What You Need to Know About Pain Management as the Opioid Overdose Crisis Evolves

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University of Connecticut School of Medicine

<u>Educational Objectives</u>:

Upon completion of this webinar, participants will….

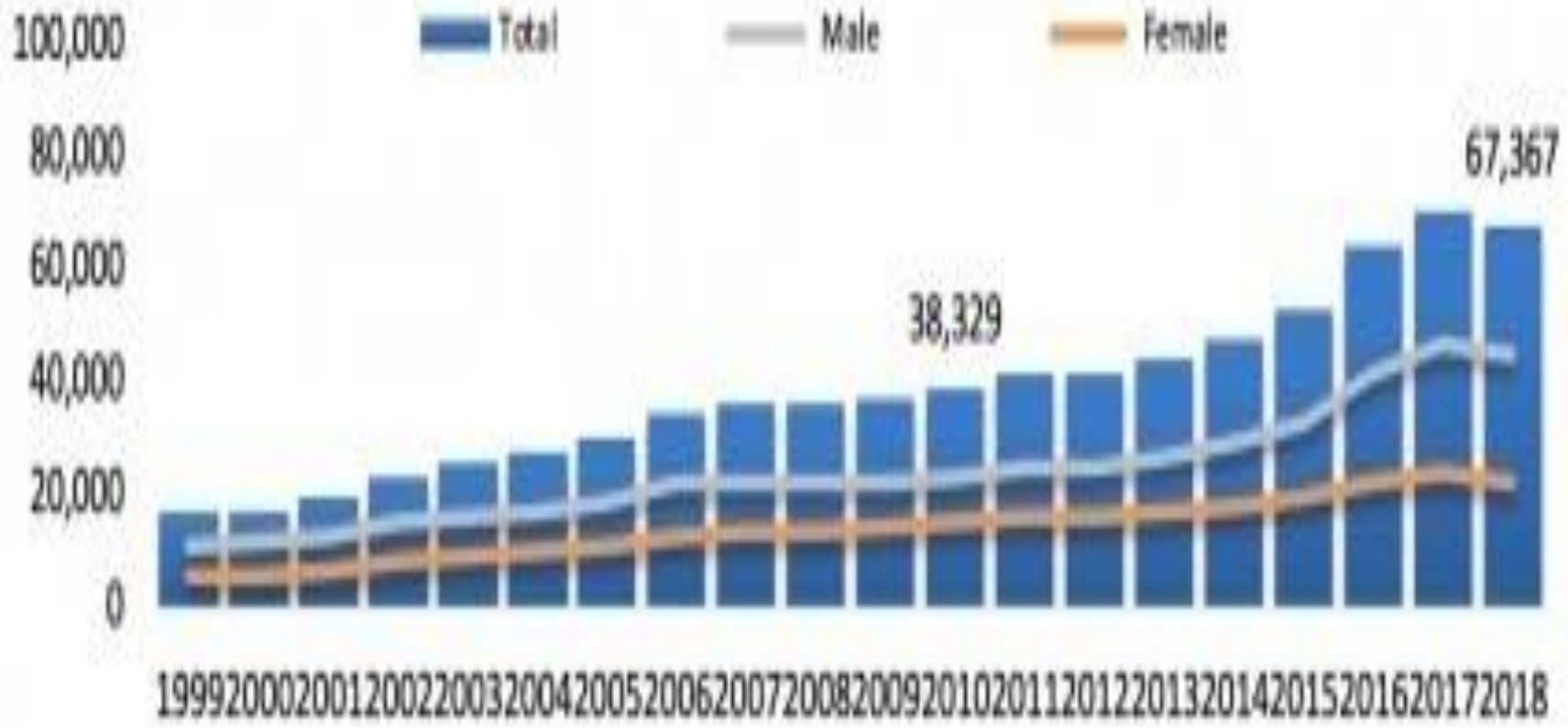
- **Be able to prevent and manage acute pain with minimal use of opioid-containing analgesics,**
- **Understand that meaningful pain relief from the patient's perspective does not require the risks of exposure to opioids that may precipitate substance abuse in vulnerable individuals,**
- **Recognize the therapeutic advantages, increased risks and appropriate dosing for combinations of an NSAID and acetaminophen for the management of acute dental pain.**

Disclosures

The presenter has consulted for GSK and Rilento Pharma in the past year and serves on the Scientific Advisory Board of Charleston Labs

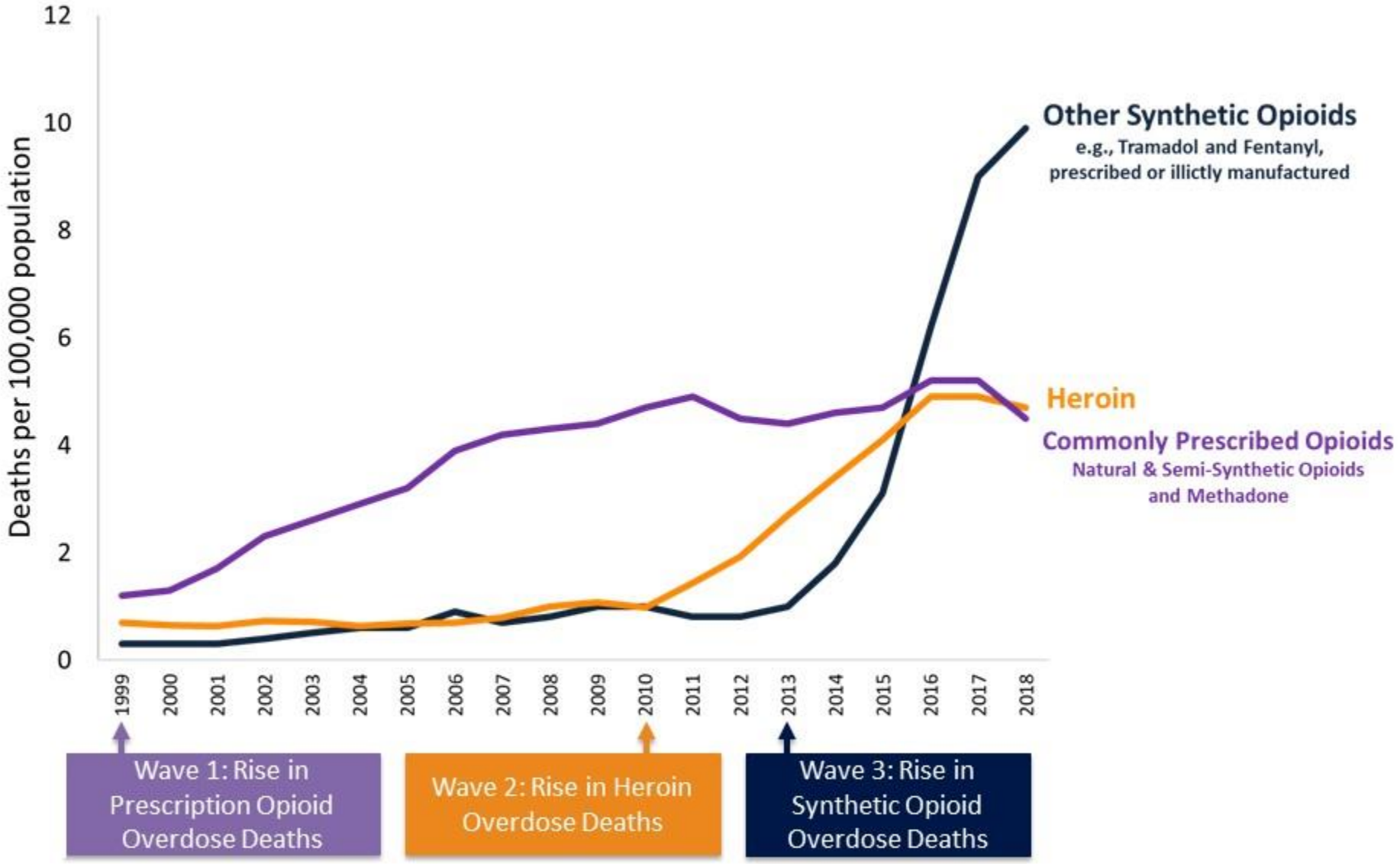
National Drug Overdose Deaths

Number Among All Ages, by Gender, 1999-2018



Source: Centers for Disease Control and Prevention, National Center for Health Statistics. Multiple Cause of Death 1999-2017 on CDC

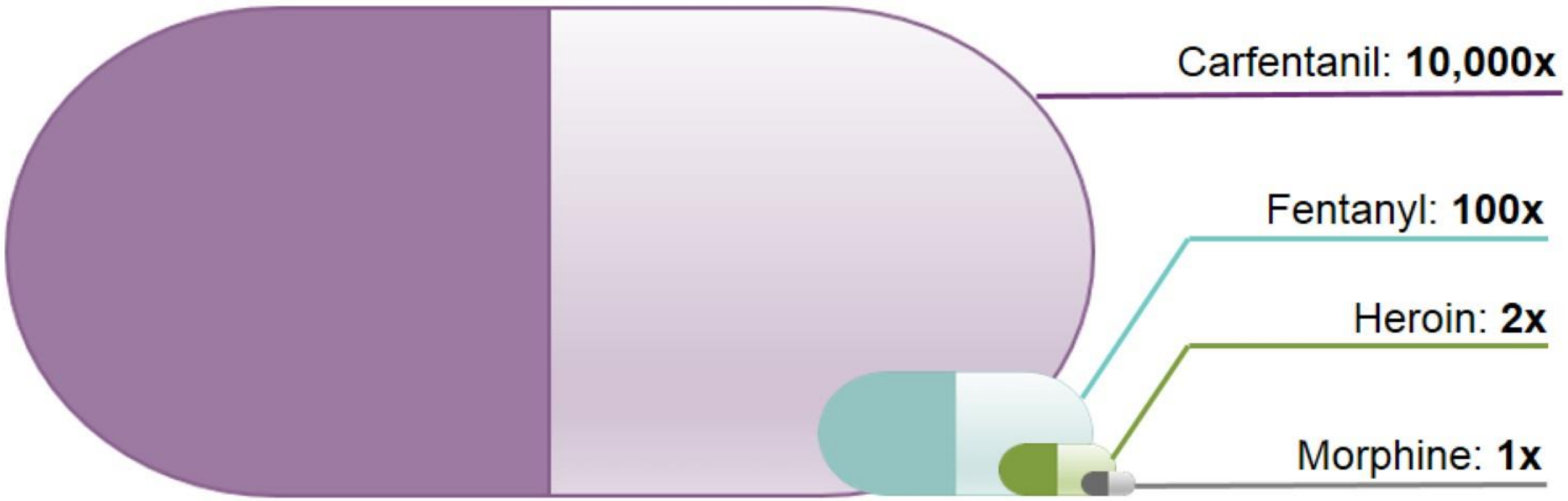
3 Waves of the Rise in Opioid Overdose Deaths



SOURCE: National Vital Statistics System Mortality File.

