The Opioid-Pain Nexus: Safe Opioid Prescribing at this Cultural Moment

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Nothing to Disclose
Director, Opioid Stewardship Program
Director, Comprehensive Pain Management
US Opioid Prescribing
~30% of World’s Opioids, ~5% World’s Population

Prescription Opioid Analgesics

Units Dispensed
(e.g., tablets, patches, milliliters, blue bars)

Oral morphine equivalents
(in metric tons, green bars)

FDA and IQVIA 2018
✓ Poor Illicit Quality Control
✓ Also ↑ Cocaine & Meth
✓ Polypharmacy
✓ ↓ Life Expectancy (3 yrs.)

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

Polypharmacy

Alcohol in 7-22% also

Regional Variation in Overdose Deaths
2014-2016 c/w 2002-2004

Monnat 6/20/19. Institute for New Economic Thinking

Economic Distress + Opioid OD Deaths
Motivation & Reward

Mesocorticolimbic Circuitry

- Natural Rewards
- Addiction
- Mood
- Chronic Pain
- Sleep

PRIORITIZING
Prefrontal cortex

Hedonic Valuation
Hedonostat

Opioids
LIKING

Dopamine
WANTING (drive)

Cingulate gyrus
(ACC)

Striatum

Substantia nigra

Ventral tegmental area

Hyman et al. 2006, modified
Neurocircuitry of Addiction

Hyman et al. 2006
Substance Use Disorder Risks

Exposure, Gateway, Common Liability Models of Susceptibility

- **Exposure** (% SUD in NMU)
  - EtOH 9%, MJ 11%, Heroin 67%
  - Rx Opioid Abusers → OUD 16%

- **Genetics** 40-70%

- **Epigenetics** – ACEs & stress

- **Adolescence** – impulsivity, PFC fxn

- **SUD & Mental Health Conditions**
  - >40% with SUD had MHC
  - Multiple SUDs common

- **Context** – McCabe et al. Pain 2016
  - Medical use only in HS seniors NOT associated w/ SUD at 35
  - NMUPO + Medical AOR 1.49, NMUPO only 2.61 for SUD Sx
  - SUD most commonly AUD

*Facing Addiction in America, HHS, 2016*
2011 IOM: *Relieving Pain in America*

- Major public health problem
- 100 million adults
- $635 billion/year
- $19.5 billion/year for children

2016 National Pain Strategy
New IASP Pain Definition

An aversive sensory and emotional experience typically caused by, or resembling that caused by, actual or potential tissue injury

Notes:
1. Always subjective and biopsychosocial
2. Pain and Nociception are different phenomena
3. Learn concept of pain and its applications through experiences
Pain Processes & Pathways

- Learning
- Action
- Interpretation
- Perception
- Modulation
- Transmission
- Transduction
Opioids for CNCP?

- Nociception & Pain Perception - opioids affect both
- Cochrane Review, Noble et al. 2010: weak evidence of significant pain relief, inconclusive fxn & QOL
- Annals of IM, Chou et al. 2015: No long-term opioid studies (similar to other analgesics); unable to evaluate pain, fxn, QOL outcomes

- Neuropathic pain – improved efficacy with longer duration Tx
  - Lancet Neurology, Finnerup et al. 2015 – tramadol 2nd & strong opioids 3rd line
  - Pain Physician, Howard 2012 – methadone (NMDA), buprenorphine, Nav blockers

- Inflammatory Pain – later stages may be opioid responsive
- German Guideline: contraindicated for primary HA and Functional PS (e.g., FM, IBS)
CDC Opioid Guideline
for Adults with Chronic Pain – 2016

Cornerstone for regulations and statutes, e.g., new TJC standards

Increasing pushback occurring

Recommendation 1
Opioids Are Not First-Line Therapy

Recommendation 2
Establish Goals for Pain and Function

Recommendation 3
Discuss Risks and Benefits

Recommendation 4
Use Immediate-Release Opioids When Starting

Recommendation 5
Use the Lowest Effective Dose
50 MME/day, 90 MME/day

Recommendation 6
Prescribe Short Durations for Acute Pain
3 days, 7 days

Recommendation 7
Evaluate Benefits and Harms Frequently

Recommendation 8
Use Strategies to Mitigate Risk

Recommendation 9
Review PDMP Data

Recommendation 10
Use Urine Drug Testing

Recommendation 11
Avoid Concurrent Opioid and Benzodiazepine Prescribing

Recommendation 12
Offer Treatment for Opioid Use Disorder
Pain Management Best Practices
HHS Inter-Agency Task Force Report – May 2019

