Surgery and Opioids: Can we limit our contribution to the opioid crisis?

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Objectives

- To be aware of the extent of the opioid “crisis” and how opioids for acute pain contribute
- To understand the risks of prescribing opioids, particularly when co-prescribed benzodiazepines or other sedatives, psychoactive drugs.
- To understand the role of opioid tolerance and hyperalgesia in the development of chronic pain
- To develop an understanding of how to manage post op/post trauma pain so as to decrease chronic opioid use
The “crisis”

- In 2015, 33,091 (63.1% of all overdose deaths in US) involved an opioid. Heroin-related death rates increased 20.6% from 2014 to 2015, totaling 12,989 deaths in 2015. Overdose deaths involving synthetic opioids (e.g. illicitly-made fentanyl) increased by 72.2% from 2014 to 2015.

- The US overdose death rate increased from 12.3/100,000 population in 2010 to 16.3 in 2015.

- In 2015, death rates involving synthetic opioids were highest among males aged 25–44 years (8.9 per 100,000), increasing 102.3% from 2014 to 2015. Heroin death rates also were highest in this demographic group, increasing 22.2% from 2014 to 2015.

Rudd R. Increases in Drug and Opioid-Involved Overdose Deaths — United States, 2010–2015 MMWR December 30, 2016 / 65(50-51);1445–1452
Overdose deaths in Virginia

- Between 2010-2015, OD rate increased 6→10/100,000 in VA
  - (nb: WVA 30→40)
- Deaths due to natural and semisynthetic opioids decreased 33.4% from 2014-2015
- Deaths due to synthetic opioids not methadone (i.e. heroin, fentanyl) increased 38.7% during from 2014-2015
- NB: The percentage of drug overdose deaths with specific drugs identified on the death certificate varies widely by state, ranging from 47.4% to 99%, making these data difficult to accurately quantify.

Rudd R. Increases in Drug and Opioid-Involved Overdose Deaths — United States, 2010–2015 MMWR December 30, 2016 / 65(50-51);1445–1452
Carfentanil

- A synthetic opioid called is an animal tranquilizer used on livestock and elephants.
- Fentanyl is 50 times more potent than heroin.
- Carfentanil is 100 times more potent than fentanyl.
- 10,000 x as potent as morphine
- Amounts smaller than a snowflake can be fatal.
- Cincinnati had rash of ODs: 20 or 30 calls each day, caused 238 of Cincinnati’s 414 fatal overdoses in 2015. Emergency responders sometimes had to give people two, three or five doses of naloxone to revive them.
- Epidemic levels in Ohio, West Virginia, Indiana, Kentucky
- Recently found heroin laced with Carfentanil in Hampton Roads (Oct 2016)
Risks associated with opioid prescribing

- Risk of abuse is dose related (Edlund MJ Clin J Pain 2014)
  - $\leq 36$ MME/d $0.7\%$
  - $>120$ MME/d $6.1\%$

- Risk of overdose is dose related (Gomes T. Arch Int Med 2011)
  - Hazard ratio vs. $1<20$ MME/day
    - $20-49$ MME/d $1.44$
    - $50-99$ MME/d $3.73$
    - $\geq 100$ MME/d $8.87$
Polypharmacy increases risk of AE

- Wunsch reviewed OD deaths in SW Virginia between 1997-2003
- Overall, 57.9% of the cases classified as polydrug deaths.
- Prescription opioids were identified in 658 of the cases (74.0%).
  - methadone (28.0%), hydrocodone (20.4%), and oxycodone (19.6%).
  - 6-Acetylmorphine, the metabolic marker for heroin, in only 2.4% of cases.
- Antidepressants were identified in 436 cases (49.0%).
  - Sertraline (22.7%), venlafaxine (20.8%), amitriptyline (9.8%), nortriptyline (9%), and citalopram (6.1%) or fluoxetine (6.1%).
- Benzodiazepines were identified in 349 cases (39.3%).
  - Diazepam (24.3%) and alprazolam (15.4%)
- Alcohol was identified in 29% of the cases.
- Illicit drugs of abuse: cocaine 12.0%, THC 0.3%, methamphetamine or amphetamine 1.4%

