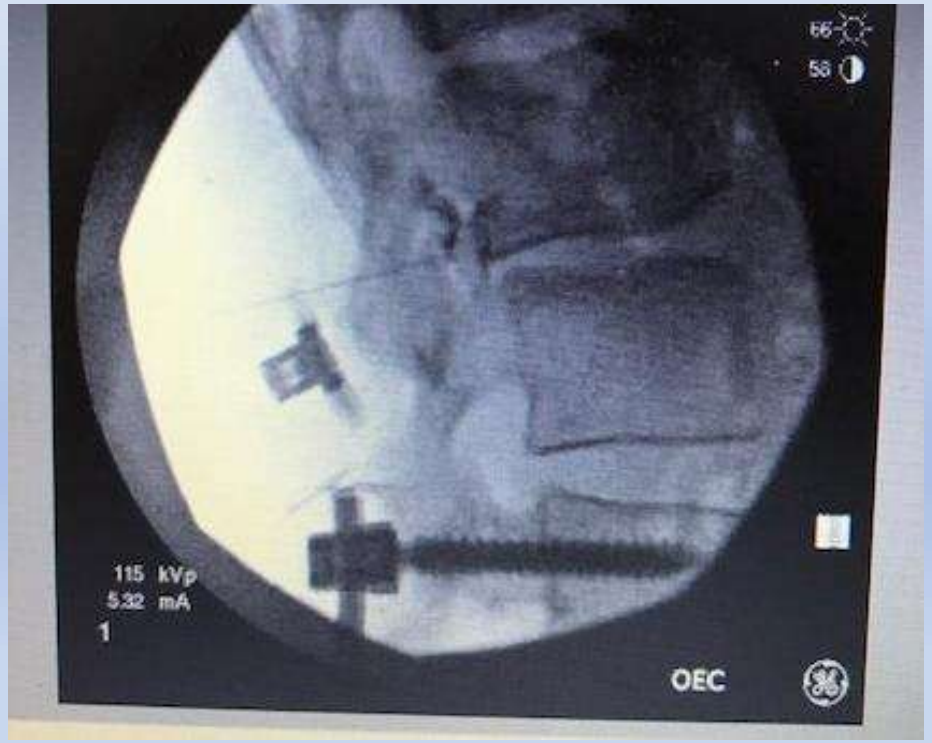






PRO SPINE & PAIN

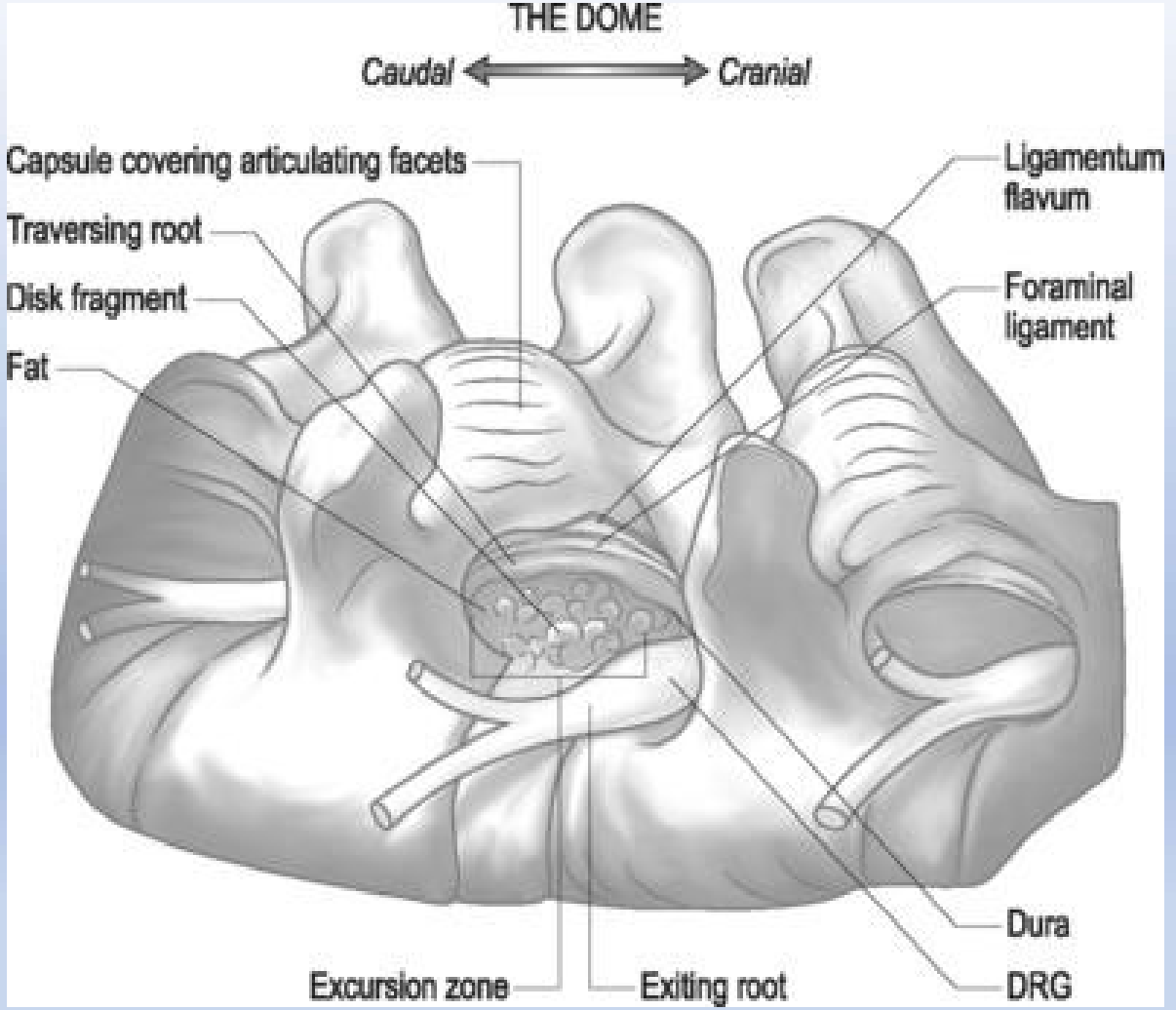
Complimentary Techniques



- Treatment of Adjacent Segment Disease
  - Interspinous spacer placement
  - Transforaminal epidural steroid injection

PRO SPINE & PAIN

Anticoagulation Considerations



PRO SPINE & PAIN

Procedures	Medications to Hold
Low Risk Procedures: Thoracic MBB, Lumbar MBB, SI Joint Injection, TPI, Peripheral NB, Joint Injection, Thoracic RFA, Lumbar RFA, Intercostal NB, Peripheral NB, Lateral Femoral NB, Pudendal NB, Genitofemoral NB, Ilioinguinal NB, Suprascapular NB	Lovenox (Therapeutic and Prophylactic), Heparin (IV and Sub Q), Fibrinolytic Agents, Fragmin, ReoPro, Integrilin, Aggrastat *6 Hour hold Sub Q Heparin*
Medium Risk Procedures: Cervical MBB, Cervical RFA, Lumbar ESI, Genicular NB, Genicular RFA, Caudal ESI, Sympathetic NB, Trigeminal NB, Ganglion Impar NB, Stellate Ganglion NB, Hip Block (femoral/Oburator), Hip