What is New in Pain Management in Anesthesia?

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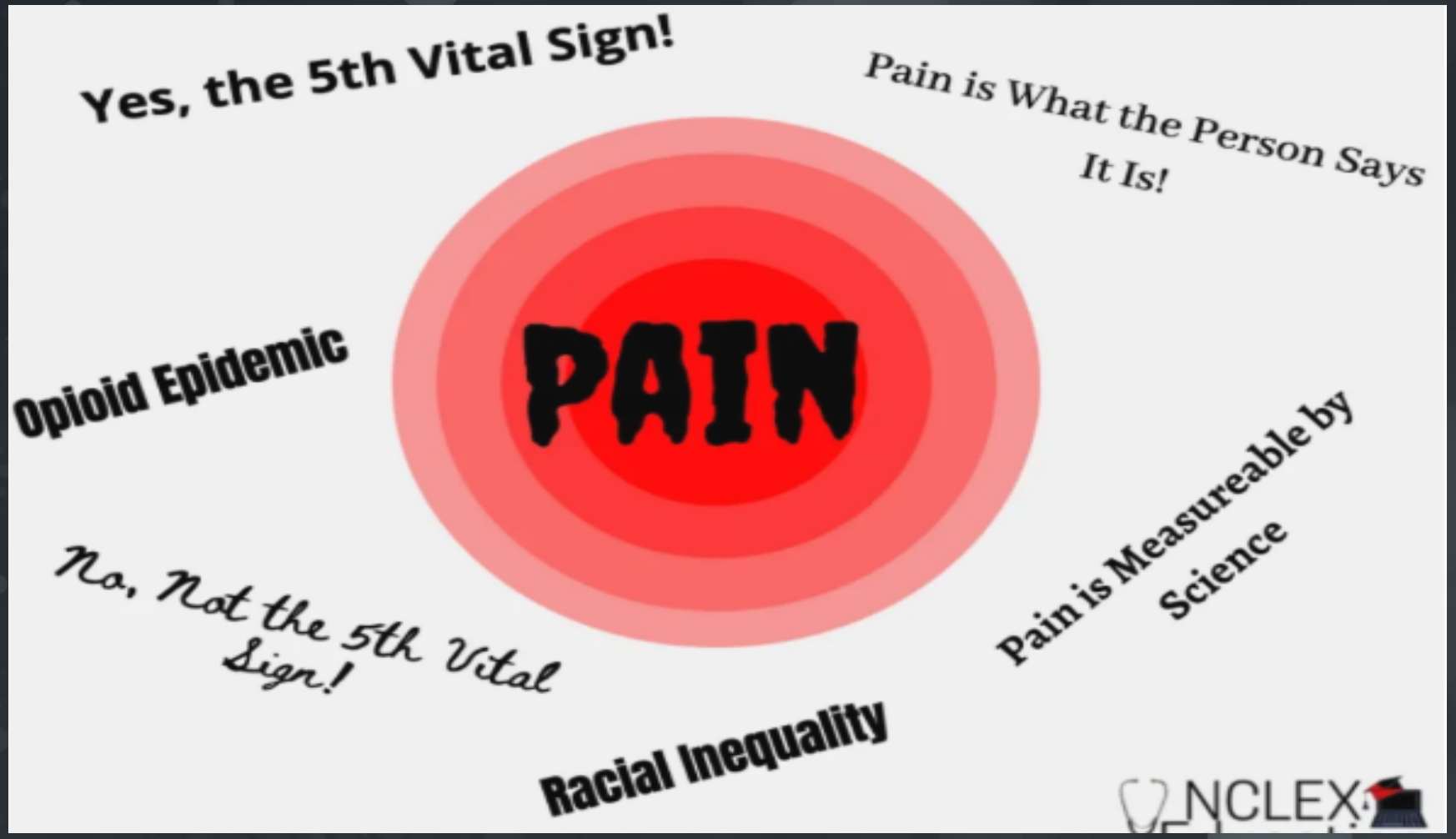
Pain Management: A Journey Across the Decades



Pain Management Specialists versus Anesthesia Care Pain Management

Pain Needs Assessment

Pain Management Plan of Care including patient

Challenges of New Medications

Anesthesia Plan of Care for Pain Management

- Preoperative medication review
- Pain Medications from Home
- Narcotics? Cannabis?
- Methadone?
- Suboxone Subutex?