Opioid Addiction Resulting from Legitimate Medical Prescriptions

Christopher P. Chiodo,

Source of Initial Exposure to Opioids

- Provider Prescribed: 58%
- Friend or Family: 14%
- Dealer, other: 28%
Opioid Addiction Resulting from Legitimate Medical Prescriptions

Source of opioids by age (% of group)

- Provider Prescribed
  - 19-30 yo: 7
  - 31-59 yo: 80

- Friend or Family
  - 19-30 yo: 53
  - 31-59 yo: 16

- Dealer, other
  - 19-30 yo: 40
  - 31-59 yo: 4
Why do physicians feel pressured to prescribe?

“Doctors who refuse to prescribe opioids to certain patients...are likely to get a poor rating from those patients.”

Press-Ganey

Pain as the 5th vital sign

“Obligation” to treat patient’s pain

Lembke A, NEJM, 2012
Risks of chronic opioid prescribing

- Overdose risk increases with:
  - Younger age
  - Major depression, psychotropic medications
  - Obstructive sleep apnea
  - History of SAD (including EtOH)
Risks of chronic opioid prescribing

- Other risks associated with opioids
  - Addiction/misuse/abuse/diversion
  - Increased osteoporosis, fracture risk
  - Cardiovascular events
  - Immunosuppression
  - Endocrine dysfunction, most notably low testosterone
  - > 20 MME/d is associated with increased risk of MVA
Differential Opioid Tolerance and Opioid-induced Hyperalgesia: A Clinical Reality

- Tolerance -- requirement for increased doses of an opioid to achieve the same analgesic effect.
- Chronic opioids don’t confer tolerance to respiratory depression but analgesic tolerance develops quickly.
- OIH -- increased sensitivity to painful stimuli as a result of opioid use.
  - Initial response is analgesia
  - Repeated (esp high) doses lead to increasing pain
  - NMDA, glutamate, dynorphin, adenylate cyclase mediated
- Both lead toward use of increased doses of opioids

(Paronis and Wood 1997)
Opioid-induced Hyperalgesia

- Intraoperative fentanyl and remifentanil caused more pain post op than esmolol infusion. (Collard 2007)
- The earlier the admin, higher the dose, more rapid onset/higher lipid solubility, the greater the impact on post op pain.
- Measures that attenuate OIH (Angst 2015)
  - Ketamine, methadone, and nitrous oxide via NMDA receptor inhibition
  - Gabapentanoids and α-2 receptor agonists (e.g. clonidine) attenuate wound hyperalgesia, mechanism unclear
Effect of opioids on pain transmission

- Morphine upregulates cold TRPm8 in the dorsal root ganglion (Gong J Pain 2016)
  - Opioids activate microglia → migrate → release cytokines
- Peter Grace: Second hit concept:
  - First hit: nerve injury causing release of cytokines → IL1B
  - Second hit: morphine activates macrophages → IL1B
  - Result is allodynia
  - Repeated doses of opioid increase magnitude and duration of allodynia (Grace PNAS 2016)
Modulating the Pain Message

- Descending inhibitory pathways
  - Serotonin, dopamine, NE mediated
  - TCA, SNRI augment inhibitory pathways (Start preop?)
- Preventing/ treating allodynia/hyperalgesia, neuropathic pain
  - Mediated via NMDA as well as microglia
  - Ketamine
  - Gabapentin (start preop?)
  - Lidocaine
  - Minimize opioids and second hit
- Anxiety/depression lower tolerance for pain - -> catastrophizing
  - Correlate with severity of post op pain
  - Preop education: single intervention decreased post op opioids by 45%
Lidocaine Effects

- Low-dose lidocaine inhibits in vitro
  - Voltage-gated sodium channels
  - Glycinergic system
  - Some potassium channels
  - Gαq-coupled protein receptors
- Higher lidocaine concentrations
  - Block potassium and calcium channels
  - Block NMDA receptors (hence effect on prevention and/or reduction of OIH?)
    - ? Enhanced efficacy in pts presenting on chronic opioids with preexisting OIH
  - Benefits in acute and neuropathic pain syndromes and anti-inflammatory effects early in the inflammatory response