RFA	Coumadin, Plavix, Xarelto, Eliquis, Effient, Aggrastat, Brilinta, Lovenox (Therapeutic and Prophylactic), Heparin (IV and Sub Q), Fibrinolytic Agents, Acenocourmarol, Edoxaban, Aggrastat, Fragmin, Kengreal, Pradoxa, Arixtra, ReoPro, Integrilin *6 Hour hold Sub Q Heparin*
High Risk Procedures AND Surgeries: Cervical ESI, Thoracic ESI, Celiac Plexus NB, Hypogastric NB, SCS Trial, SCS Perm/Revision/Explant, Pump Trial, Pump Perm/Revision/Explant, Vertebral Augmentation, SI Joint Fusion, Spinal Spacer, Lumbar Discogram, Via Disc	Aspirin, Ketorolac, Ibuprofen, Diclofenac, Etodolac, Indomethacin, Meloxicam, Naproxen, Nabumetone, Oxapozin, Piroxicam, Pletal, Aggrenox, Coumadin, Plavix, Effient, Xarelto, Eliquis, Lovenox (Therapeutic and Prophylactic) Aggrastat, Brilinta, Pradaxa, Vitamin E and Fish oil, Acenocoumarol, Heparin (IV and Sub Q), Fibrinolytic Agents, Arixtra, Fragmin, Kengreal, Edoxaban, ReoPro, Integrilin *24 Hour hold Sub Q Heparin*