With unprecedented availability of cheap heroin and fentanyl…

MORE PEOPLE ARE DYING



Opioid Potency

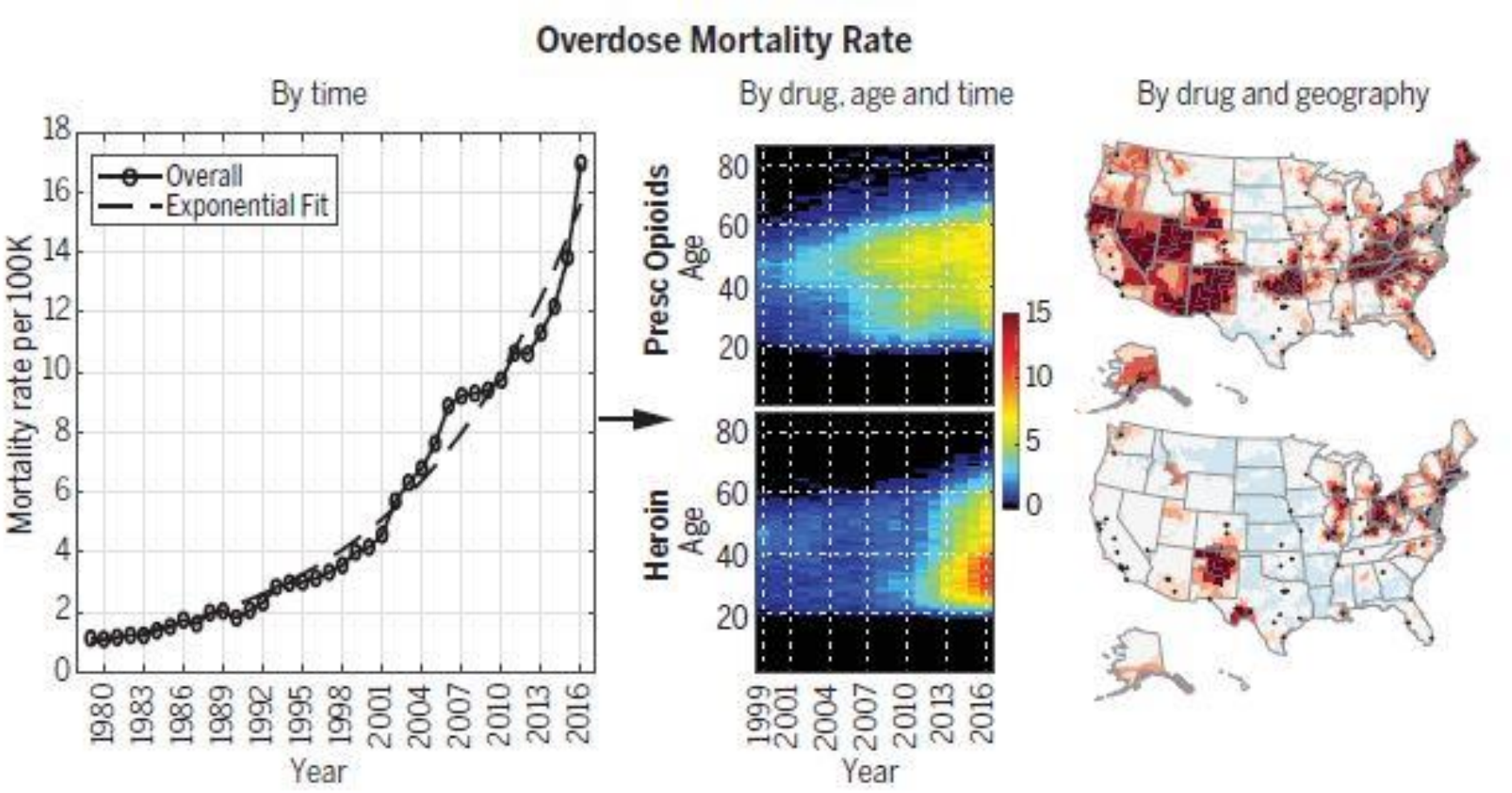
North Carolina Injury & Violence PREVENTION Branch

‘The Drug Became His Friend’: Pandemic Drives Hike in Opioid Deaths

In the months since the pandemic took hold in the U.S., the opioid epidemic has taken a sharp turn for the worse. More than 40 states have seen increases in overdoses.

Family and friends mourned Jefrey Scott Cameron, who died of an accidental overdose earlier this year, in Barre, Vt.

Changing dynamics of the drug overdoses in the US from 1979 to 2016



’ ..the current opioid epidemic may be a more recent manifestation of an ongoing longer-term process’

‘Understanding the forces that are holding multiple sub-epidemics together…may be important in revealing and effectively dealing with the root causes of the epidemic’

Early Exposure to Opioids May Trigger an Opioid Use Disorder

JAMAInternalMedicine | OriginalInvestigation

Association of Opioid Prescriptions From Dental Clinicians for US Adolescents and Young Adults With Subsequent Opioid Use and Abuse

Alan R. Schroeder, MD; Melody Dehghan, BA; Thomas B. Newman, MD, MPH; Jason P. Bentley, PhD; K. T. Park, MD, MS

Table 2. Outcomes in the Opioid-Exposed and Opioid-Nonexposed Cohorts

Outcome (N = 44 664)	Cohort, No. (%)		*P* Value[a]	Adjusted Absolute Risk Difference, % (95% CI)[b]
	Opioid-Exposed (n = 14 888)	Opioid-Nonexposed (n = 29 776)		
Opioid prescription at 90 to 365 d	1021 (6.9)	30 (0.1)	<.001	6.8 (6.3 to 7.2)
>1 Opioid prescription	387 (2.6)	3 (0.01)	<.001	2.5 (2.2 to 2.7)
At least 1 diagnosis of opioid abuse in subsequent 365 d	866 (5.8)	115 (0.4)	<.001	5.3 (5.0 to 5.7)
Site of encounter[c]				
Office visit	790 (5.3)	97 (0.3)	<.001	4.9 (4.5 to 5.3)
Emergency department visit	25 (0.2)	24 (0.1)	.005	0.1 (0.02 to 0.2)
Hospitalization	74 (0.5)	79 (0.3)	<.001	0.2 (0.1 to 0.4)
Most common diagnoses of opioid abuse[c]				
Opioid type dependence, unspecified	602 (4.0)	66 (0.2)	<.001	3.8 (3.5 to 4.1)
Poisoning by opium (alkaloids), unspecified	82 (0.6)	8 (0.03)	<.001	0.5 (0.4 to 0.6)
Opioid abuse, unspecified	51 (0.3)	25 (0.08)	<.001	0.3 (0.2 to 0.4)
Death	1 (0.007)	1 (0.003)	.62	0.003 (−0.002 to 0.005)

[a] *P* value obtained from χ^2 analysis.

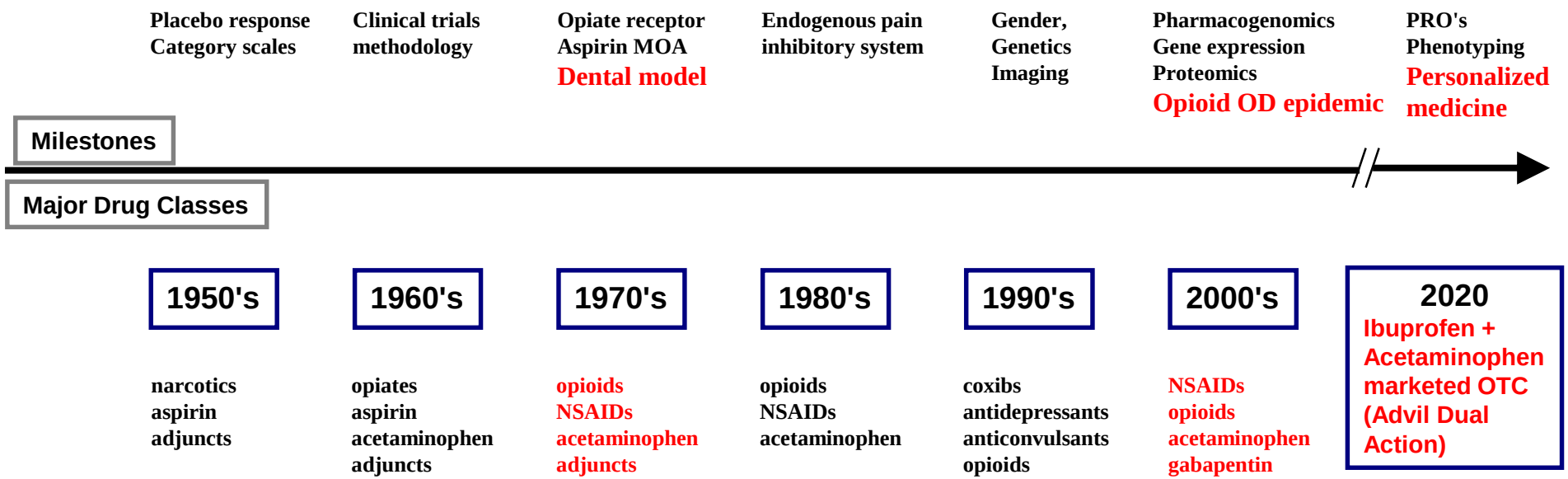
[b] Adjusted for race/ethnicity and previous nonopioid substance abuse.

[c] Some patients had more than 1 site of encounter or diagnosis of opioid abuse.

16-fold increase in opioid use/abuse after a single opioid Rx for acute pain following oral surgery

'Use of these prescriptions may be associated with an increased risk of subsequent opioid use and abuse.'

Challenges to Improved Pain Management: Little Progress After A Century of Analgesic Drug Research



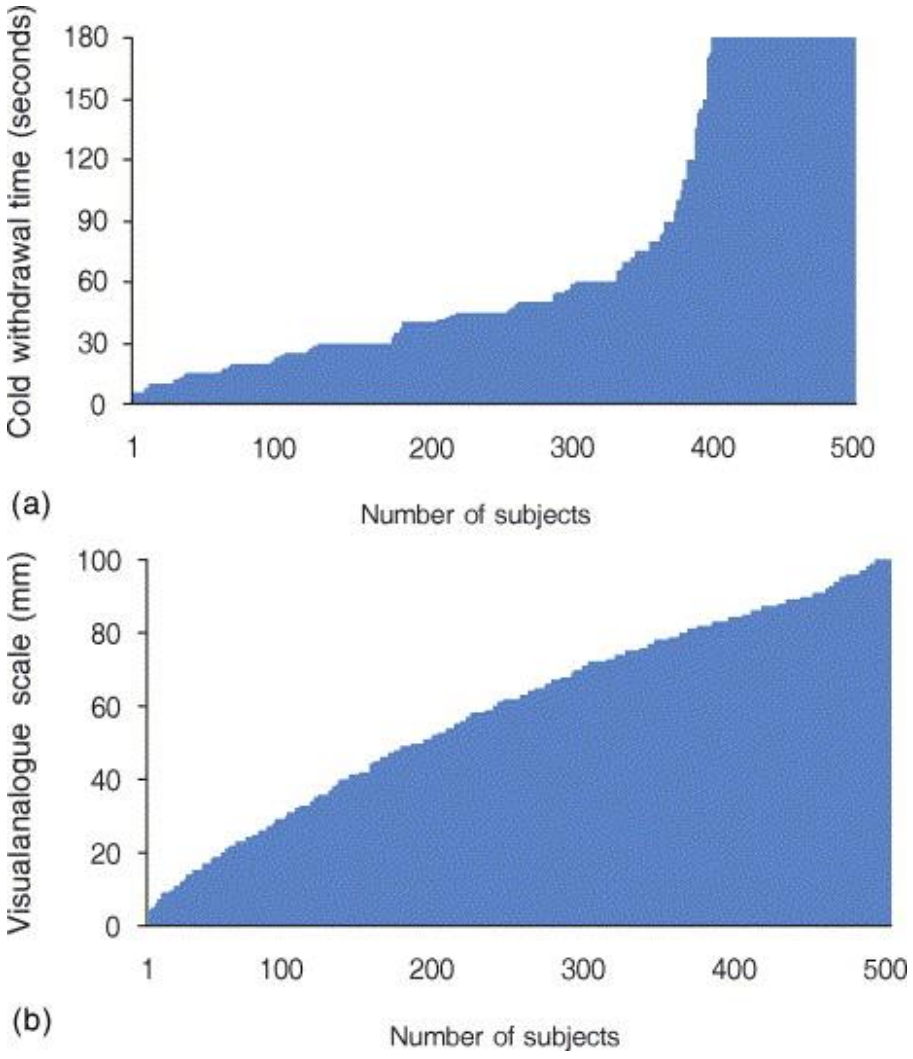
The Void in Opioid Research

The National Institutes of Health's plans to tackle the opioid epidemic in the United States can treat only the symptoms, not the cause.

