The Opioid Epidemic: Clinical Dental Update

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The Opioid Epidemic

Clinical Dental Update 2018

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Opium Empire
Opioids and their mechanism of action

Types of Opioids

- **Natural** (derived from opium): morphine, codeine
- **Endogenous** (in your body): endorphins
- **Synthetic**: Heroin, oxycodone (Oxycontin®), hydrocodone (Vicodin®), methadone, fentanyl, remifentanil (Ultiva®), Percocet® (oxycodone + acetaminophen)

Side effects: Sedation, constipation, respiratory depression, nausea, euphoria, severe withdrawal
Clinical Pain management

- **Acute Pain**: moderate to severe acute pain – acetaminophen and/or an NSAID may be the most effective, with immediate release opioids used if severe
  - Use of extended-release or long-acting opioids initially and for >1 wk associated with increased risk of unintended long-term use\(^1,2\)

- **Chronic (‘second pain’) management** by reducing the perception of pain and increasing pain tolerance
  - Approved for severe chronic cancer pain
  - Chronic non-cancer pain is controversial due to limited evidence of efficacy, risk of overdose and abuse, and development of tolerance\(^3\)
  - Non opioid drugs appear to be equally effective\(^4\)

- **Neuropathic Pain**: antidepressant or antiepileptic can be used (combined for synergy)
  - Opioids are not recommended

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Pain management: dependence and tolerance

- Pain
  - Increased perception of pain (hyperlgesia)
  - Anger, Anxiety, fear, distress
  - Further activity avoidance
  - Over reliance on medication
  - Hyperalgesia
  - Depression and Anxiety
  - More medication

- Psychological Dependence
  - Progressive Deconditioning and Muscle Tension
  - Insomnia

- Tolerance to Pain Medication
  - Activity Avoidance
  - Pain with decreasing activity
  - More medication
  - Fatigue

- Physical Dependence
  - More medication
Opioids produce physical dependence and severe withdrawal, but risk of relapse remains high beyond physical withdrawal signs.

Symptoms Peak
- Nausea
- Vomiting
- Stomach Cramps
- Diarrhea
- Insomnia
- Tremors
- Irritability
- Drug Craving

Opiate Withdrawal Timeline
- Last Dose
- Symptoms Begin
- 6-12 hours Short-Acting Opiates
- 30 hours Long-Acting Opiates
- 72 hours

Courtesy of the American Addiction Centers
Management of opioid withdrawal and abuse

Methadone
• long-lasting opioid with reduced euphoric effects
• Outpatient daily distribution
• Correct dose can prevent withdrawal symptoms and ease drug craving

Naltrexone
• Opioid receptor antagonist
• Can NOT ease withdrawal symptoms or cravings but can prevent subsequent “highs”
• No abuse liability
• Must start after detox period
• Taken orally or by injection

Lofexidine
• First FDA approved non-opioid based medication
• selective alpha 2-adrenergic receptor agonist that reduces the release of norepinephrine
• Specific for treating withdrawal symptoms but NOT abuse disorder
Management of opioid withdrawal: buprenorphine

- Mu opioid receptor partial agonist and a kappa-opioid receptor antagonist.
- Withdrawal management performed in outpatient setting
- Use caution when patients are taking SSRIs (Serotonin Syndrome)
- Advantages: long-lasting and administered without clinic visits, Schedule II (lower abuse potential)
The growing opioid ‘epidemic’

- Estimated 26-36 million abuse opioids worldwide
- 2.1 million Americans abused prescription opioids in 2012
  - Jump from 79 million (1992) to 212 million Rx (2012)
- Estimated 467,000 Americans addicted to heroin

Drug overdose deaths, 1980 to 2016

NY Times (June 2015)
Wisconsin’s opioid ‘epidemic’

- 2,900 overdose related incidents, with 304 deaths in Milwaukee county alone last year
Men more likely to report using heroin in the past year, but rate at which women are using heroin has increased 100% in last 7 years.

During abstinence, women report greater craving\textsuperscript{14-17} and are more likely to relapse compared to men.

Women escalate drug use more rapidly than men and exhibit greater tendency to experience a shift in loss of voluntary control of drug intake to compulsive drug use more rapidly in females.
Data suggests that addiction ultimately impairs participation, in part because addiction-related criminality and associated consequences of a felony record can drastically reduce employment possibilities.
Impact of opioid epidemic on labor force

Combined Effect of Opioid Prescription Rates and Change in Labor Force Participation Rate
Prime Age Adults, Ages 25–54
Impact of opioid epidemic on human longevity (life span)

Life is Shorter
Life expectancy drops for the second consecutive year, reversing steady increases

Source: CDC
Economic impact of the epidemic

Costs of the Opioid Epidemic by Year and Type

$1 Trillion Total

Projected burden at current rates

$500 Billion

*Data between labeled estimates interpolated using constant growth rates*
Some states have more opioid prescriptions per person than others.

Number of opioid prescriptions per 100 people

- 52-71
- 72-82.1
- 82.2-95
- 96-143

SOURCE: IMS, National Prescription Audit (NPA™), 2012.
Decline of opioid prescription fill rate by state (2013-2017)

2017 report from Blue Cross Blue Shield

483% increase from 2010
Epidemic has moved beyond prescription opioids

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

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

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### Days’ Supply

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<td>5.32</td>
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<td>56-64</td>
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- 31% of the opioids prescribed for all age groups were associated with nonsurgical dental visits.