Blood Thinning Medication Hold Length	
Aspirin	6 Days
Ibuprofen (Advil/Motrin) NSAID	1 Day
Ketorolac (Toradol) NSAID	1 Day
Diclofenac (Voltaren) NSAID	1 Day
Etodolac (Lodine) NSAID	2 Days
Indomethacin (Indocin) NSAID	2 Days
Meloxicam (Mobic) NSAID	4 Days
Naproxen (Aleve) NSAID	4 Days
Celebrex (celecoxib) NSAID	4 Days
Nabumetone (Relafen) NSAID	6 Days
Oxapozin (Daypro) NSAID	10 Days
Piroxicam (Feldene) NSAID	10 Days
Pletal (Cilostazol)	2 Days
Aggrenox (Dipyridamole)	2 Days
Coumadin (Warfarin)	5 Days
Plavix (Clopidogrel)	7 Days
Effient (Prasugrel)	7-10 Days
Xarelto (Rivaroxaban)	3 Days
Eliquis (Apixaban)	3 Days
Aggrastat (Tirofiban)	8-24 Hours
Brilinta (Ticagrelor)	5 Days
Pradaxa (Dabigatran)	4 Days
Acenocoumarol	3 Days
IV Heparin	6 Hours
Sub Q Heparin	6 Hours * Certain procedures to hold for 24 Hours*
Fibrinolytic Agents	48 Hours
Arixtra (Fondaparinux)	4 Days
Lovenox (Enoxaparin)- Therapeutic	24 Hours
Lovenox (Enoxaparin)- Prophylactic	12 Hours
Fragmin (Dalteparin)	24 Hours
Kengreal (Cangrelor)	3 Hours
Edoxaban	3 Days
ReoPro (Abciximab)	2-5 Days
Integrilin (Eptifibatide)	8-24 Hours
Vitamin E/Fish Oil	7 Days

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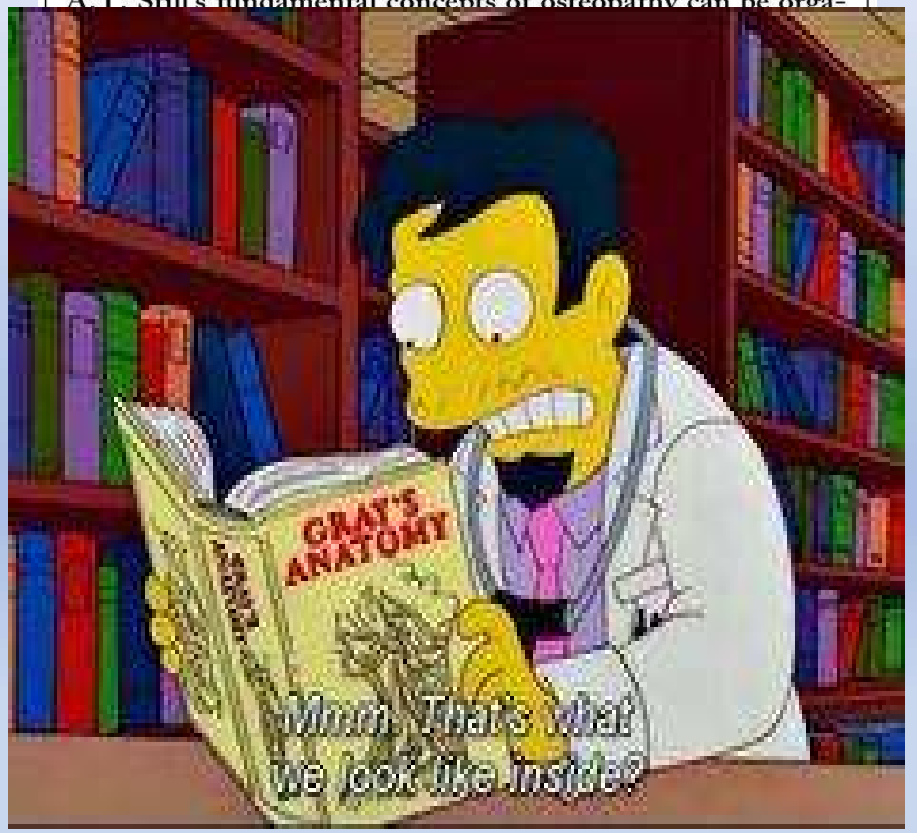
“Think Back to Medical School…”

1. The body is a unit; the person is a unit of body, mind, and spirit.
2. The body is capable of self-regulation, self-healing, and health maintenance.
3. Structure and function are reciprocally interrelated.
4. Rational treatment is based upon an understanding of the basic principles of body unity, self-regulation, and the interrelationship of structure and function.

Classical Osteopathic Philosophy

A.T. Still's fundamental concepts of osteopathy can be orga-



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Madison Clinic
34 Schroeder Court, Madison, WI 53711

Franklin Clinic
4202 W. Oakwood Park Court, Franklin, WI 53132

Kenosha Clinic
10105 74th Street, Suite 101, Kenosha, WI 53142

Layton Clinic
2500 W. Layton Ave, Ste 200, Milwaukee, WI 53221

Waukesha Clinic
1200 Delafield Street, Waukesha, WI 53188

Thank
You!

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