Nature June 2018

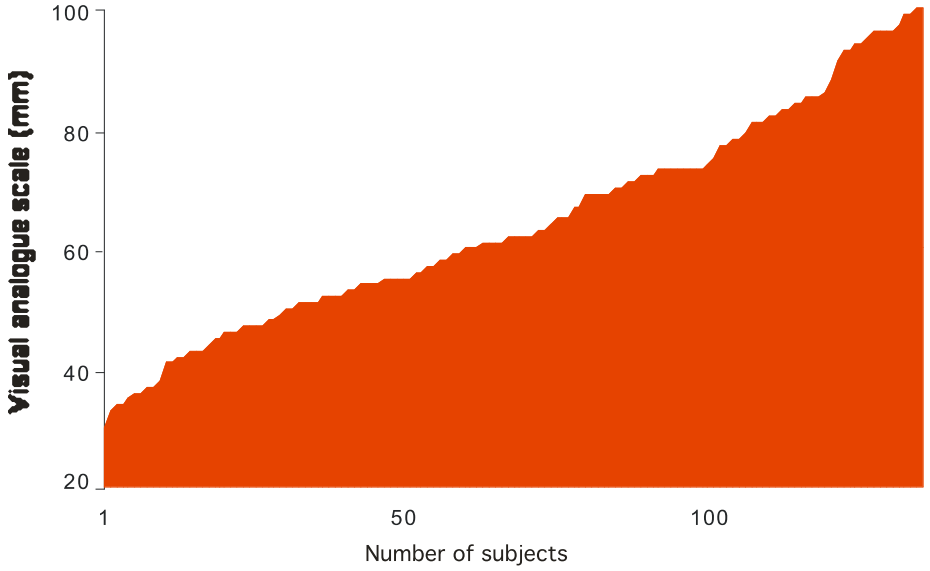
Challenges in Pain Management: Wide Variability in Pain and Analgesia Across Patients Mitigates 'One-Size Fits All' Prescribing

Experimental Pain



Kim H et al., Pain 2004

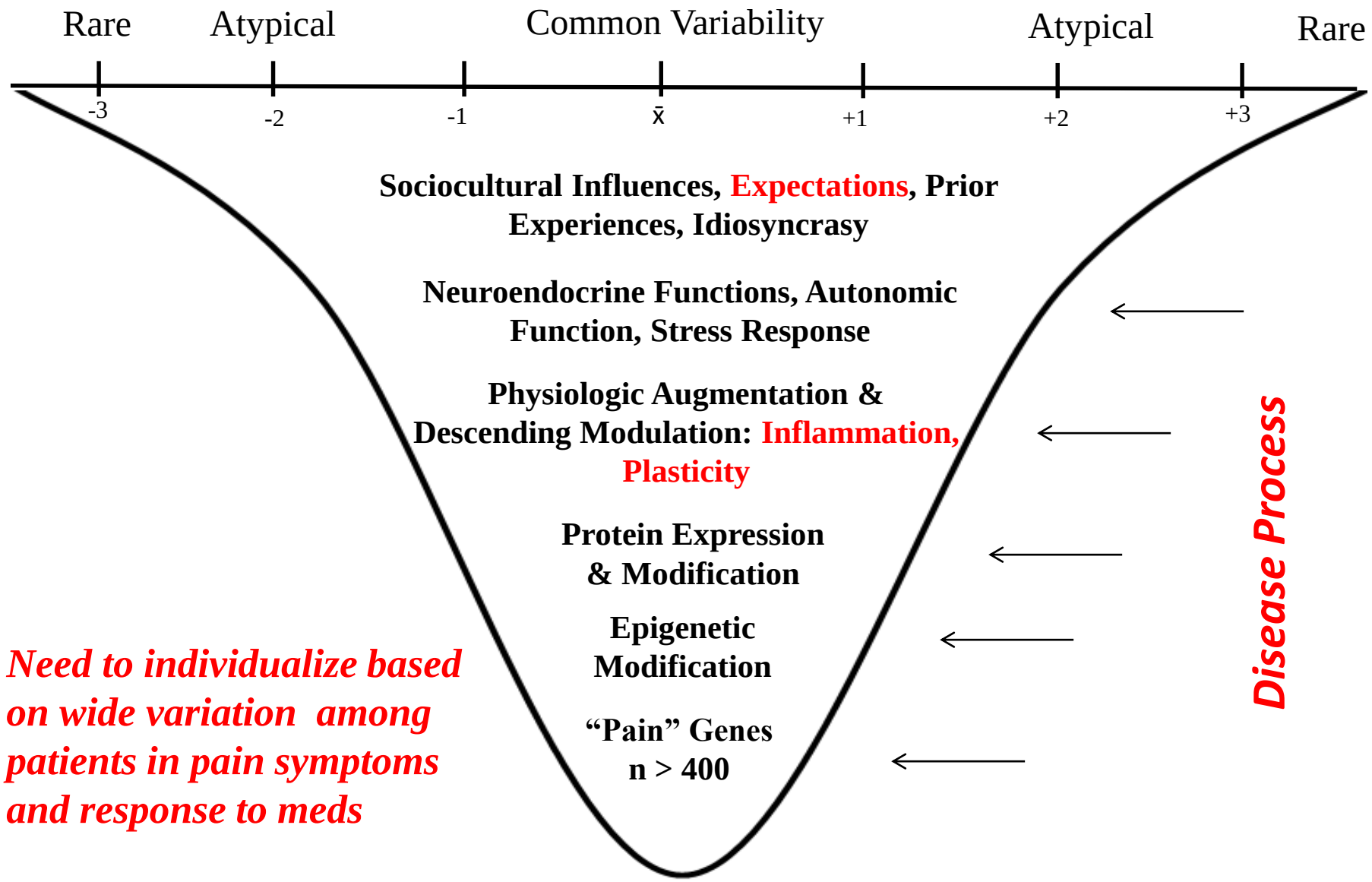
Clinical Pain (3rd Molar Extraction)



Variability in *self-administered morphine* dose for post-general surgery pain: 1 – 48 mg
mean dose = 13.3 mg

Aubrun et al. Anesthesiology 2003; 98:1415

Challenges in Pain Management: Many Other Factors Influence the Efficacy of a Drug at the Level of Individual Patients



Need to individualize based on wide variation among patients in pain symptoms and response to meds

Opioid Overdose Epidemic 2020

- **Leveling off in national death rate but little sign of improvement in some parts of the country: increase in opioid overdose deaths in 40 states during pandemic**
- **Decreased life expectancy in US due to opioid overdoses**
- **Overall drug overdose mortality has grown exponentially over the past 40 years** Jalal et al. Science 2018
- **Victims not just those who OD – 'opioid orphans'**
- **'Economic cost of the opioid crisis: $1 trillion and growing faster'** CNBC.com, 2/13/2018
- **Drug rehabilitation 15 - 20% recovery**
- **Overdose rescue in ED with naloxone – 6.5% dead < 1 year**

Current Status: Substance abuse is endemic in the US, likely that some of your patients are at risk to develop substance abuse or experience an overdose, no long-term solution is apparent as social determinants and genetics also drive overdoses

Steps to Optimize Analgesia, Minimize Side Effects and Lower the Risk of Opioid Abuse

1. Modulate the Inflammatory Etiology of Acute Pain

- ***Nociceptive - transient, protective/prevent further tissue damage***
- ***Inflammatory – to protect the injured tissue***
- ***Neuropathic* – peripheral NS damage**
  - Diabetic neuropathy
  - AIDS
  - Chemotherapy - induced peripheral neuropathy
- ***Functional* – abnormal processing or function of CNS**
  - Fibromyalgia

