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

Raymond Dionne, DDS, MS, PhD
Professor of Cell Biology
University of Connecticut School of Medicine

Educational Objectives:
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

- **Wave 1:** Rise in Prescription Opioid Overdose Deaths
- **Wave 2:** Rise in Heroin Overdose Deaths
- **Wave 3:** Rise in Synthetic Opioid Overdose Deaths

**Other Synthetic Opioids**
e.g., Tramadol and Fentanyl, prescribed or illicitly manufactured

**Heroin**
Commonly Prescribed Opioids
Natural & Semi-Synthetic Opioids and Methadone

With unprecedented availability of cheap heroin and fentanyl...

MORE PEOPLE ARE DYING

Opioid Potency

- Carfentanil: 10,000x
- Fentanyl: 100x
- Heroin: 2x
- Morphine: 1x
‘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 Jeffrey 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

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

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

**Major Drug Classes**

- **1950's**
  - narcotics
  - aspirin
  - acetaminophen
  - adjuncts

- **1960's**
  - opioids
  - NSAIDs
  - acetaminophen
  - adjuncts

- **1970's**
  - opioids
  - NSAIDs
  - acetaminophen
  - adjuncts

- **1980's**
  - opioids
  - NSAIDs
  - acetaminophen

- **1990's**
  - opioids
  - NSAIDs
  - acetaminophen
  - coxibs
  - antidepressants
  - anticonvulsants
  - opioids
  - NSAIDs
  - acetaminophen

- **2000's**
  - NSAIDs
  - opioids
  - acetaminophen
  - gabapentin

- **2020**
  - Ibuprofen + Acetaminophen marketed OTC (Advil Dual Action)

**Milestones**

- Placebo response
- Category scales
- Clinical trials methodology
- Opiate receptor
- Aspirin MOA
- Dental model
- Endogenous pain inhibitory system
- Gender, Genetics
- Imaging
- Pharmacogenomics
- Gene expression
- Proteomics
- Opioid OD epidemic
- PRO's Phenotyping
- Personalized medicine

**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**

**Clinical Pain (3rd Molar Extraction)**

V**ariability 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*

*Kim H et al., Pain 2004*
Challenges in Pain Management: Many Other Factors Influence the Efficacy of a Drug at the Level of Individual Patients

Rare    Atypical    Common Variability    Atypical    Rare

-3       -2           -1             \( \bar{x} \)             +1        +2       +3

Sociocultural Influences, **Expectations**, Prior Experiences, Idiosyncrasy

Neuroendocrine Functions, Autonomic Function, Stress Response

Physiologic Augmentation & Descending Modulation: **Inflammation**, Plasticity

Protein Expression & Modification

Epigenetic Modification

“Pain” Genes, \( n > 400 \)

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
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

Ongoing pain + Hyperalgesia
NSAID Prior to Tissue Injury Suppresses COX


Graph showing the suppression of prostaglandin E2 (pg/mL) over time post-surgery (mins) for Placebo, Celecoxib, and Ibuprofen.
Need to Balance GI and Cardiovascular Adverse Effects

Cardiovascular Risk
- Thrombosis, Myocardial infarction
- Discontinuation
- Blood pressure increase

Gastrointestinal Risk
- Bleeding, Ulcer complications
- Discontinuation

Degree of Selectivity
- COX-2
- COX-1

Drugs:
- Etoricoxib
- Rofecoxib
- Celecoxib
- Diclofenac
- Ibuprofen
- Naproxen
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’
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
‘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

![Graph showing pain relief VAS over time with annotations and bar chart showing adverse events. The graph indicates that ibuprofen 400 and 10 Oxycodone have similar pain relief effects compared to ibuprofen 400 alone. The bar chart shows a significant increase in drowsiness compared to nausea and vomiting. * P < 0.05 vs. Ibuprofen 400]
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

Long-acting Local Anesthetic

Nociceptive Input

Pre- or Post-op Anti-inflammatory

Inflammatory Response

Pain Onset

Moderate Pain

Sensitization

1 2 3 n

24 48

+ / - Opioid
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

PGE$_2$ (pg/mL)

Time Post-Surgery (min)

- placebo
- acetaminophen
- rofecoxib*
- ketorolac*
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**

- **Preoperative:** Saline, Postoperative: Saline, Lidocaine, Saline, Bupivacaine

- **Sum Postoperative Pain 0-4 h**
  - Saline: 500
  - Lidocaine: 300
  - Bupivacaine: 200

* P < 0.001 Bupivacaine drug effect, 2-ANOVA

**Pain at 48 Hours**

- **Pain Intensity at 48 h**
  - Saline: 100
  - Lidocaine: 90
  - Bupivacaine: 60

* P < 0.05 Bupivacaine drug effect, 2-ANOVA

Gordon SM et al. 2002
Dual COX-1/COX-2 Suppression Minimizes Postoperative Hyperalgesia

Pain Postoperatively

Sum VAS (1 - 4 Hr.)

PLBO  RCOX  IBU

Pain at 24 and 48 hr

Pain (100 mm VAS)

PLBO  RCOX  IBU

24 Hr. Postop.

PLBO  RCOX  IBU

48 Hr. Postop.
Additive Preemptive Analgesia for NSAID and Long-Acting Local Anesthetic

Dionne et al. 1984
Comparison of Conventional Approach to Targeted Strategies

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

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

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.

**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 regimens 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.

**TABLE 2:**
Comparison of Conventional Approach to Targeted Strategies

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

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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

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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

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.
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

- NSAIDS, APAP
- Preventive Analgesia
- Clinical Judgment
- Monitoring
- Training & Experience
- Adverse Drug Reactions
- Patient Risk Factors
- Drug-Drug Interactions
- Inter-Individual Variability
- Dose, Route & Rate of Administration
- Pharmacologic Properties of Drugs

Patient Safety & Needs

- Adverse Events
- Substance Abuse
- Overdose Deaths

‘Meaningful pain relief’ ~ 50% decrease from starting pain