Opioids Should not be Used for Treating Chronic Pain
The Pitts Lectures 2019

Disclosures for Dr. Malcolm in Last 12 Months:

- Dr. Malcolm has received partial FTEs for serving as PI, Co-I and Safety Officer for Janssen Pharmaceuticals, Novo-Nordisk, NIH and DOD
- Dr. Malcolm declares he has no ownership in any of the products or treatments discussed today
- Dr. Malcolm is not receiving an Honorarium for this lecture
- My sincere thanks to Keri Holmes-Maybank, M.D. MSCR, SFHM for her scholarly research and lending me some of her slide materials

Learning Objectives

- The learner will identify fallacies in the opioid debate
- The learner will list the real world risks/liabilities of Opioids
Outline of Presentation

- The Central Proposition
- The "Straw Man" misdirection
- A Case Report
- The Claim
- The Evidence
- Tying the Claim to the Evidence: Conclusions

The Proposition:

All Patients Should Have Treatments Available to Diminish Chronic Pain and Suffering by the Safest Possible Methods.
The “Straw Person” Misdirection

- 1970s, much evidence had accumulated that opioid administration for acute pain in the E.D. and hospital DID NOT lead to “ADDICTION”
- 1996 Pain as the “Fifth Vital Sign”
- 2001 Joint Commission (JCAHO) requirements
- 2000s “marketing” of legal and illegal semi-synthetic and synthetic opioids by the billions!

Opioid Use Disorder (ADDICTION) was/is not really the Problem!!

Case Report 1: The JAHCO Surveyor vs. Malcolm

- I brought up JAHCO’s “Green Light” endorsement of under-utilization of Opioids for chronic pain
- Surveyor read to me a “Public Relations” statement on the issue: JAHCO was not at fault-JAHCO sets standards not drug prescribing policies
- I ventured that those remarks seemed “defensive” and “hair spitting”
- I was accused of being an “Insensitive Neanderthal Luddite Physician!”
- I made a weak reply as she left the bus…………………

The Titles and Claims

- Opioids May Be Appropriate for Treating Chronic Pain (Christo)
- OR: Opioids Are Appropriate for Treating Chronic Pain
- Opioids Should Not Be Used for Treating Chronic Pain (Malcolm)
- OR: Opioids Usually Should Not Be Used for Treating Chronic Pain
The “Real Problems” with Opioids

- **Prima Facie, Ipso Facto, Est per se nota Est** evidence
- Complex medical class that alters the patients’ pharmacodynamics responses: Tolerance is variable; Withdrawal reactions are frequent and severe
- Toxic in non-tolerant individuals
- Evidence for long term effectiveness in chronic pain is moot
- Real world issues of: 1) Failure of “War on Drugs”; 2) Potent widely available synthetic opioids; 3) Aggressive legal and illegal marketing; 4) The “personal” losses
- Contemporary Primary Care cannot manage complexities of opioid treatments for chronic pain (clinical time is the enemy of REMS)

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**Prima Facie, Ipso Facto, Est per se nota Est**

In 2017 and 2018, 70,000 PEOPLE died of Opioid related deaths

NPR, March 13, 2019

Or, about 100 INDIVIDUALS per day

Or, six fifth grade STUDENTS, that my wife taught who died in their early twenties

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**Overdose Deaths Involving Opioids, By Type of Opioid, United States, 2000–2016**

www.cdc.gov
Opioids: Complex

- Bind to mu, kappa and delta opioid receptors in the CNS
- Inhibition of ascending pain pathways
- Alters the perception of and response to pain
- Produces generalized CNS depression, especially respiration
- Releases dopamine
- Euphoria (if depressed, return to baseline)
- Exogenous opioids alter receptor functions: tolerance and withdrawal sx
- Interacts with multiple drugs in adverse ways

Goodman and Gilman, 2018

Differential Opioid Tolerance and Opioid-induced Hyperalgesia
A Clinical Reality
Christina J. Hayhurst, M.D., Marcel E. Durieux, M.D., Ph.D.