Inflammatory Pain

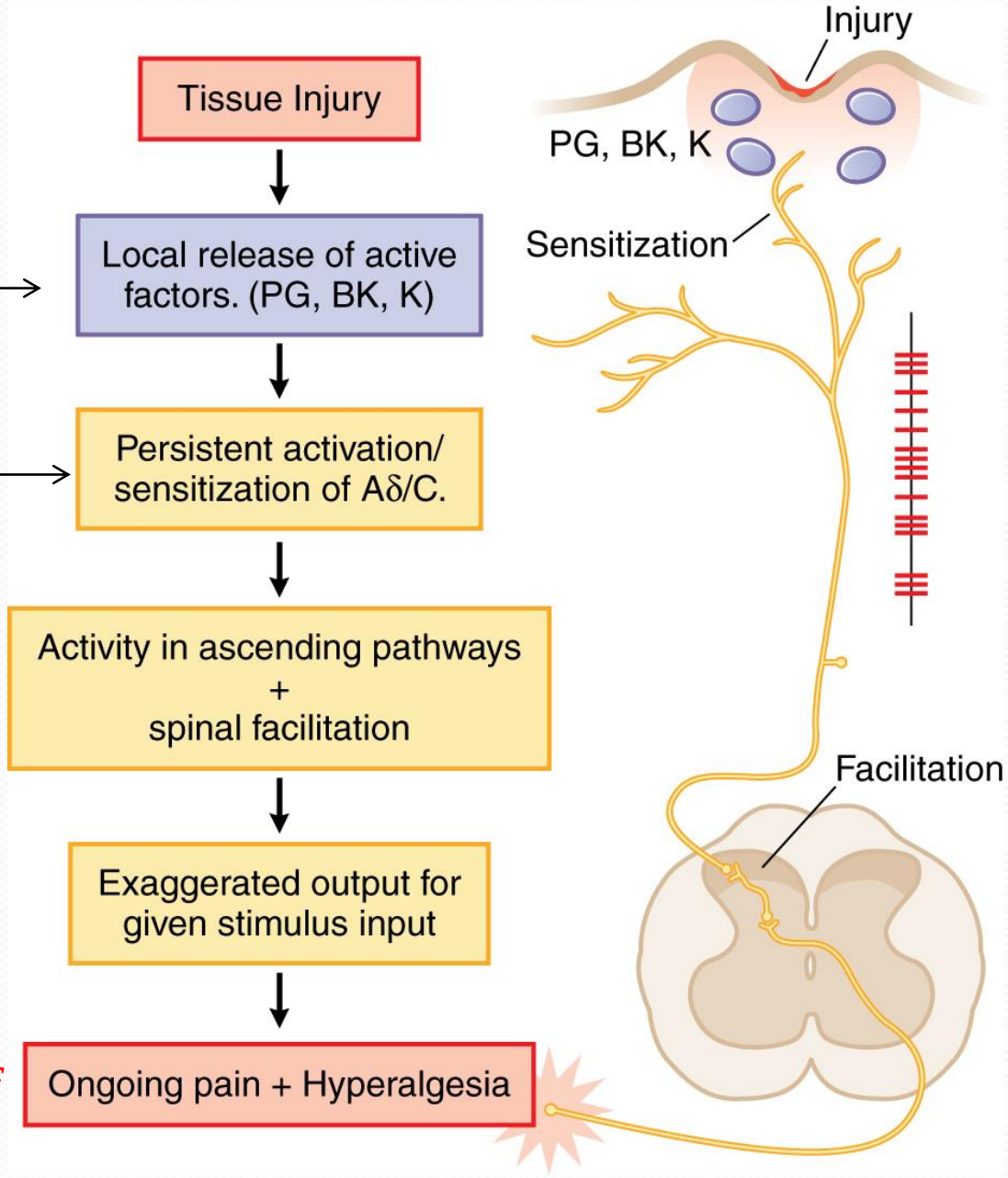
Blocked by NSAIDs

Minimizes

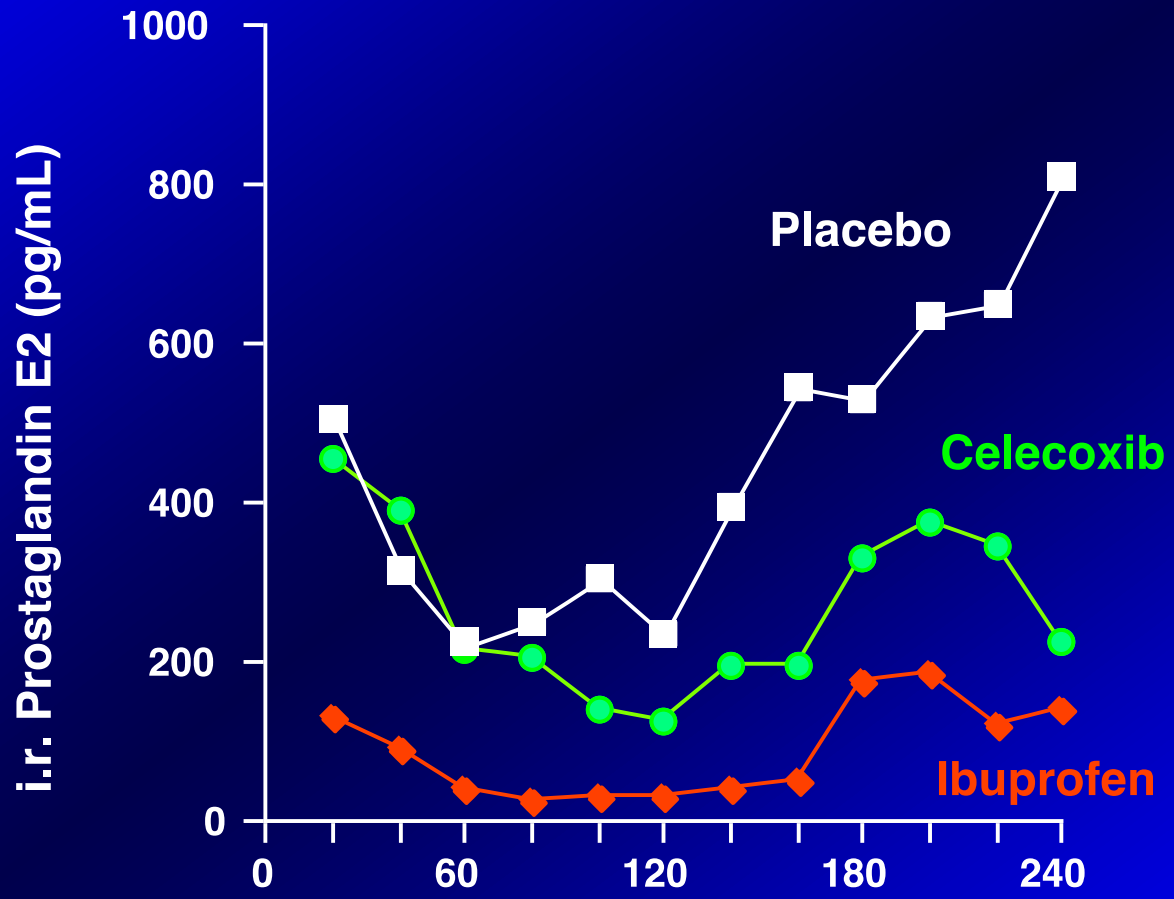
Resulting in Much Less

Produces Little or No

'Slight' Pain after LA offset, instead of

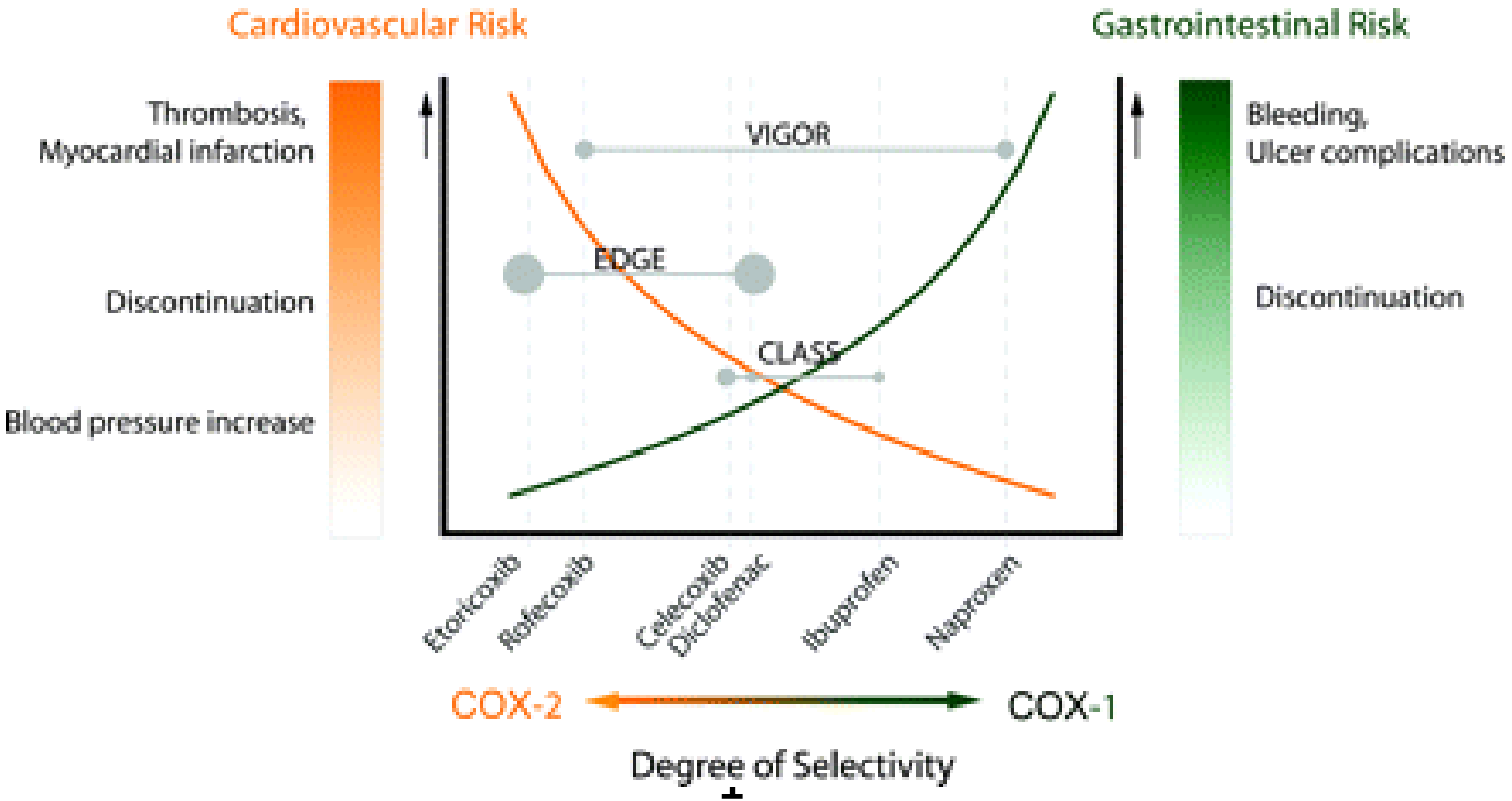


NSAID Prior to Tissue Injury Suppresses COX



Khan AA et al.
Clin Pharmacol Ther. 2002

Need to Balance GI and Cardiovascular Adverse Effects



2. Minimize Diversion of **Opioids Contributing to Drug Abuse**

Most commonly prescribed opioid amount is 20 doses and a 3-day supply.

What Happens to These Drugs?

- Used in totality as prescribed
- Stored "for a rainy day"
- Sold on the street
- Given to friends/family

< Half of opioids prescribed for pain after oral surgery were used, only 5 patients used all of the prescribed pills (N=28)

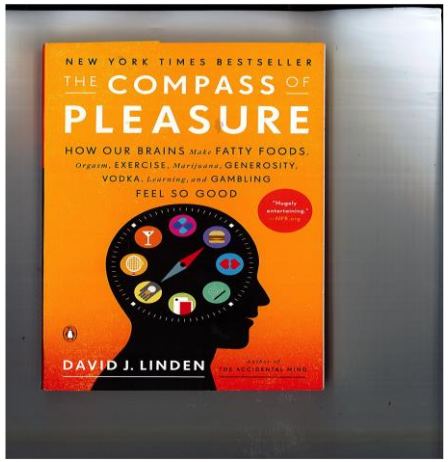
Maughan BC et al. Drug and Alcohol Dependence 2016

Extrapolates to millions of pills available for diversion after dental procedures

Individual Variability in Drug Abuse is Heritable

The **addictions are *moderately to highly heritable*,** which is paradoxical because **these disorders require use … the addictions are interrelated and related to other psychiatric diseases by common neurobiological pathways,** including those that modulate reward, behavioral control and the anxiety or stress response.

Goldman D et al. Nature Reviews/Genetics 2005

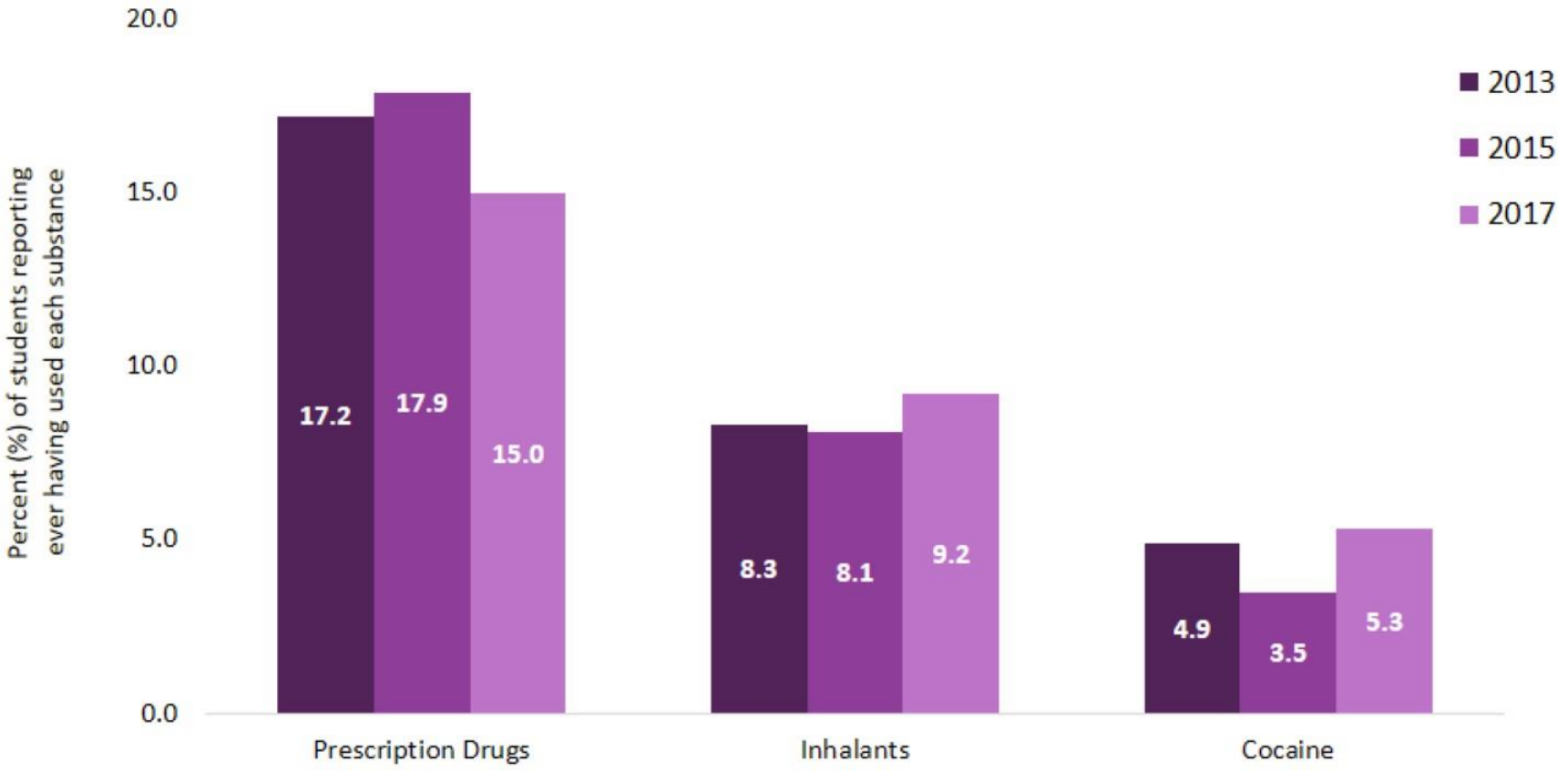


'the dark side of pleasure is addiction'
'brain imaging shows that heroin, orgasm and fatty foods all activate the same pleasure circuits'

Outcome from Short Course of Opioid Abuse Associated with Heritability

Substance abuse starts in early adolescence

15% of N.C. High School students report using prescription drugs recreationally in 2017



Technical Notes: Question based on self-reported lifetime use of substances among High School students
Source: N.C. Department of Public Instruction, N.C. Youth Risk Behavioral Survey (YRBS), 2013-2017
Analysis: Injury Epidemiology and Surveillance Unit

#3 Prescribe Analgesics Based on Scientific Evidence not Tradition

Established prescribing behaviors

- Efficacy of APAP-opioids established in 1970's**, before NSAIDs introduced**
- Improved clinical analgesic research (Cooper & Beaver 1976)
- **NSAIDs efficacy and safety >> opioid combinations**

Misperception of DEA Scheduling of Opioids

- Schedule 2 drugs have greater ***abuse potential***, not efficacy

Placebo response contribution to analgesic efficacy

- Placebo response is 30-40% for simple extractions
- **Misperception that Rx analgesics are more potent than OTC analgesics**

Prescribing for Most Severe Outcome

- Often prescribe to manage the worse case scenario
- May benefit 20% with worse pain, but not needed for the other 80%

Unfounded Expectations of APAP Efficacy

- Maximum dose reduced from 1000 mg to 650 mg

Patient Expectations and Demands

- **Not providing an opioid can be perceived as less than optimal treatment**
- **Need to educate patients that NOT providing an opioid is the best treatment**

***Why Do We Prescribe Vicodin?* Moore, Dionne, Cooper, Hersh: JADA July 2016**

Original Contributions

Cover Story

Opioid prescribing practices from 2010 through 2015 among dentists in the United States

What do claims data tell us?