Preoperative Pain Assessment

- Are there any medications which could impact intraoperative care?
- Are there any pharmacokinetic or pharmacodynamic impacts on intraoperative pain management?

Anesthesia Preoperative Pain Management Plan

- Upregulation: Enzyme induction of CP 450 or Down Regulation?
- Prolonged Half Life of Existing Medications?
- Agonist or Antagonist to Intraoperative Medications for Pain?

Refresher on Enzyme Induction or Inhibition?

- Induction: Enzyme induction increases the synthesis of drug-metabolizing enzymes, resulting in faster medication breakdown and potentially decreased drug efficacy

- Inhibition: Enzyme inhibition decreases the activity of these enzymes, leading to slower drug metabolism, higher drug levels, and an increased risk of adverse effects. Both processes are major concerns in anesthesiology and critical care, where they can cause profound drug interactions with serious consequences

Journavx & CP450

- Anesthesia Medication metabolism primary areas within the cytochrome P450 (CYP450) system that control the metabolism of anesthesia medications are the CYP2B6, CYP2D6, CYP2E1, and CYP3A4 enzymes
- Key metabolism impacts including Liver, Renal and Biliary elements of pharmacokinetics
- Note CYP 3A4**

Enzymes	Substrates	Inhibitors	Inducers
CYP 3A4	amlodipine, simvastatin, warfarin, amiodarone, sildenafil, midazolam, fluoxetine, haloperidol, codeine, oxycodone, methadone, fentanyl	ciprofloxacin, ketoconazole, ritonavir, methylprednisone, imatinib, tamoxifen, cimetidine, grapefruit juice	simvastatin, efavirenz, pentobarbital, carbamazepine, phenobarbital, phenytoin, valproic acid, caffeine
CYP 1A2	alosetron, caffeine, duloxetine, melatonin, ramelteon, tacrine, tizanidine	ciprofloxacin, enoxacin, fluvoxamine, oral contraceptives, phenylpropanolamine	montelukast, phenytoin, smoking components of cigarettes
CYP 2C8	repaglinide, paclitaxel, methadone	gemfibrozil, fluvoxamine, ketoconazole, trimethoprim	rifampin
CYP 2C9	celecoxib, warfarin, phenytoin	amiodarone, fluconazole, miconazole, oxandrolone, capecitabine, etravirine, fluvastatin, metronidazole, sulfinpyrazone, tigecycline	carbamazepine, rifampin, aprepitant, bosentan, phenobarbital, St. John's wort
CYP 2D6	lidocaine, metoprolol, haloperidol, fluoxetine, amitriptyline, metoclopramide, codeine, oxycodone, tramadol	amiodarone, chlorpromazine, citalopram, bupropion	rifampin, dexamethasone

Feature	Enzyme Induction	Enzyme Inhibition
Mechanism	An "inducer" drug enhances the production of specific enzymes, primarily in the liver, by increasing gene transcription.	An "inhibitor" drug or substance binds to and reduces the activity of an existing enzyme.
Time to onset	Gradual, requiring repeated administration over several days to weeks to build up new enzyme levels. The half-life of the inducing drug determines the onset.	Rapid, occurring as soon as the inhibitor concentration is high enough to bind to the enzyme, often within a few hours to days.
Effect on metabolism	**Increases** the metabolic rate of other drugs (substrates) processed by the same enzyme.	**Decreases** the metabolic rate of other drugs (substrates) processed by the same enzyme.
Effect on drug levels	**Decreases** plasma concentrations of the other drug, which can reduce its effectiveness.	**Increases** plasma concentrations of the other drug, which can raise the risk of toxicity or side effects.
Effect on prodrugs	If the enzyme activates an inactive prodrug, induction can lead to an **increase** in the active form, potentially causing toxicity.	If the enzyme activates an inactive prodrug, inhibition can lead to a **decrease** in the active form, reducing its therapeutic effect.
Clinical management	May require increasing the dose of the affected drug to maintain its therapeutic effect.	May require decreasing the dose of the affected drug to prevent toxicity.
Examples in anesthesia	Chronic use of certain medications like phenytoin or rifampicin can induce cytochrome P450 enzymes. This can increase the metabolism of anesthetic opioids and sedatives, potentially requiring higher doses to achieve the desired effect.	Co-administration of certain antibiotics (e.g., erythromycin), antifungals (e.g., ketoconazole), or even grapefruit juice can inhibit cytochrome P450 enzymes. This can cause the levels of anesthetic agents to build up to dangerous levels, leading to severe respiratory depression or coma.