Acute and Chronic Pain Management: Individualized, Multimodal, Multidisciplinary

Medication
Restorative Therapies
Interventional Procedures
Behavioral Health Approaches
Complementary & Integrative Health

Risk Assessment
Stigma
Access to Care
Education

Medications Section

Common Classes of Pain Management Medications

- Acetaminophen
- NSAIDs
- Anticonvulsants
- Antidepressants
- Musculoskeletal Agents
- Anxiolytics
- Opioids

This list is not exhaustive

Deprioritized, not eliminated

Opium & Opiates

- Opium is dried latex from seed pod of opium poppy (Papaver somniferum)
- Phenanthrene alkaloids
  - Morphine (12%)
  - Codeine
  - Thebaine (semi-synthetics)
# Exogenous Opioids

<table>
<thead>
<tr>
<th>Opium-Derived Phenathrenes (opiates)</th>
<th>Fully Synthetic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>Phenylpiperidines</td>
</tr>
<tr>
<td>Thebaine</td>
<td>Codeine</td>
</tr>
<tr>
<td>Codeine§*</td>
<td></td>
</tr>
<tr>
<td>Hydrocodone</td>
<td></td>
</tr>
<tr>
<td>Oxycodone</td>
<td></td>
</tr>
<tr>
<td>Hydromorphone</td>
<td></td>
</tr>
<tr>
<td>Oxymorphone</td>
<td></td>
</tr>
<tr>
<td>Buprenorphine</td>
<td></td>
</tr>
<tr>
<td>Naloxone</td>
<td></td>
</tr>
<tr>
<td>Nalbuphine</td>
<td></td>
</tr>
<tr>
<td>Naltrexone</td>
<td></td>
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</tbody>
</table>

§ Naturally-derived; other opium-derived are semi-synthetic  
* Prodrugs, CYP2D6 metabolism – new FDA contraindication/warning (<12,T&A, OSA)
# Endogenous Opioid System

<table>
<thead>
<tr>
<th>Precursors</th>
<th>Ligands</th>
<th>Receptors</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pro-opiomelanocortin</td>
<td>β-endorphin</td>
<td>μ/MOR</td>
<td>HPA+, analgesia, acupuncture, massage, placebo, stress opponent</td>
</tr>
<tr>
<td>(also ACTH, MSH)</td>
<td>(also also ACTH, MSH)</td>
<td>κ/KOR δ/DOR</td>
<td></td>
</tr>
<tr>
<td>Pro-enkephalin</td>
<td>Enkaphalins</td>
<td>δ (also μ)</td>
<td>GI motility, less respiratory depression</td>
</tr>
<tr>
<td>Pro-dynorphin</td>
<td>Dynorphins</td>
<td>κ</td>
<td>Dysphoria, μ opponent, mood</td>
</tr>
<tr>
<td>Pro-nociceptin</td>
<td>Nociceptin</td>
<td>NOR</td>
<td>Pain threshold modulation</td>
</tr>
<tr>
<td>?</td>
<td>Endomorphins</td>
<td>μ</td>
<td>Analgesia selective, fewer SEs</td>
</tr>
</tbody>
</table>

Spinal Cord: μ 70%, δ 20%, κ 10%
Opioid Mechanism of Action

G-Protein Coupled Receptors

$\downarrow$Ca$^{2+}$ influx  $\uparrow$K$^+$ efflux  $\downarrow$cAMP

Inhibition

1. Opioid agonist G-protein activation
2. Receptor phosphorylation
3a. Arrestin recruitment
3b. Internalization
4. MAPK Signaling
5. Recycling

$\downarrow$Ca$^{2+}$ influx  $\uparrow$K$^+$ efflux  $\downarrow$cAMP

Transcriptome $\Delta$

Al-Hasani et al. 2011
# Receptor/Channel Affinity

<table>
<thead>
<tr>
<th>Drug</th>
<th>MOR</th>
<th>KOR</th>
<th>DOR</th>
<th>NOP</th>
<th>NE</th>
<th>5HT</th>
<th>NMDA</th>
<th>QT</th>
<th>Metabolism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>+++</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>UGT2B7 [➔M6G, M3G]</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>++</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>UGT2B7</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CYP3A4, CYP2D6</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CYP2D6, CYP3A4</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>+++</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CYP3A4</td>
</tr>
<tr>
<td>Methadone</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
<td>-</td>
<td>Yes</td>
<td>CYP3A4, CYP2B6, CYP2C8, CYP2C19, CYP2D6, CYP2C9</td>
</tr>
<tr>
<td>Levorphanol</td>
<td>+++</td>
<td>++</td>
<td>++</td>
<td></td>
<td>+</td>
<td>+</td>
<td>--</td>
<td></td>
<td>UGT2B7*</td>
</tr>
<tr>
<td>Tramadol</td>
<td>+</td>
<td></td>
<td></td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td>CYP2D6*, CYP3A4</td>
</tr>
<tr>
<td>Tapentadol</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td>UGT1A9, UGT2B7, CYP2C9/19 (no active metabolites)</td>
</tr>
</tbody>
</table>