Niodita Gupta, MD, MPH, PhD; Marko Vujicic, PhD; Andrew Blatz, MS

ABSTRACT

Background. Dentists wrote 6.4% of all opioid prescriptions in the United States in 2012. The purpose of this study was to examine opioid prescription rates, dosage of opioids prescribed, type of opioid drug prescribed, and type of dental visit at which dentists prescribe opioids.

Methods. The authors used the 2010 through 2015 Truven Health Marketscan Research databases and the Prescription Drug Monitoring Program (PDMP) Training and Technical Assistance Center conversion data set. The authors conducted descriptive analyses for days' supply, quantity prescribed, and daily morphine milligram equivalent dose.

Results. The opioid prescription rate per 1,000 dental patients increased from 130.58 in 2010 to 147.44 in 2015. Approximately 68.41% of all opioids prescribed were during surgical dental visits and approximately 31.10% during nonsurgical dental visits. During nonsurgical dental visits at which dentists prescribed an opioid, most of the procedures were restorative.

Conclusions. Among a population of dental patients with private insurance, opioid prescribing rates in the United States increased slightly from 2010 to 2015. The largest increase was among 11- through 18-year-olds. Almost one-third of opioid prescriptions written by dentists were associated with nonsurgical dental visits.

Practical Implications. Use of PDMP resources and use of nonopioid analgesics could help reduce the number of opioid prescriptions in dentistry.

Key Words. Opioids; prescriptions; dentists.

JADA 2018:149(4):237-245
https://doi.org/10.1016/j.adaj.2018.01.005

Check for updates

ADA CE Program

Supplemental material is available online.

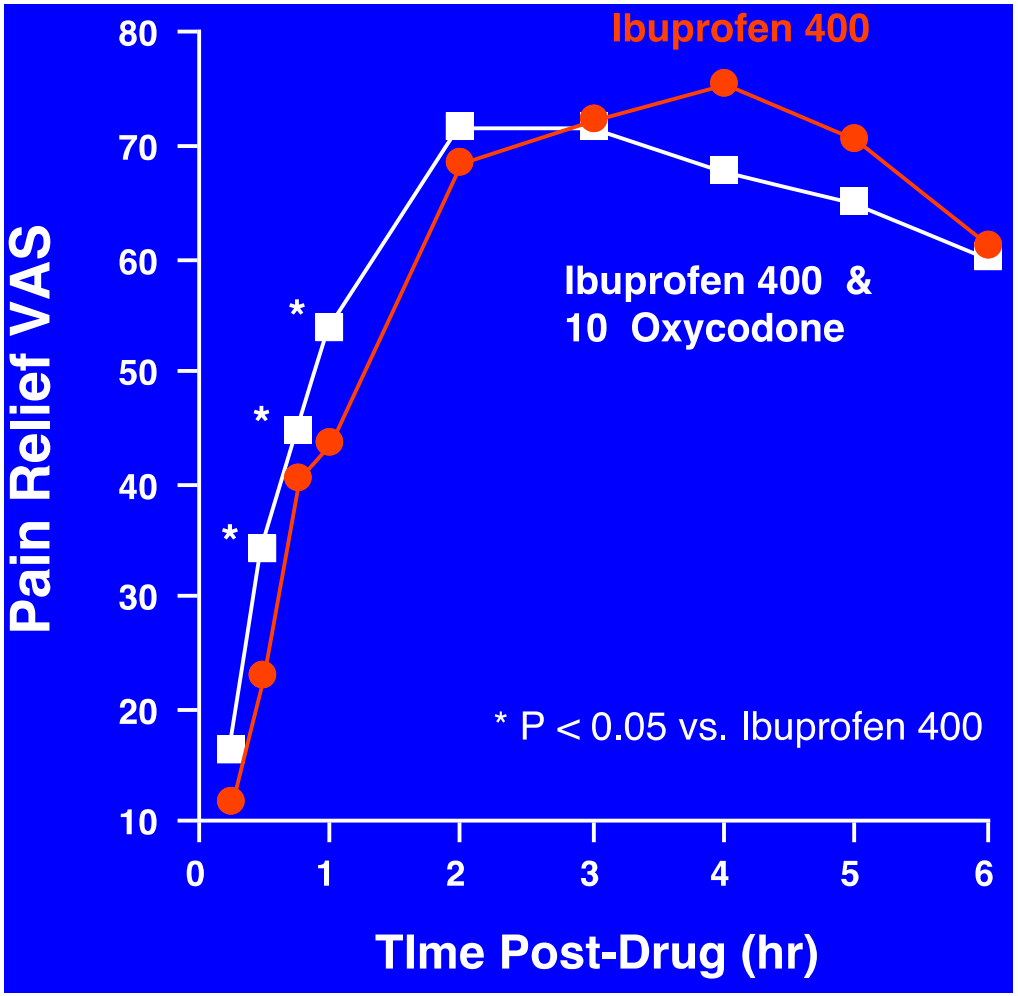
The United States is facing a severe opioid addiction epidemic. In 2015, approximately 12.5 million people misused prescription opioids.[1] Approximately 2.1 million people misused prescription opioids for the first time, and an estimated 2 million had a prescription opioid use disorder.[1] Opioid overdoses caused 33,091 deaths in 2015 alone.[1] The amount of opioids prescribed in 2010 was 782 morphine milligram equivalents (MMEs) per capita, which decreased to 640 MME per capita in 2015.[2] Investigators estimated the economic burden of opioid overdose, abuse, and dependence in 2013 to be $78.5 billion from a societal perspective.[3]

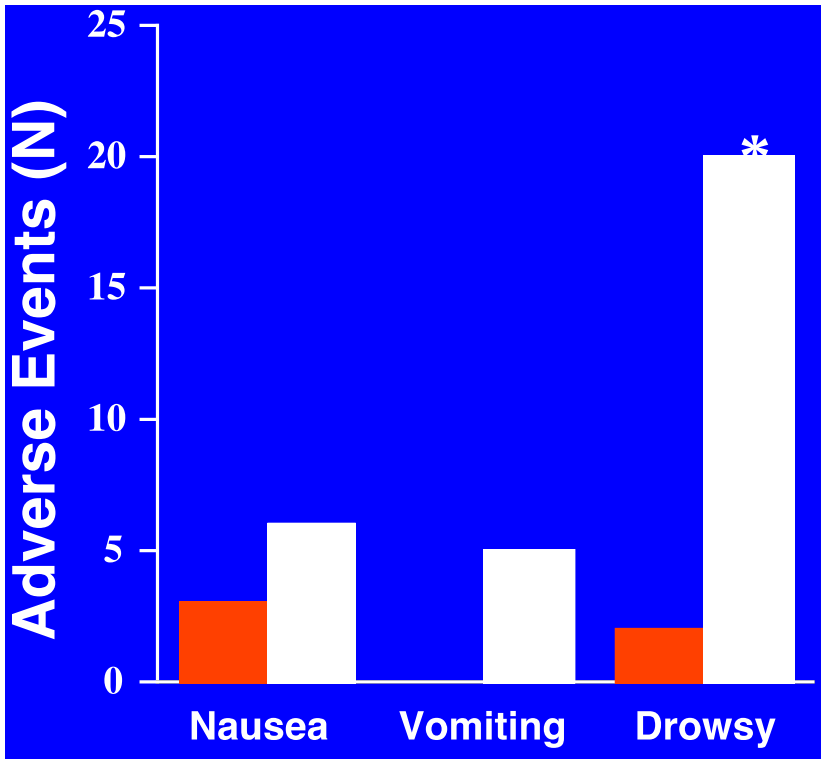
In 1998, dentists were the top specialty prescribers of immediate-release opioids, accounting for 15.5% of all immediate-release opioid prescriptions.[4] However, by 2009, the amount of opioid prescriptions written by dentists decreased to 8% of all opioid prescriptions in the United States,[5] and by 2012, this amount further decreased to 6.4%.[6] More recent and detailed data are available in some states. For example, in South Carolina during 2012 and 2013, dentists accounted for only 8.9% of all opioid prescribers but prescribed 44.9% of the initial opioids dispensed to patients.[7] Patients younger than 21 years received 11.2% of the total amount of opioids that dentists prescribed.[7] Investigators conducted a study in Indiana and used 2011 data, and their results showed that access to dentists and pharmacists increased the availability of prescription opioids and that this

This article has an accompanying online continuing education activity available at: http://jada.ada.org/ce/home.

'Approximately 31% of the opioids prescribed for all age groups were associated with nonsurgical dental visits… suggests there might be opportunities to reduce opioid prescribing by targeting nonsurgical dental visit prescribing practices.'

Little additive analgesic effect in combination with an NSAID





Use an Atypical Centrally-Acting Analgesics if an Opioid is Indicated

Tramadol (Ultram®)

- Moderate-strong analgesic
- Agonist at mu receptors and blocks uptake of NE and 5-HT so spinal pain processing is less efficient
- **Minimal potential for dependence or abuse**
- **Minimal potential for respiratory depression**
- Effects partially blocked by naloxone
- Metabolized by CYPs (CYP2D6 and others) to 5 different metabolites
  - Desmethyltramadol is 200 times more potent
  - Depending on genetics analgesic effects can either increase or decrease

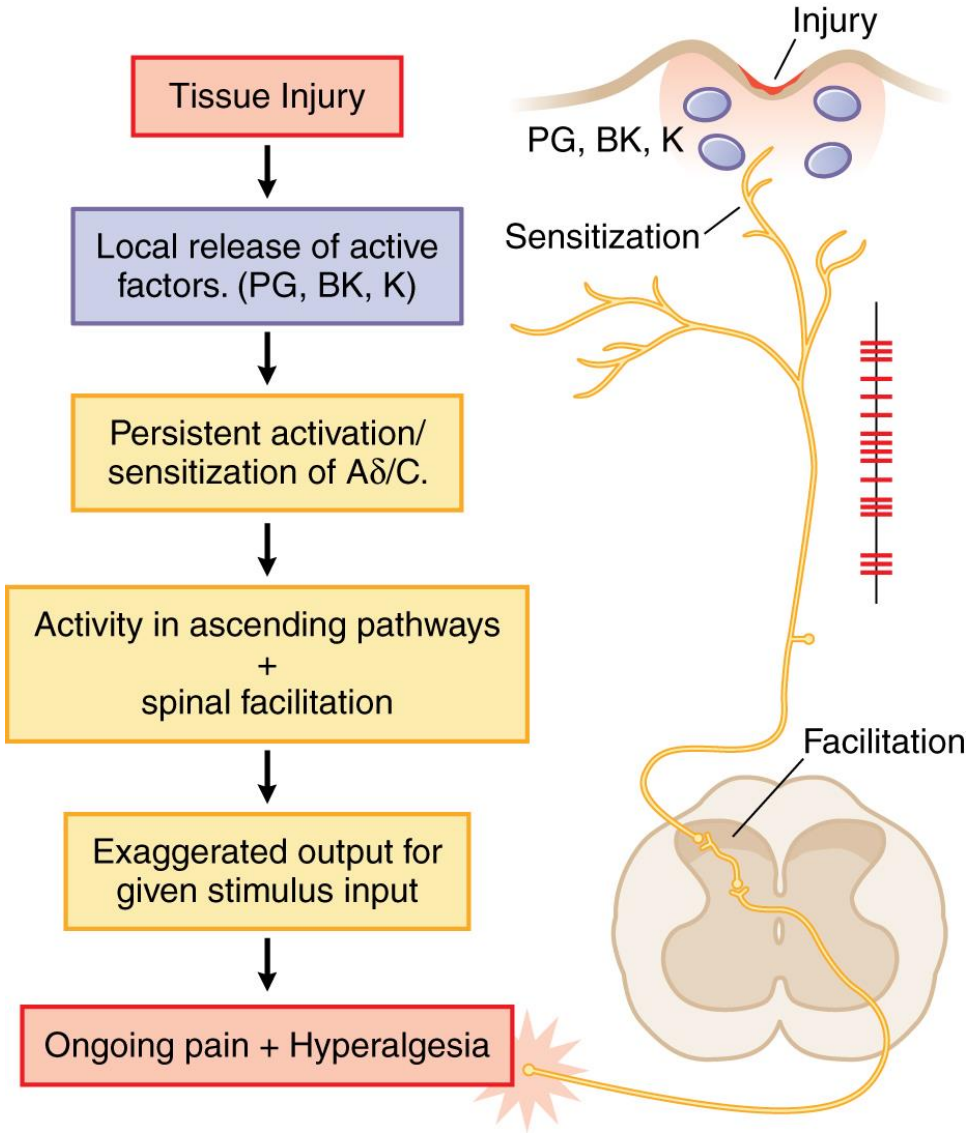
FDA states that tramadol is contraindicated < 12 years of age for pain