(van der Wal 2016)
Ultra–low-dose Naloxone as an Adjuvant to Patient Controlled Analgesia (PCA) With Morphine for Postoperative Pain Relief Following Lumber Discectomy: A Double-blind, Randomized, Placebo-controlled Trial

- 80 pts, mean age 37 (N), 38 (P), mean BMI 38.
- Single level discectomy, L4-5 or L5-S1
- Infusion of naloxone 0.25 µg/kg/hr with morphine PCA
- N + MS → less post op pain, nausea, pruritis than just MS PCA
- The median (interquartile range) MS consumption post op in N + MS group was 26 (24.25 to 28)mg.
- Significantly lower consumption than the placebo group, with 34 (32 to 36)mg (P < 0.001)

(Firouzian 2016)
Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis

**Treatment of neuropathic pain NNT:**
- TCA (amitrip, nortrip, desip) 3.6 (95% CI 3.0–4.4)
- SNRI (duloxetine, venlafaxine) 6.4 (95% CI 5.2–8.4)
- Gabapentin 6.3 (95% CI 5.0–8.3)
- Pregabalin 7.7 (95% CI 6.5–9.4)
- Tramadol weak recommendation
- Tapentadol inadequate data
- Opioids worsened chronic pain

Finnerup 2015
The difficult situations

- A new patient presents to you requesting elective surgery. They report taking high dose opioids with an empty vial in hand but no or old medical records....

- What to do?
Elective surgery

- Make sure they have a PCP, don’t operate without one.
- Get pertinent medical records
- Check PMP?
- Check UDS at that visit?

- Don’t fill their rx without adequate documentation.
  - If withdrawing, clonidine 0.1 mg pm 3-4 times a day helps with symptoms
A 43 yo morbidly obese woman presents to ED with a ruptured appendix. She’s lives in Utah, but is here visiting a friend. She reports taking MS contin 100 mg TID and MSIR 30 mg qid for breakthrough to treat her low back pain and fibromyalgia. She has vials that support those doses, but they’re empty because she increased her intake due to abdominal pain.
What to do?

Issues:
- Morbid obesity = disease of addiction
- Misuse of medications
- OSA? Probably
- Needs surgical intervention

How to manage preop?
- Post op?
- Discharge?
Evaluation and Pre/intra op treatment

- OSA screen
- Urine drug screen
- Check PMP if accessible
- Call prescribing physician

Pre and intra op, utilize all possible opioid-sparing strategies including NSAIDs, wound infiltration with local
Maximize opioid-sparing strategies including NSAIDs

Aim treatment at type of pain: inflammatory, neuropathic, muscle spasm

PCA: Starting dose? Adjustments?

Switch to home medications as soon as taking well PO (and lose the PCA)

Follow clinical status (VS, O₂ Sats, activity, incentive spirometer volume) rather than VAS to guide titrations

Consider addictions consult if having significant behavioral issues (then BeSafe when you can’t get it)

Discharge?

- Coordinate with prescribing physician
- Provide 1 week prescriptions (with Do not fill before dates) with built in wean
Conclusions:

- The opioid crisis is real. Try not to be part of it.
- The majority of people who end up with addiction are first exposed to opioids for legitimate reasons.
- Educate patients (and families):
  - The pain will never be zero (unless they’re comatose).
  - There are multiple other options to minimize opioid dose (risk of AE)
- Trust but verify.
- Maximize opioid-sparing modalities, treatments perioperatively.
- For high doses, coordinate with prescribing physician for discharge planning.
- Call the pain service (or psychiatry) if you’re struggling: consult 1415, APS 1593
- Learn to embrace “no” – it’s not a four letter word.
You've got to know when to hold 'em
Know when to fold 'em
Know when to walk away
And know when to run...

Kenny Rogers, 1978
References

- Firouzian A. Ultra–low-dose Naloxone as an Adjuvant to Patient Controlled Analgesia (PCA) With Morphine for Postoperative Pain Relief Following Lumber Discectomy: A Double-blind, Randomized, Placebo-controlled Trial. J Neurosurg Anesthesiol 2016; Volume 00, pp
- Van der Wal S. The in vitro mechanisms and in vivo efficacy of intravenous lidocaine on the neuroinflammatory response in acute and chronic pain. EJP 2016; 20: 665-74
McCauliffe has declared a state of emergency in November 2016.