Beyond CP 450 Drug Metabolism: Small Neighborhoods within The City

- Sub-areas of the cytochrome P450 (CYP) system that significantly impact drug metabolism include the specific isoforms responsible for processing most medications, their genetic variations, and their interactions with other drugs and substances
- Out of 57 functional CYP enzymes, the following six isoforms account for approximately 90% of drug metabolism

- CYP3A4
- CYP2D6
- CYP2C19
- CYP2C9
- CYP1A2
- CYP2E1

Journavx & Pharmacokinetics

Suzetrigine — novel non-opioid selective Nav 1.8 sodium channel inhibitor

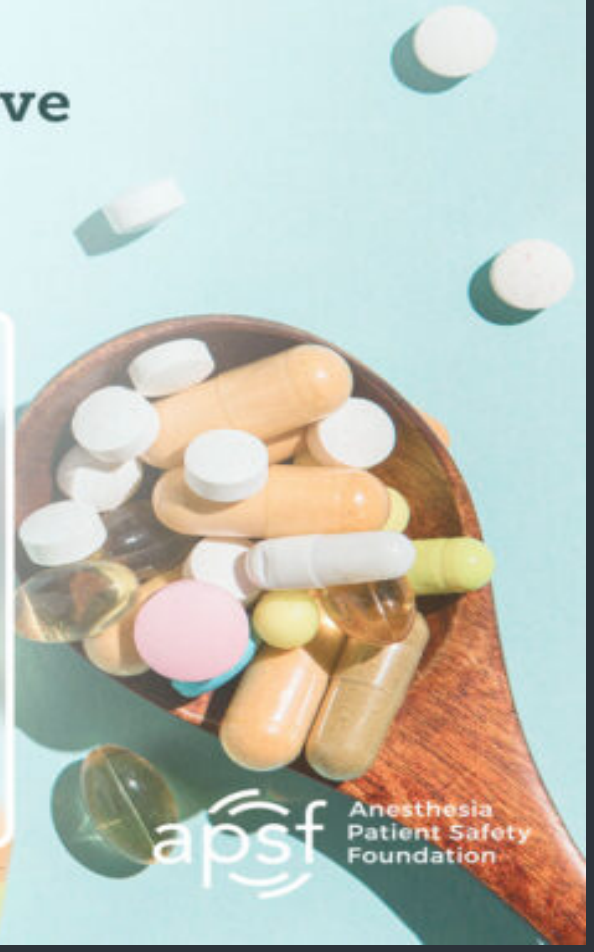
Pharmacokinetic Drug-Drug Interactions (DDIs)

Suzetrigine is a P450 3A4 substrate

- Levels of suzetrigine can be increased by 3A4 inhibitors, such as itraconazole and clarithromycin
- Levels of suzetrigine can be decreased by 3A4 inducers, such as carbamazepine and phenytoin

Suzetrigine is also a P450 3A4 inducer

- Suzetrigine can decrease levels of 3A4 substrates, such as midazolam and propofol



Journavx, CYP3A & Anesthesia

- CYP3A is one of the most important drug-metabolizing enzymes in the human body
- CPY3A belongs to the cytochrome P450 superfamily, which is responsible for the oxidation of various endogenous and exogenous compounds, including drugs, toxins, and steroids
- CYP3A is highly expressed in the liver and intestines, making it a key determinant of drug bioavailability and clearance
- CYP3A contributes to the metabolism of approximately 50% of all clinically used drugs, making it one of the most significant enzymes in pharmacokinetics

Anesthesia Pain Management: New Drugs, New Challenges & Successes

- Journavx is a new oral pain management medication released for use January 2025
- Journavx is covered by the No Pain Act
- Journavx: Preoperative Medication list or Preoperative Order Sets?