Can be prescribed over the phone or electronically per CVS

Not listed in N.C. STOP Act provisions to limit opioids misuse

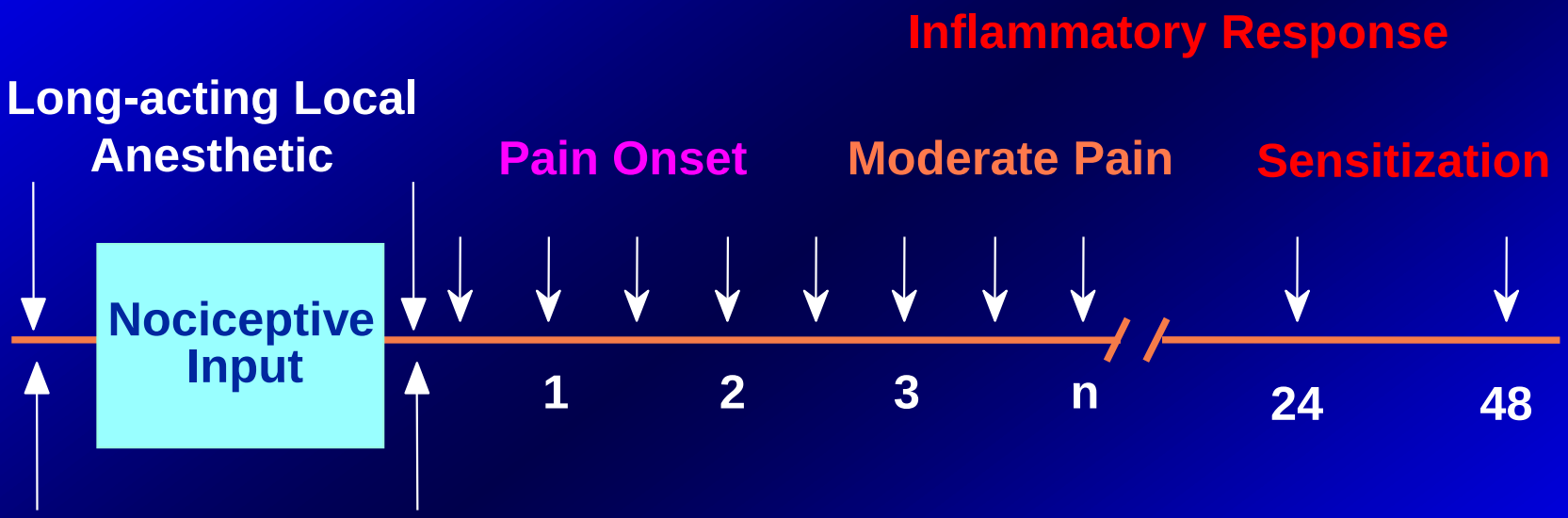
#4 Use the *PAIN* Management Paradigm

- P = **Preventive**
- A = **Anti-inflammatory**
  Acetaminophen
  Anesthetics
- I = **Individualize**
- N = **Narcotics (opioids)**



A milligram of prevention is better than a pound of rehabilitation

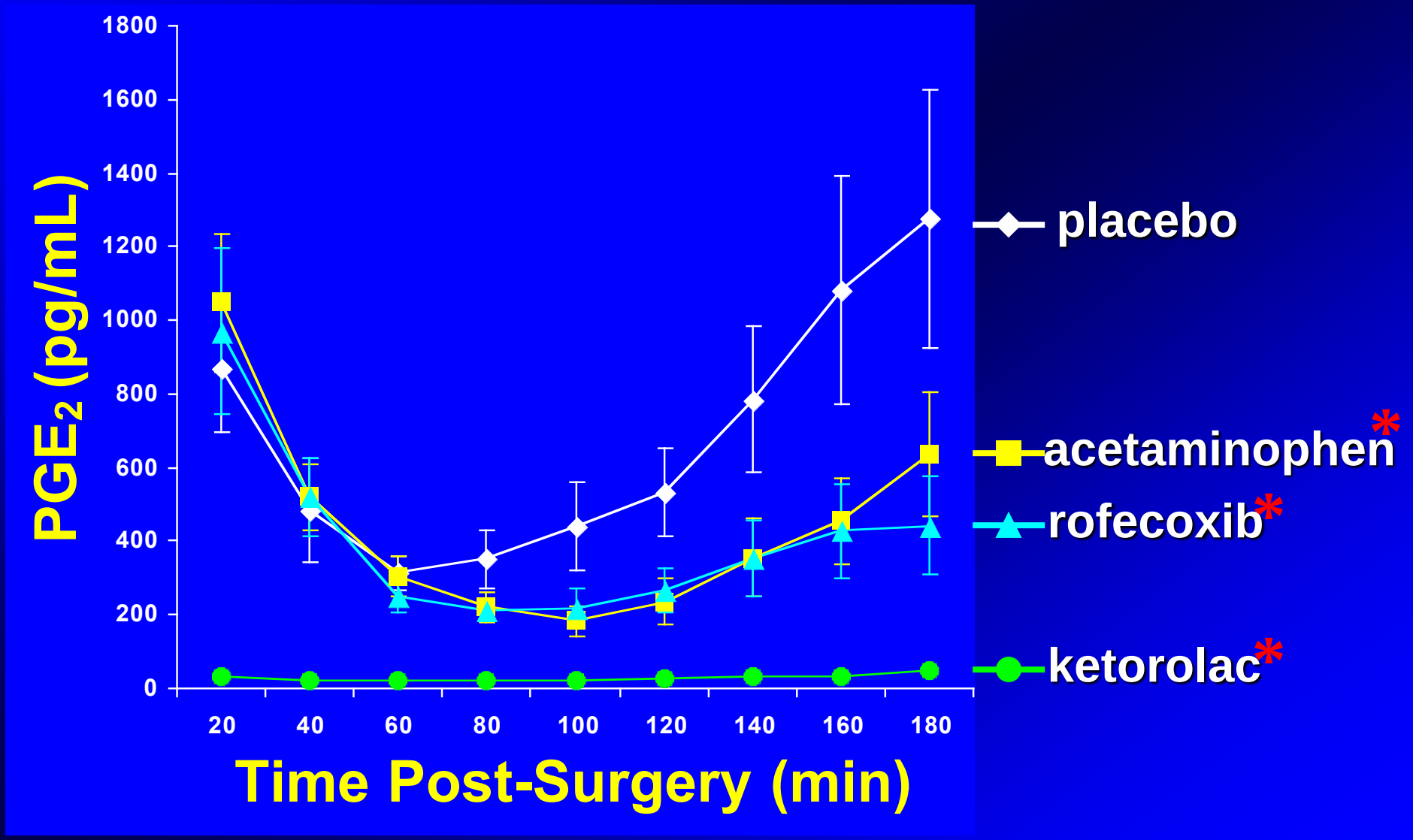
Rationale for Preventive Strategies



5. Use Acetaminophen for Additive Analgesia

- Inhibits Prostaglandin Hydroperoxidase
- Metabolites of acetaminophen act on TRPA1-receptors in the spinal cord to suppress the signal transduction from the superficial layers of the dorsal horn, to alleviate pain.
- One metabolite (AM-404) inhibits Na channels and the reuptake of endogenous cannabinoids

Acetaminophen COX-2 Inhibition



OTC Formulation of Ibuprofen plus Acetaminophen

OTC formulation: 250 mg acetaminophen + 125 mg ibuprofen
Recommended dose: 2 tablets every 8 h, not to exceed 6 tabs in 24 h
Dosing: 500 mg acetaminophen + 250 mg ibuprofen

Recommended OTC doses of each drug alone:

600-650 mg acetaminophen
400 mg ibuprofen ('gold standard')

Criteria for rational analgesic combination:

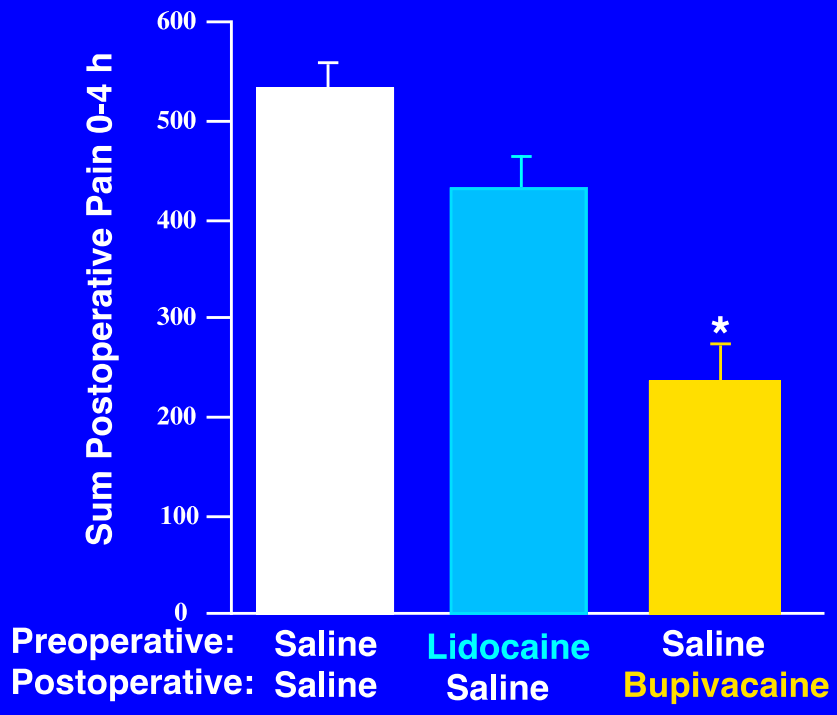
Effective dose of one drug combined with an effective dose of another drug to provide additive analgesia, or
Decrease adverse events by lowering doses of each drug

Clinical Review of FDA Drug Approval Package for Advil Dual Action:

OTC formulation did not differ from 400 mg ibuprofen for pain relief
Adverse events for OTC formulation typical of those for ibuprofen or acetaminophen (nausea, vomiting, dizziness, headache) N=1375 subjects
Manufacturer claims that combination should result in fewer adverse effects than increasing the dose of either agent alone