State Health Commissioner Dr. Marissa J. Levine has issued a standing order that allows all Virginians to obtain the drug Naloxone, which can be used to treat narcotic overdoses in emergency situations.

Hence, don’t need to write a prescription, however....

- Consider writing prescription for naloxone when prescribing opioids esp >50 MME/d
- Provide educational information regarding signs/symptoms of overdose and use of naloxone
- Include risk of death from overdose in your treatment agreement.
Federation of State Medical Boards Guidelines for Safe Opioid Prescribing (2013, 2017)

- Defines process for chronic opioid prescribing
- Focus on patient pain care, intentionally cautious re. being so rigid as to be a weapon to use against diligent prescribers.
  - Initial evaluation and risk stratification including documenting a pain diagnosis and previously ineffective treatments, psych and SAD screening
  - Treatment plan and goals: focus on improved function
  - Treatment agreement (informed consent) including safe storage and disposal
  - Initial trial (warning re. coincident use of benzos)
  - Ongoing monitoring and adapting the treatment plan
  - Periodic and unannounced drug testing
  - Adapting treatment based on SEs, function, PMP, drug test results, aberrant behavior
  - Consultation and referral (PT, pain specialist, surgeon, psych, addiction medicine)
  - Discontinuation of opioid therapy when indicated
  - Medical records that are accurate and up to date
  - Compliance with state and federal controlled substance laws and regulations
CDC Guidelines (2016)

- Goal: limit adverse events and overdose deaths
- Addresses issue as a public health crisis, not focused on quality of pain care
- Overdose death definitely linked to dose as well as coincident use of depressants, especially benzodiazepines
- Fails to take into account genetic variations (especially ultra rapid metabolizers), very long term use with significant tolerance
- Doesn’t limit to 50 MME/d but creates mandate to
  - Start and treat at lowest effective dose (note not VAS 0)
  - Carefully reassess plan before going higher
  - If increasing > 50 and, especially > 90 MME/d, carefully justify decision,
    - Show evidence of good compliance and improved function (RJH)
- NB: Acute pain recommend limit to 3 days (max 7 days)
What gets the attention of the BOM?

- Complaints (pt, pharmacist, other physician, law enforcement—re prescribing, suspicious activity around your office, etc)
- Patient deaths due to overdose
- Now starting to look at outliers re. prescribing practices compared to your practice cohort.
  - TN tracks top 10%, provides feedback regarding comparison to colleagues (MME/d)
- Can request chart audit
What are the FBI and DEA looking for?

--Multiple overdose deaths of your pts, vials with your name on them being picked up at drug busts, complaints, armed guards at your office, shingle saying you’re a pain doctor with a full parking lot and people lined up out in the street...

--The investigation:
Dumpster diving, interviewing your patients, asking your pt to wear a bug, FBI agents posing as patients. Once they have enough data, they subpoena records.
Your defense/protection

- Did you follow the FSMB guidelines: complete evaluation including exam, and a pain diagnosis that warrants opioid trial, screen for psychiatric disease/addiction, review outside records for new patients, including documentation of failure on non-opioid therapies.

- If prescribing, do you document well, including effect of prescribing on reaching functional goals? Do you monitor for compliance? (PMP, drug screening)

- If you have aberrant behaviors or results, do you change your plan? Document your rationale for continuing, changing?

- Can you identify evidence of addictive behaviors? Do you wean and refer to an addiction specialist or just keep prescribing?
National Academy of Clinical Biochemistry: Laboratory Medicine Practice Guidelines for Chronic Pain, 2017

- Review of 8000 articles to evaluate existing data by a group of clinical chemists, and pain practitioners
- Lots of data for addiction and workplace, but limited for chronic pain
- Expect it to be published in early 2017—in clinical biochem as well as pain literature
- Helps define current standard for drug monitoring
  - Aimed at both clinical chemists and prescribers
- Urine and other matrices: collection, what to test for, processing, adulteration testing, interpretation of results
- Role of genetic testing