- Combination of ibuprofen and acetaminophen can be more effective than opioids, with fewer adverse effects (for 3rd molar extractions).

- Dental prescriptions on the decline since 1999 (15.5%) vs. 2015 (6.8%)

Gupta et al., *JADA* (2018)
Overview of what got us here…

- Pharmaceutical companies:
  - Lack of appropriate study and information reporting
  - Lobbyists (incentives, scare tactics, deception)

- Insurance company lack of regulations contributing to the problem (Utilization Management)
  - “Quantity limits” not following CDC recommendation
  - Lack of required “step therapy” (only 9% of Medicaid plans, 4% of commercial)
  - Lack of “prior authorization”
  - Low cost (74% in Tier 1)

- Clinicians
  - Prescription overwriting/lack of monitoring
  - Lack of coordinated strategies following drug cessation
  - Lack of non-opioid receptor based withdrawal therapies

- Increased development of synthetic opioids and distribution of “impure” street drugs

- General public apathy (until now) and lack of public education (especially youth)
What neuroscience has taught us about drug addiction

• Progressive, chronic relapsing disorder

• Compulsive drug seeking and use, despite harmful consequences.

• Considered a brain disease because drugs produce enduring changes in the structure and function of the brain that can lead to the harmful behaviors seen in people who abuse drugs.

• Biological, psychological, and social influences in development of addiction

• Preclinical understanding of opioid-related changes in the brain is far less than other abused drugs (psychostimulants)

Source: From the laboratories of Drs. N. Volkow and H. Schelbert
Stages of the Addiction Cycle

First Drug exposure euphoria

Increased desire for the drug and the euphoria

Preoccupation with obtaining the drug/craving

Psychological problems and compromised social, work and family activities

Drug-induced adaptations in receptors/signaling

Development of Dependence/Tolerance

Binge/Intoxification

Withdrawal

1-YR RELAPSE RATES ESTIMATED TO BE CLOSE TO 40%

RELAPSE
Determinants of susceptibility to and intensity of addiction

- Mental illness
- Parent’s use
- Gender
- Pattern/duration of drug use
- Stress
- Chaotic home/abuse
- Parent’s use/attitudes
- Peer influences
- Community influences/attitude
- Education

DRUG USE
ENVIRONMENT
GENETICS
Our experiences produce long-lasting changes in the strength of connections between neurons that make up circuits.

Neurons communicate by releasing neurotransmitters that are released from one and bind to a receptor on another.
Drug-induced changes in reward circuits drive development and persistence of addiction behavior.

Opioids increase dopamine by disinhibiting dopamine neurons

**Before drug use**

**After drug use**

Drug-seeking/taking behavior becomes well learned and driven by enhanced strength within glutamate prefrontal cortex-nucleus accumbens circuits.
Prefrontal cortex exerts top-down control of behavior and emotion

- Decision-making
- Inhibitory behavior
- Goal-directed (motivated) behavior
- Making learned associations
Dichotomous role of altered PFC function in addiction

Social Use → ‘Regulated relapse’ → Uncontrollable drug-taking

Prefrontal Cortex
Inhibitory Control

Cortico-striatal (dorsal striatum) habit circuitry

The inability to control drug intake likely involves a pathological strengthening of behaviors and conditioned associations as well as an impaired capacity to control behavior.
Opioid self-administering female mice exhibit reduced activation of prefrontal cortex neurons on a faster time scale than male mice.

‘Hypo’frontality aligns with deficits in cognitive control over behavior.
Finding new uses for old drugs to treat addiction

Antibiotic administration during withdrawal can produce changes in the brain that reverse effects of opioids.

Ceftriaxone + behavioral (extinction)

Opioid Reward

Opioid Relapse

Prefrontal Cortex Neuron

Nucleus Accumbens Neuron
New technology to treat addiction: controlling neuron activity to reverse opioid-related changes

Stimulation of neurons in the PFC-NAc circuit
Reverse changes made by opioids

Light on

Non Prefrontal Cortex Neuron
Prefrontal Cortex Neuron
Nucleus Accumbens Neuron

Opioid Reward
What to do moving forward?

- Evaluate better/alternative means of regulation
  - Absolute limits vs more rigid restrictions and education of clinicians

- Increase education amongst adolescents and adults

- More coordination amongst clinicians and preclinical researchers
  - Model development
  - Impact of pain itself on the brain
  - Development of alternative therapies to target withdrawal and relapse
Moving forward: treatment considerations

- Opioid therapy should be considered only if expected benefits for pain and function are anticipated to outweigh risks to the patient

- Immediate release formulations should be started at the lowest effective dose

- Treatment goals for pain and function should be established before starting therapy

- If pain relief is inadequate, opioid therapy is poorly tolerated, or there is evidence of misuse, treatments should be optimized and opioids should be tapered to a lower dosage or tapered discontinued

- Opioid antagonist naloxone should be offered to patients at risk for opioid overdose

- CYP2D6 gene expression
  - CYP2D6 poor metabolizers -- (up to 10% of the population) or those taking drugs that inhibit CYP2D6 (fluoxetine) may not be able to convert codeine to morphine and experience analgesic effects
  - CYP2D6 ultra-rapid metabolizers rapidly convert to higher than usual levels of morphine and may be at risk for toxicity