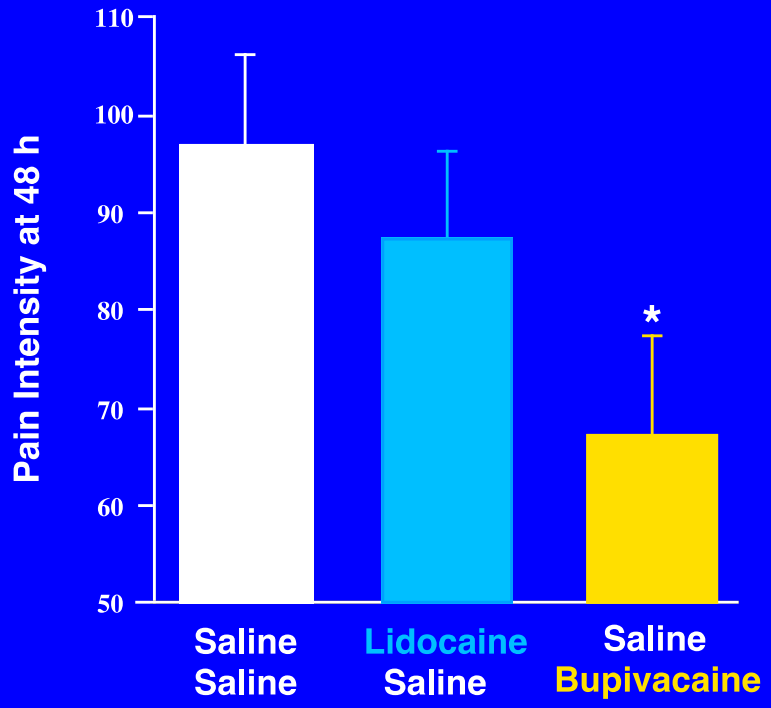
Preventive Effects of Postop Pain Control

Immediate Postop. Pain



* P < 0.001 Bupivacaine drug effect, 2-ANOVA

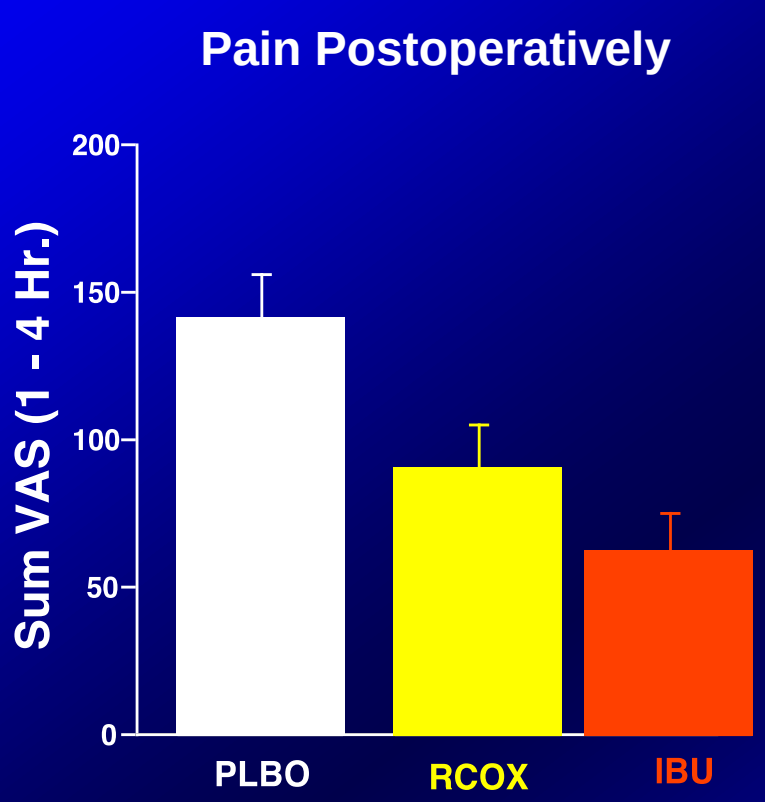
Pain at 48 Hours

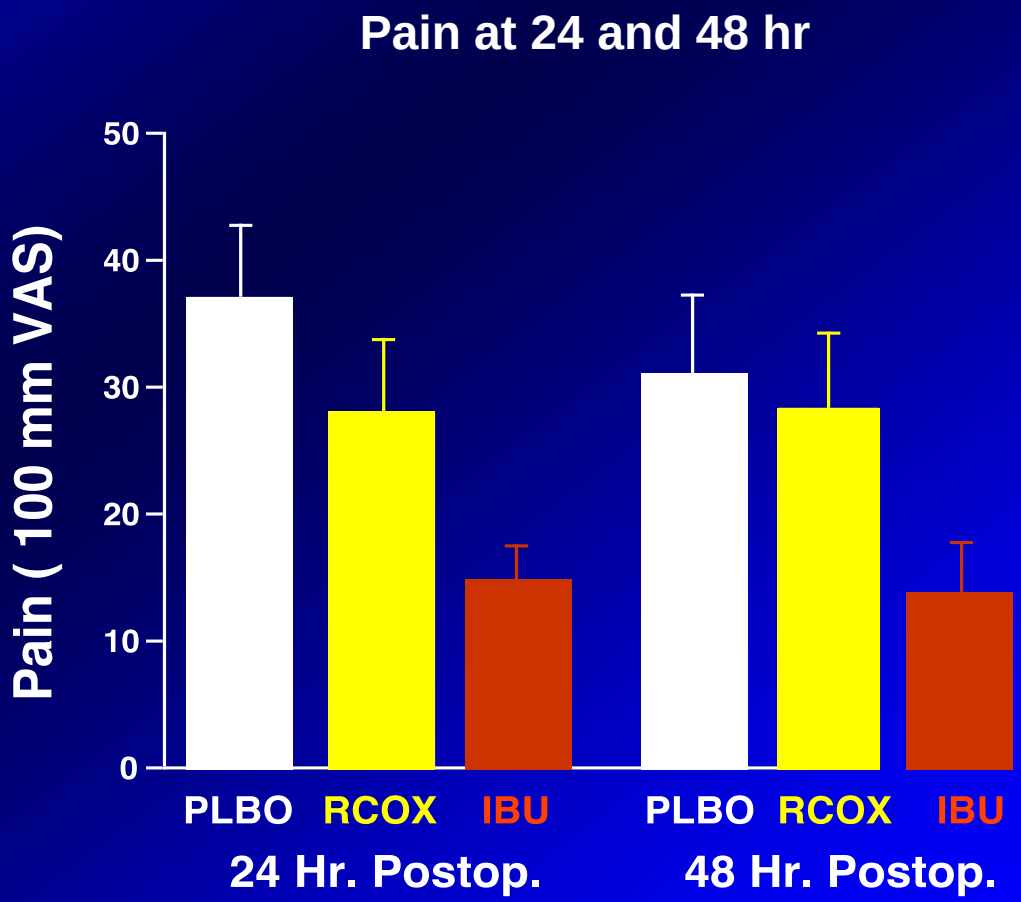


* P < 0.05 Bupivacaine drug effect, 2-ANOVA

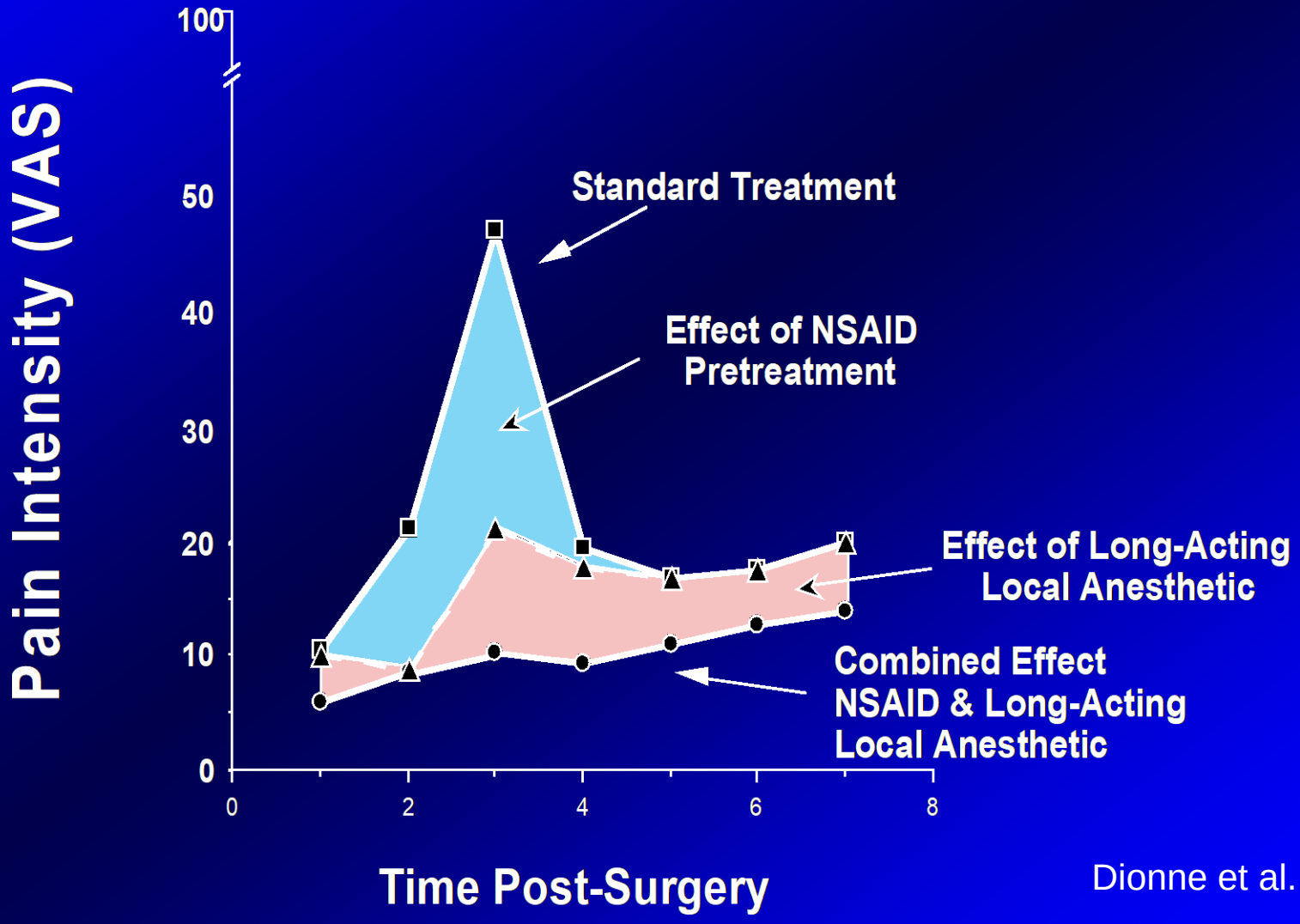
Gordon SM et al. 2002

Dual COX-1/COX-2 Suppression Minimizes Postoperative Hyperalgesia





Additive Preemptive Analgesia for NSAID and Long-Acting Local Anesthetic



Dionne et al. 1984

Comparison of Conventional Approach to Targeted Strategies

	Opioid Combinations	Preventive/Additive/Adaptive
Analgesia	++	+++
Adverse Effects	+++	+
Abuse Potential	+++	0 (without opioid) + (with tramadol) ++ (with oxycodone or hydrocodone)
Overdose Risk	++	0 (without opioid) + (with tramadol) ++ (with oxycodone or hydrocodone)

Relative effects based on well-established pharmacology of drug classes and specific agents in Table 1

Dionne, Gordon, Moore: Compendium 2016; 37:372-378

8. Individualize Prescribing for Acute Pain to Minimize Opioid Misuse or Abuse Based on Procedure, Pain Level and Validated Drugs and Combos

Mild Pain

OTC ibuprofen, naproxen or ketoprofen as needed

Moderate Pain

Ibuprofen 400-600 mg every 4-6 hours by the clock for first 48-72 hours, not to exceed maximum recommended daily dose. As needed until pain subsides

Moderately Severe Pain

Prescription dose of NSAID administered prior to the procedure or immediately afterwards

Administration of long-acting local anesthetic 0.5% bupivacaine with epinephrine for procedural anesthesia and postoperative analgesia

Postoperative administration of prescription dose of NSAID administered by the clock for 48-72 hours combined with administration of acetaminophen 600/650 mg by the clock; the two medications can be given concurrently or alternated to maintain blood levels of both medications

Dionne, Gordon, Moore: Compendium 2016; 37:372-378

Opioid Analgesic Rx Table

Raymond A. Dionne, DDS, PhD

TABLE 1:

Prescribing Options for Acute Pain to Minimize Opioid Misuse or Abuse

Mild Pain
OTC ibuprofen, naproxen or ketoprofen as needed.

Mild to Moderate Pain
Ibuprofen 400-600 mg every 4-6 hours by the clock for first 48-72 hours, not to exceed maximum recommended daily dose. As needed until pain subsides.