*UGT1A9, UGT2B7, CYP2C9/19 (no active metabolites)

**METABOLISM**

- **MOR**: Opioid Receptor
- **KOR**: Kappa Opioid Receptor
- **DOR**: Delta Opioid Receptor
- **NOP**: Nueral Opioid Receptor
- **NE**: Norepinephrine
- **5HT**: Serotonin
- **NMDA**: N-Methyl-D-aspartate
- **QT**: QT Interval

**Notes**
- UGT2B7: Uridine Diphosphate Glucuronosyltransferase 2B7
- CYP3A4, CYP2B6, CYP2C8, CYP2C19, CYP2D6, CYP2C9: Cytochrome P450 Enzymes
Dependence

Abstinence Syndrome

- Onset: 8-12 hrs (IR drugs)
- Peak: 2-4 days
- Duration: 7-10 days (IR)
- Anxiety/Agitation
- Muscle effects
  - Tension
  - Cramps
  - Aching
- Bone Aching
- Sleep Disturbance
- Sweating
- Hot & Cold Flushes
- Piloerection
- Lacrimation
- Rhinorrhea/Sneezing
- Abdominal Cramps
- Nausea
- Vomiting
- Diarrhea
- Palpitations
- HTN
- Tachycardia
- Mydriasis
- Yawning!
Tolerance & OIH

*Highly Plastic, Allostatic Load ➔ Overload*

- Fentanyl > Morphine > Methadone > Endomorphin
- Euphoria > Analgesia > RD/OIVI > Constipation
- Goldilocks Phenomena
  - Ultra-low Naloxone: Down Tolerance (filamin A); Suboxone relevance
  - Low & high Morphine pro-nociceptive
- OIH MOA (like nociplastic pain)
  - Glutamate activity (↑NMDA, ↑KOR, AMPA Δs, ↓Uptake) - LTP
  - Spinal Dynorphin
  - Descending facilitation
  - MOR & G-protein coupling Δs
  - Nociceptin activity Δs
  - Neuro-inflammation (microglia, BDNF, Cl- current Δs)

*Children's Mercy*

Velayudhan et al. 2013
Endogenous Opioids “Purposes”

- Pain/Nociception Regulation
- Salience Network – Motivational Valence
- Stress Management
  - Opponent to stress
  - Activity of LC (BP/HR)
- Brain Opioid Theory of Social Attachment (BOTSA)
  - Beyond oxytocin/vasopressin
  - Social grooming – ↑ trust
  - Laughing, music, dramas
  - Dysregulated in antisocial PD
  - Insecure relationships style
“...give patients all the opioids they need, but none that they don’t.” - Barry Meisenberg (Anne Arundel MC)
Regulations, Statutes, Guidelines…

- **New TJC Standards**
  - Medical Staff involved
  - Risk Assessment (OUD, OIVI)
  - Broaden Toolbox
  - PDMP facilitation

- **SUPPORT Act (federal)**
  - CHIP Prevention/Tx (MH/SUD parity)
  - Buprenorphine NP waivers permanent
  - Research $ E-prescribing of CS by 2021
  - MAT/OAT must be offered
  - PDMP must be checked for Medicaid

- **FDA**
  - Commissioned 2017 Report – like OSP
  - Acute Pain Guidelines (SUPPORT Act)
  - *New Opioid REMS (IR & LA)*
    - opioidanalgesicrems.com

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- **Pain Management & Opioids**
  - Earn your state mandated CME credits
  - Case-based questions mapped to the FDA Opioid REMS blueprint
  - Up to 10 hrs CME

- **Internal Medicine Board Review**
  - Earn your ABIM MOC points and CME credits
  - >5,400 questions guided by the ABIM blueprint
  - Learn more.
Opioid Stewardship Program

- **Supply** (wise prescribing, disposal)
- **Demand** (big toolbox, expectation shaping)
- Mitigate risk (assessment, contracts, UDS, PDMP, naloxone, ETCO₂)
- Measure & inform (EBP, data analytics)
- Integrate in workflow (links bar, point of prescribing)
Reduce Supply