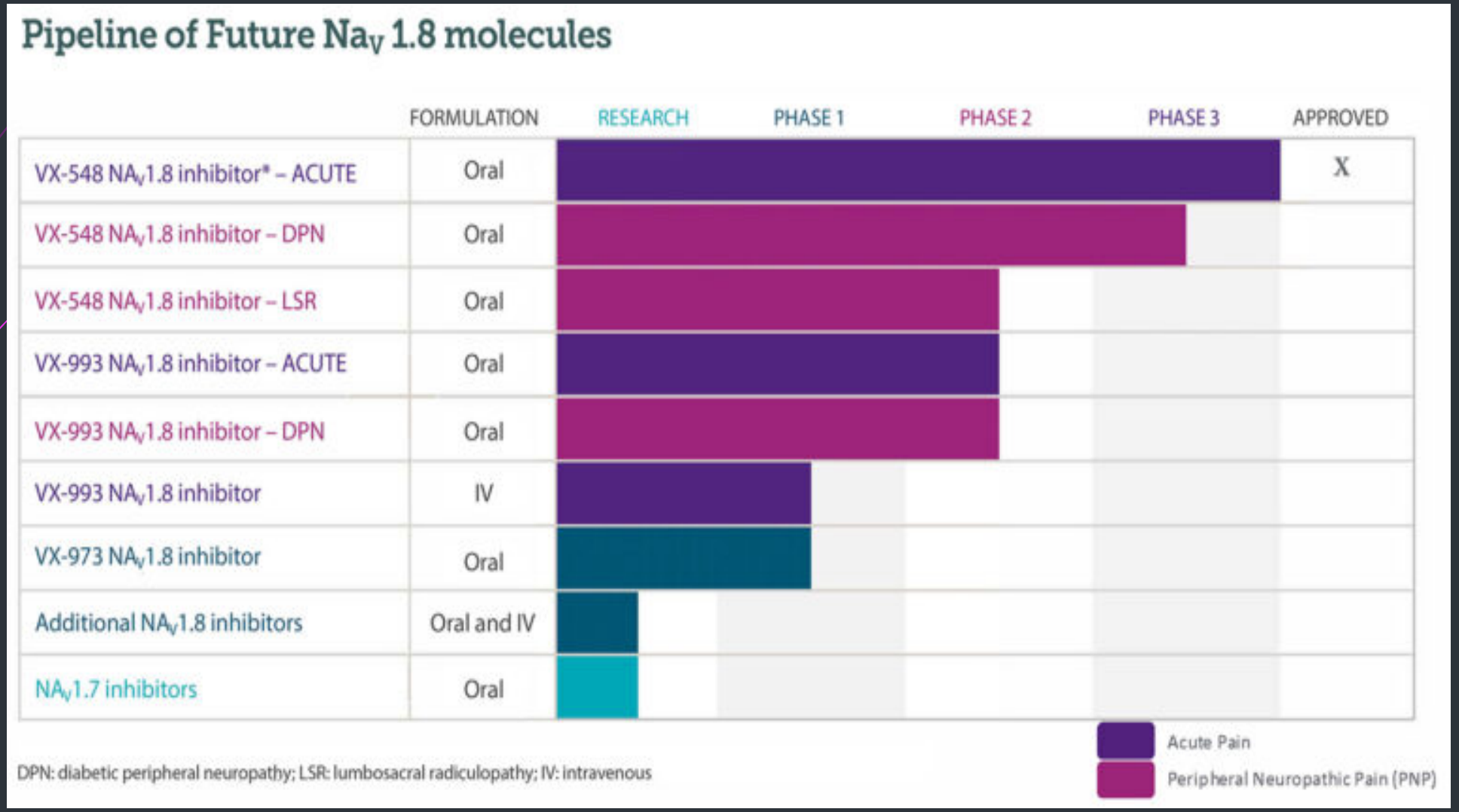
NO PAIN: Must Pay Rules to Combat Opioid Epidemic