Moderately Severe Pain
Prescription dose of NSAID administered prior to the procedure or immediately afterwards. Administration of long-acting local anesthetic 0.5% bupivacaine with epinephrine for procedural anesthesia and postoperative analgesia.

Alternative, if the above recommendation does not relieve pain sufficiently.
Postoperative administration of prescription dose of NSAID administered by the clock for 48-72 hours combined with administration of acetaminophen 600/650 mg by the clock; the two medications can be given concurrently or alternated to maintain blood levels of both medications.

Severe Pain
Provide a prescription of an opioid drug in combination with acetaminophen to be filled and administered only if needed for pain not relieved by regimen for moderately severe pain.

Example: 2 tablets of 325 mg acetaminophen plus 37.5 mg tramadol (Ultracet) every 4-6 hours for pain, not to exceed 8 tablets every 24 hours.

NB: Separate dosing of 600/650 mg acetaminophen needs to be discontinued.

Dionne, Gordon, Moore: Compendium 2016; 37:372-378

TABLE 2:

Comparison of Conventional Approach to Targeted Strategies

	Opioid Combinations	Preventive/Additive/Adaptive
Analgesia	++	+++
Adverse Effects	+++	+
Abuse Potential	+++	0 (without opioid) + (with tramadol) ++ (with oxycodone or hydrocodone)
Overdose Risk	++	0 (without opioid) + (with tramadol) ++ (with oxycodone or hydrocodone)

Relative effects based on well-established pharmacology of drug classes and specific agents in Table 1 ranked on a 0 to ++++ ranking.

Provided by Eastern Dentists Insurance Company (EDIC), April 2018.
The information contained is only accurate to the day of publication and could change in the future.

EASTERN DENTISTS INSURANCE COMPANY
MALPRACTICE INSURANCE | BY DENTISTS, FOR DENTISTS® | WWW.EDIC.COM

Checklist for Prescribing Opioids for Acute Dental Pain

When Considering Opioids for Short-Term Management of Acute Pain

- ✔ Estimate pain intensity and duration associated with procedure
- ✔ If the pain is due to acute inflammation, can it be suppressed with anti-inflammatory drugs; opioids do not have any acute anti-inflammatory actions
- ✔ Inform the patient and family members of the risks of opioids: increased incidence of nausea, vomiting and drowsiness, possible risk of misuse leading to dependence, risk of death due to opioid overdose
- ✔ Evaluate the risk of harm or misuse:
  - History of substance use disorder including marijuana, alcohol, cocaine, and stimulants
  - History of mental health conditions such as depression or anxiety
  - Concurrent benzodiazepine use
  - Check the Prescription Drug Monitoring Program (PDMP) data
- ✔ Set criteria for using opioids for therapeutic intent:
  - Follow instructions for dose and dosing interval
  - No replacement for lost medications
  - Only provide a 2-3 day supply
  - No refills provided without a clinical exam
  - Discuss the greater safety of tramadol in comparison to oxycodone and hydrocodone
  - Requests for specific opioid drugs will be considered as drug seeking
  - Do not expect total pain relief, e.g., meaningful pain relief is a 50% reduction
  - Instruct the patient and family member on safe storage and disposal of opioid drugs
- ✔ Educate the patient that non-opioid drugs such as ibuprofen, naproxen and ketoprofen are more effective for post-surgical pain than opioid combination drug formulations.

When reassessing the need for additional opioids

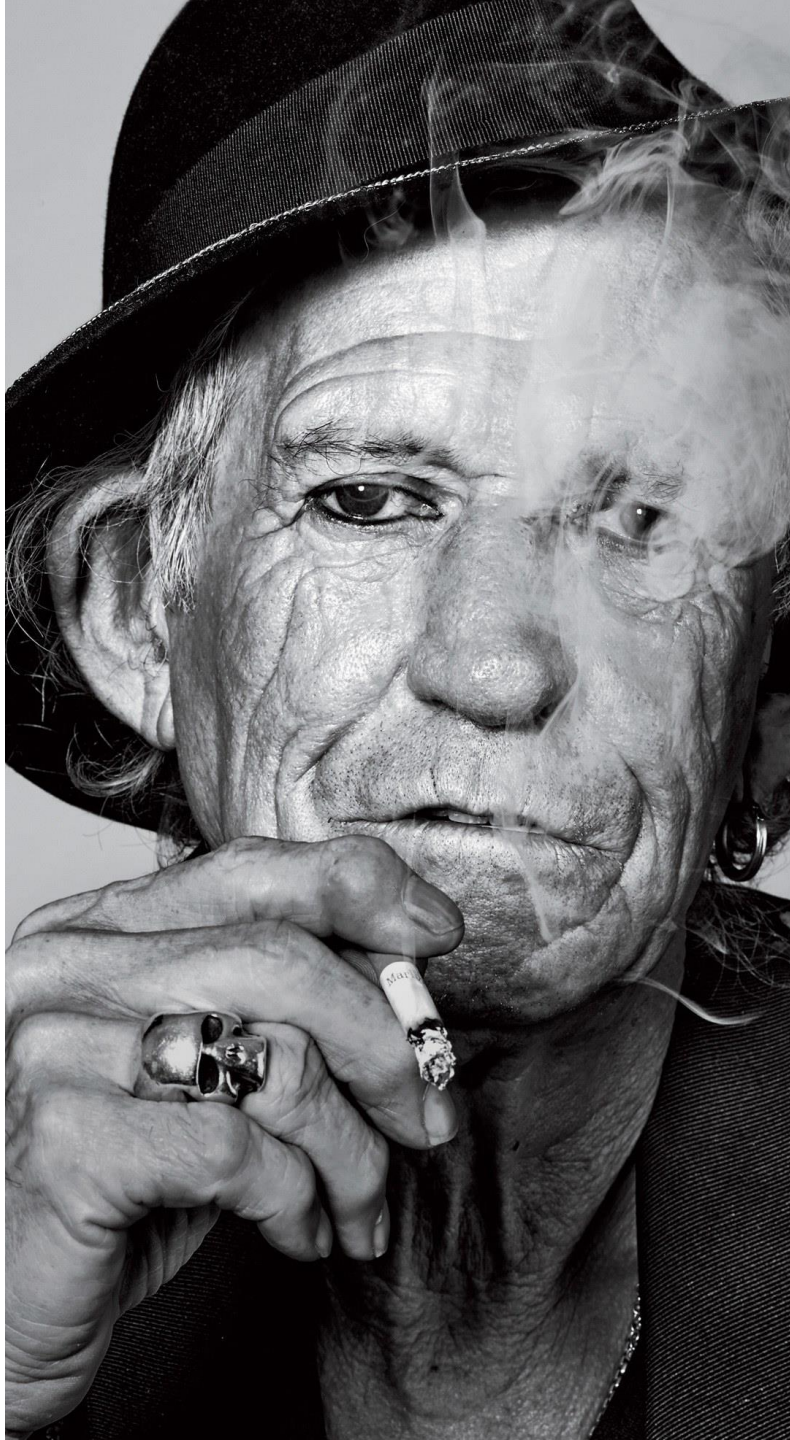
- ✔ Assess the need for additional opioids based on clinical exam and the usual 2-3 day time course of acute inflammatory pain
- ✔ Evaluate the risk of harm or misuse due to drug-seeking
- ✔ Check the PMDP for any other opioid prescriptions since initial visit
- ✔ Check that nonopioid medications are optimized and taken as prescribed
- ✔ Evaluate other possible causes of pain report: infection, nerve damage, alveolitis

Modified from Checklist for Prescribing Opioids for Chronic Pain, Centers for Disease Control, US Department of Health and Human Services, www.cdc.gov/drugoverdose/prescribing/guidelines

How to identify drug seeking behavior?

- **Drug being requested**: opioids, benzodiazepines, methylphenidate, dexamphetamine, anabolic steroids, anti-psychotic drugs
- **Asking for a specific drug** by name or brand name
- **Claiming allergy** to alternative drugs
- Doctor shopping
- **Anger** when questioned about symptoms such as pain
- **Unscheduled** clinic visits for **refills**
- Unauthorized **dose escalation**
- Claiming to be **unable to afford dental work** needed to manage dental pain
- **Multiple visits** for the same complaint
- **More concerned** about the **drug** than medical/dental **problem**

How can we identify vulnerability for developing an SUD prior to Rx?



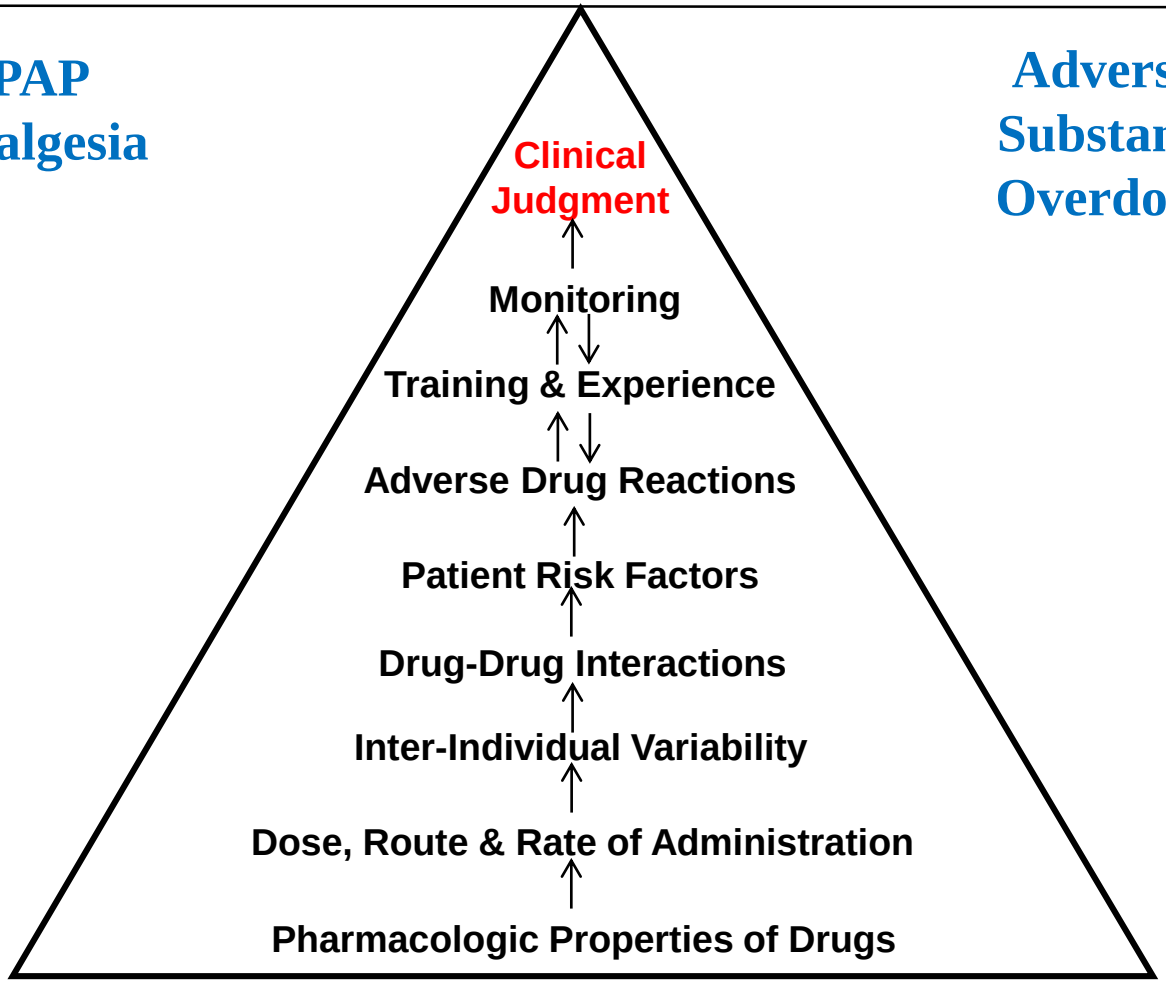
Determinants of Safe, Effective, and Patient-Centered Therapeutics

Therapeutic Efficacy

Patient Safety & Needs

NSAIDS, APAP
Preventive Analgesia

Adverse Events
Substance Abuse
Overdose Deaths



'Meaningful pain relief' ~ 50% decrease from starting pain