Unfortunately, these arguments are probably wrong, at least to some degree. The perioperative period may be relatively short, but we now know that opioid tolerance can develop in a shorter time frame, possibly within hours when patients are exposed to high doses (i.e., a phenomenon that classically is referred to as tachyphylaxis). More importantly, many patients are already using opioid drugs for pain control before surgery and, therefore, are tolerant before they even arrive in the operating room. As to the development of tolerance to side effects, we now know that not all opioid targets develop tolerance at the same rate and to the same degree. This differential tolerance can put patients at significant risk.

Anesthesiology, 124, 2, Feb, 2016

Case Report 2: Opioids toxic in non-tolerant individuals

D.M. a 42 y.o., mother of one, relapsed to four months of increasing heroin use after clean and sober for 19 years.

After an informal family intervention, she went to a residential treatment center in upstate New York for six weeks. She was home for two weeks, attending NA, had seen an addiction psychiatrist once, refused medication assisted therapy.

After failing to return family calls for 48 hours, she was found “stone cold dead” in a friend’s apartment. Toxicology report later indicated heroin and a benzodiazepine.
Opioid-Induced Hyperalgesia: Not Helpful

A paradoxical increase in pain states has been observed in response to acute (hours to days) and chronic opiate exposure. This increase may be reflected by unexplained increases in pain reports, increased levels of pain with increasing opiate dosages, or a diffuse sensitivity unassociated with the original pain (Lee et al., 2011). The mechanisms of this increased pain profile is not understood, although an enhanced excitability of central systems with chronic opiate exposure is considered relevant. Other avenues have pointed to the stimulatory effects of opioids on innate immune signaling through Toll-like receptor 4 activation, leading to central sensitization (Grace et al., 2014).

Goodman and Gilman, The Pharmacologic Basis of therapeutics, 2018

Neuropathic Pain: Opioids Not as Effective

Although nociceptive pain usually is responsive to opioid analgesics, neuropathic pain is typically considered to respond less well to opioid analgesics. There is a growing perception that, in the face of chronic tissue injury or inflammation (e.g., arthritis), there can be a transition from an inflammatory to a neuropathic pain phenotype. Such a transition has important implications for analgesic drug efficacy.

Goodman and Gilman, The Pharmacologic Basis of therapeutics, 2018

Aggressive Marketing: Purdue Pharma

- Purdue Pharma settles with the State of Oklahoma for $270 Million
  BBC and ABC News, March 26, 2019

- There are 50 States!
CDC GUIDELINE FOR PRESCRIBING OPIOIDS FOR CHRONIC PAIN

- 12 Recommendations
- When to initiate or continue opioids
- Opioid selection, dose, duration, follow up, discontinuation
- Assess risk and address opioid harms

Time Intensive In Primary Care

DETERMINING WHEN TO INITIATE OR CONTINUE OPIOIDS FOR CHRONIC PAIN

Nonpharmacologic therapy and nonopioid pharmacologic therapy are preferred for chronic pain. Clinicians should consider opioid therapy only if expected benefits for both pain and function are anticipated to outweigh risks to the patient. If opioids are used, they should be combined with nonpharmacologic therapy and nonopioid pharmacologic therapy, as appropriate.

Alternatives/Multimodal: $$$, Time or XX

- Medication
- NSAIDs, anticonvulsants, antidepressants, topicals
- Physical
- Exercise, PT, acupuncture, TENS, cold, heat, stretch
- Psycho-Behavioral
- CBT, ACT, meditation
- Procedural
- Nerve block, steroid injection, trigger point injections
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Determining When to Initiate or Continue Opioids for Chronic Pain

2. Before starting opioid therapy for chronic pain, clinicians should establish treatment goals with all patients, including realistic goals for pain and function, and should consider how opioid therapy will be discontinued if benefits do not outweigh risks. Clinicians should continue opioid therapy only if there is clinically meaningful improvement in pain and function that outweighs risks to patient safety.