- The NOPAIN Act (Non-Opioids Prevent Addiction In the Nation) is a law enacted in 2022 that began to take effect in 2025, requiring Medicare to provide separate reimbursement for qualifying non-opioid pain management treatments used in outpatient settings, thereby increasing access and reducing financial barriers for patients and providers to use these safer alternatives to opioids for postsurgical pain
- NO PAIN ACT was designed to minimize the financial obstacles to non-opioid options, and it expands access across Ambulatory Surgery Centers (ASCs) and Hospital Outpatient Departments (HOPDs)
- NO PAIN ACT requires minimum reimbursement at 120% of Medicare rates

NO PAIN ACT & Medication Reimbursement Reform

- Purpose: The act aims to minimize financial barriers for healthcare providers to offer clinically proven non-opioid treatments for postsurgical pain.
- Target population: The law specifically impacts Medicare beneficiaries undergoing outpatient procedures in hospital outpatient departments (HOPDs) and ambulatory surgical centers (ASCs).
- Medicare reimbursement: For 2025 through 2027, the Centers for Medicare & Medicaid Services (CMS) provides a separate, temporary payment for certain non-opioid drugs, biologics, and devices. Previously, reimbursement for these treatments was bundled into the overall procedure payment, which financially disadvantaged them compared to inexpensive opioids.
- Approved products: CMS has approved specific non-opioid products for separate reimbursement under the act. Examples include the pain medications Exparel and Zynrelef, Inovera, Journavx
- Expiration: Without additional congressional action, the separate reimbursement for non-opioid treatments will expire and revert to bundled payments after December 31, 2027.

Future Nav1.8 Research Trials



Journavx Clinical Trials

- Vertex Pharmaceuticals: two large randomized clinical trials: an abdominoplasty trial that enrolled 1,118 patients and a bunionectomy study with 1,073 patients. Patients were randomly assigned to one of three groups: a placebo, a combination of acetaminophen and hydrocodone, or Journavx
- The recommended loading dose of Journavx is 100 mg orally, followed by 50 mg every 12 hours.1 In addition to receiving the randomized treatment, all participants in the trials who experienced breakthrough pain were permitted to use ibuprofen as needed for "rescue" analgesia
- Both trials demonstrated a statistically significant superior reduction in pain with Journavx compared to placebo
- Superiority versus the combination of hydrocodone 5 mg/acetaminophen 325 mg was not demonstrated. However, a responder's analyses at various timepoints (12h, 24h, and 48h) showed similar 30/50/70% reductions in Numeric Pain Rating Scale of Journavx versus hydrocodone 5 mg/ acetaminophen 325 mg. Side effects of suzetrigine reported by patients were similar to those taking the placebo.

Journavx & Contraceptives

- Journavx increase risk of adverse reactions with the concomitant use of moderate to strong CYP3A inhibitors
- Journavx risk of drug interactions with certain hormonal contraceptives: and patients taking Journavx should use nonhormonal contraceptives (such as condoms) or use alternative contraceptives containing levonorgestrel and norethindrone

Journavx

- Patients with moderate to severe hepatic impairment may have higher systemic exposure of Journavx and its active metabolites
- Journavx should be avoided in patients with renal impairment of eGFR < 15 mL/min
- Journavx most common adverse reactions: itching, muscle spasms, increased blood level of creatine phosphokinase, and rash
- Journavx was generally safe and well tolerated with a lower incidence of adverse events than placebo and the acetaminophen/hydrocodone combination. Additionally, patients should avoid food or drink containing grapefruit when taking Journavx