- Prescribe for need; Evidence-based Practice, Guidelines/CPG, Care Process Models (CPMs) etc.
- E-Prescribing for opioids – facilitates above
- Safe storage and proper disposal
- DEA: take-back events, collection sites (deadiversion.usdoj.gov)
  - FDA: coffee grounds, kitty litter, dish soap, disposal products
  - Notices when filling Rx and in Depart
Reduce Demand

- Education (R/B); expectation shaping
- Bigger toolbox
  - Non-opioids: APAP, NSAIDs, AEDs, antidepressants, topical…
  - Behavioral: CBT, ACT, mindfulness mediation, MBSR, biofeedback
  - Rehabilitative: PT, exercise, biobehavioral (e.g., yoga)
  - Interventional: injections/blocks, nerve stimulators, pumps, TENS
  - Complementary: acupuncture, massage
Multimodal Analgesia

- More than one medication or intervention
- Different mechanisms of action
- Improve or maintain analgesia
- Decrease side effects
- Some from different classes have overlapping mechanisms or clinical effects
Gabapentinoids NMDA MOA

1. Nerve injury
2. OIH
3. Esmolol note

Chen et al. Cell Report 2/27/2018
Risk Mitigation

- Initial risk assessment (CRAFFT, HEADS, ORT…)
- Ongoing assessments (5 A’s, PEG, UDS, PDMP)
- OUD treatment referral resources (MAT, OAT)
- Safe storage/disposal (↓ accidental & diversion)
- Harm Reduction: naloxone & injection sites
- OIVI risk stratification & response
Ongoing Assessment

The 5 A’s, Patient Assessment & Documentation Tool

- Analgesia
- Activity (ADLs+)
  - Physical, vocational, social, sleep
- Affect
- Adverse Events
  - N/V, constipation, pruritus, sweating, sedation, cognitive Δ, overdose

- Aberrant Behaviors
  - Purposeful sedation
  - Request early refill
  - Reports lost/stolen Rx/pills
  - Rx from other(s)
  - Requests Drug by Name
  - Increased dose w/o authorization
  - Changes Route
  - Uses for stress
  - Hoarding medications
  - Arrest/victimization
  - Alcohol or Illicit Abuse
  - Appears unkempt, intoxicated or impaired

*PEG = Pain, Enjoyment, General Activity (30 scale)
Measure & Inform

- Prescribing patterns
  - By Service, Provider & Indication
  - Evidence-based guidelines
- Naloxone for OIVI use statistics
- Serious adverse events/outcomes
- Remainder and disposal rates
Children’s Mercy ED/UC
Michelle DePhillips et al., PEC 2017 & Personal Communication

- Excess Doses
  - Leg Fractures: 9.4
  - Arm Fractures: 12.8
  - Burns: 8.0
  - Abscesses: 7.7
  - All Diagnoses: 9.9

Number of Prescriptions

- Length of Prescription (Days)
  - 0-1
  - 1.1-2
  - 2.1-3
  - 3.1-4
  - 4.1-5
  - >5

Doses Used  Doses Prescribed  Excess Doses
Workflow (EMR) Integration
Kansas & Missouri

### Kansas and KS Medicaid (PA)
- K-TRACS: kansas.pmpaware.net
- Dx: CA, SCD, Palliative (12 mo)
- Post-op/Trauma: ≤ 90 MME/day, ≤ 21 days
- CNCP: ≤ 90 MME/d, 14/60 d, PA criteria o/w
- Methadone: terminal CA
- Fentanyl patch: CA & Palliative

### MO State Level
- ≤ 7-day acute limit: documented o/w
- Prior Authorization prohibited for MAT
- STLC PDMP: missouri.pmpaware.net

### MO HealthNet
- Opioid Resources – dss.mo.gov/mhd/opioid.htm
- Opioid Policy Advisory Council (OPAC)
- Dx: CA, SCD, CNCP (6 mo), Palliative (1 yr)
- Initial: ≤ 50 MME/d., ≤ 7 d. (sentences)
- Subsequent: ≤ 90 MME/day
- “Accumulation”: ≤ 200 MME/day
- Pharmacy: 30 day “emergency” fill – stable 6 mo
- (800) 392-8030, opt. 3, or CyberAccess
- Opioid Prior Authorization (on OSP)
- Opioid Attestation form (have to ask)
- Complimentary (>21): PT & Acup, CBT, Chirop
- OxyContin not on Preferred Drug List (bankruptcy)