3. Before starting and periodically during opioid therapy, clinicians should discuss with patients known risks and realistic benefits of opioid therapy and patient and clinician responsibilities for managing therapy.
**Side Effects**

- Cognitive impairment 77%
- Delirium 60%
- Dizziness, headache, drowsiness
- Constipation 50-80%
- Nausea and vomiting 30%
- Allergic reactions
- Pruritus – 10-50%
- Urinary retention
- Hyperalgesia
- Hypogonadism

**Serious Adverse Events**

- Adrenal insufficiency
- Serotonin syndrome
- Sedation
- Respiratory depression
- Death

**Adverse Interactions: Other Common Meds**

- Benzodiazepines – alprazolam, clonazepam, diazepam, lorazepam, temazepam
- Muscle relaxants – baclofen, cyclobenzaprine, methocarbamol
- Antidepressants
- Antipsychotics
- Anticonvulsants
- Antihistamines – diphenhydramine
- Antiemetics – promethazine, metoclopramide, prochlorperazine
- Hypnotics – zolpidem, trazodone

**OPIOID SELECTION, DOSAGE, DURATION, FOLLOW-UP, AND DISCONTINUATION**

When starting opioid therapy for chronic pain, clinicians should prescribe immediate-release opioids instead of extended-release/long-acting (ER/LA) opioids.
5. When opioids are started, clinicians should prescribe the lowest effective dosage. Clinicians should use caution when prescribing opioids at any dosage, should carefully reassess evidence of individual benefits and risks when considering increasing dosage to ≥90 morphine milligram equivalents (MME)/day, and should avoid increasing dosage to ≥90 MME/day or carefully justify a decision to titrate dosage to ≥90 MME/day.

6. Long-term opioid use often begins with treatment of acute pain. When opioids are used for acute pain, clinicians should prescribe the lowest effective dose of immediate-release opioids and should prescribe no greater quantity than needed for the expected duration of pain severe enough to require opioids. Three days or less will often be sufficient; more than seven days will rarely be needed.

7. Clinicians should evaluate benefits and harms with patients within 1 to 4 weeks of starting opioid therapy for chronic pain or of dose escalation. Clinicians should evaluate benefits and harms of continued therapy with patients every 3 months or more frequently if benefits do not outweigh harms of continued opioid therapy, clinicians should optimize other therapies and work with patients to taper opioids to lower dosages or to taper and discontinue opioids.
ASSESSING RISK AND ADDRESSING HARMs OF OPIOID USE

8. Before starting and periodically during continuation of opioid therapy, clinicians should evaluate risk factors for opioid-related harms. Clinicians should incorporate into the management plan strategies to mitigate risk, including considering offering naloxone when factors that increase risk for opioid overdose, such as history of overdose, history of substance use disorder, higher opioid dosages (>50 MME/day), or concurrent benzodiazepine use, are present.

ASSESSING RISK AND ADDRESSING HARMs OF OPIOID USE

9. Clinicians should review the patient’s history of controlled substance prescriptions using state prescription drug monitoring program (PDMP) data to determine whether the patient is receiving opioid dosages or dangerous combinations that put him or her at high risk for overdose. Clinicians should review PDMP data when starting opioid therapy for chronic pain and periodically during opioid therapy for chronic pain, ranging from every prescription to every 3 months.

ASSESSING RISK AND ADDRESSING HARMs OF OPIOID USE

10. When prescribing opioids for chronic pain, clinicians should use urine drug testing before starting opioid therapy and consider urine drug testing at least annually to assess for prescribed medications as well as other controlled prescription drugs and illicit drugs.
Can Most Providers follow the 12 CDC Guidelines??

- Probably Not
- Another piece of news: REMS program for Fentanyl Formulation found to be inadequate. 2011–2018 study found problems with formulation and levels of use decline and returned to near 2011 levels. Medscape, March 1, 2019.
Conclusions: We Must Eliminate (LIMIT) Opioids

- Deaths by the tens of Thousand annually
- REMS for Opioids have marginal benefit, mostly
- Oversupply of prescription Opioids and contamination with synthetics will continue
- Drug interactions are deadly
- Alternative pain therapies are often tried late & are expertise, time and money limiting

How Will the Opioid Crisis be Rectified?

- In litigation, mostly
- Education of Clinicians, the public and patients
- Advances in opioid science and pain management

South Carolina

- 2 hours of CME training
- Prescription Drug Monitoring Program
- Expanding MAT
- Limit 7 days for acute pain