THE PAIN OF PLEASURE:
HEROIN AND OTHER OPIOIDS
THE IMPLICATIONS FOR ONCOLOGY PRACTICE:
A CLINICAL DILEMMA

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This talk is primarily focused on the new research on the pathophysiology of opioid use disorders-and the dilemma for cancer patients.
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Case Study

• A 57 year old Latino woman, who has a positive family history of breast cancer, in remission of estrogen receptor (ER) positive DCIS was treated with a lumpectomy and radiation therapy in 2015.

• She was placed on tamoxifen 20mg therapy and has been “compliant” with her treatment regime since 2015 but developed a painful inflammation in her healthy breast, possibly as a ADE of the tamoxifen. Her oncologist had placed her on several non opioid medications, which did not work after which she was placed on low dose oxycodone/ASA. She was soon requesting a higher dose, with her pain scores being reported to be in the 7-9 range, so the oncologist referred her to a pain management clinic since her cancer was in remission. The pain management clinic refused to accept her as a patient, so she bounced back to her oncologist. What does the oncologist do at this point?
The Statistics

• In 2016, an estimated 1,685,210 new cases of cancer will be diagnosed in the United States and 595,690 people will die from the disease.
• The number of people living beyond a cancer diagnosis reached nearly 14.5 million in 2014 and is expected to rise to almost 19 million by 2024.
• Approximately 39.6% of men and women will be diagnosed with cancer at some point during their lifetimes (based on 2010-2012 data).
• In 2014, an estimated 15,780 children and adolescents ages 0 to 19 were diagnosed with cancer and 1,960 died of the disease.
• As the overall cancer death rate has declined, the number of cancer survivors has increased.
What Does this Mean?

- Three populations in the cancer patient cohorts - currently in treatment, terminally ill, and survivors.
- Types of pain:
  - Treatment-related mucositis
  - Infusion-related pain syndromes
  - Chemotherapy-related musculoskeletal pain
  - Dermatologic complications and chemotherapy
  - Radiation-induced pain
- Cancer pain is associated with increased emotional distress. Both pain duration and pain severity correlate with risk of developing depression.
- Cancer patients are disabled an average of 12 to 20 days per month, with 28% to 55% unable to work because of their cancer.
- The prevalence of chronic nonmalignant pain — such as chronic low back pain, osteoarthritis pain, fibromyalgia, and chronic daily headaches — has not been well characterized in cancer patients. It has been reported to be between 2% and 76%, depending on the patient population and how pain was assessed.
- NIH Cancer Institute Report September 15, 2016
The Epidemic
Chronic Pain and Prescription Opioids

- 11% of Americans experience daily (chronic) pain
- Opioids frequently prescribed for chronic pain
- Primary care providers commonly treat chronic, non-cancer pain
  - account for ~50% of opioid pain medications dispensed
  - report concern about opioids and insufficient training
Global Market Study on Opioids

• By product, the global opioid market is segmented into morphine, codeine, fentanyl, meperidine and methadone.
• The morphine and codeine segments collectively accounted for around 62% of the overall market in 2014.
• By application, the global opioids market is segmented into analgesia, cough suppression and diarrhea suppression.
• The analgesia segment was valued at US $22,776.3 million in 2014 and is anticipated to reach US $28,436.8 million by 2021. US has 65% of the global opioid market.

Global Market Study on Opioids: Widespread Usage in Treatment of Cancer to Drive the Growth of Opioids Market During the Forecast Period PR Newswire
Since 1999, there have been more than 165,000 deaths from overdose related to prescription opioids.
American Society of Clinical Oncology (ASCO) Statement on the Opioid Epidemic

• Regulations designed to curb opioid abuse and addiction should "largely exempt cancer patients," according to a policy statement from the American Society of Clinical Oncology (ASCO)

• Characterizing cancer patients as a "special population," ASCO said a broad exemption from regulations that limit access to or doses of prescription opioids is justified because of the "unique nature of their disease, its treatment, and potentially life-long adverse health effects from having had cancer."

• ASCO Policy Statement on Opioid Therapy: Protecting Access to Treatment for Cancer-Related Pain 2016
Cancer Patients: A Special Population

- Cancer patients represent a special population that should be largely exempt from regulations intended to restrict access or limit doses, in recognition of the unique nature of the disease, its treatment, and potentially life-long sequelae. Cancer is very heterogeneous, with some diseases experiencing high rates of cure and others having an indolent biology extending over many years. Cure and prolonged remission represent trajectories that raise varying concerns and complexities, including the problem of chronic pain in survivors. Both solid tumors (with the exception of non-invasive skin cancers) and hematological neoplasms represent serious and potentially life-limiting illnesses, even if the course is relatively prolonged.
- This complexity in the presentation and course of cancer must be appreciated, as it has implications for practices and policies related to opioid therapy.
- From the clinical perspective, there is broad agreement that opioid therapy is generally the first-line approach for moderate to severe chronic pain associated with active cancer, whether or not the patient is receiving anti-neoplastic therapy; for this group of patients, access to opioids must be assured, and laws and regulations intended to address abuse and overdose should be crafted to avoid creating impediments to this treatment—particularly as there is no evidence that the treatment of cancer pain has in any way contributed to these problems. “

ASCO Recommendations for Cancer Patients

- Healthcare provider access to a choice of materials on prescribing education that is "evidence based and tailored by specialty";
- No prescription limits that would "artificially impede access to medically necessary treatment for patients with cancer";
- Patient education emphasizing safe use, storage, and disposal of prescription pain medication;
- Allowances in prescription drug monitoring programs for providers who treat cancer related pain and "may prescribe relatively large numbers of opioids or provide multiple controlled drugs at relatively high doses";
- Appropriate patient screening and assessment before and during opioid treatment, although use of compliance tools should not be mandated for all patients who receive opioids;
- Use of abuse-deterrent -- or non-abuse deterrent -- formulations of prescription pain medication, as determined by clinical and patient-specific circumstances;
- Rapid patient access to assessment, diagnosis, and treatment for opioid misuse, abuse, or addiction;
- Increased access to naloxone, "a life-saving medication in cases of opioid overdose"; and
- Prescription "take-back" programs to decrease availability of unused or unwanted opioids, including readily available authorized collection sites for patients.

SHARP INCREASE IN OPIOID PRESCRIPTIONS  INCREASE IN DEATHS

![Graph showing the increase in opioid prescriptions and deaths from 1999 to 2013.](image)

National Vital Statistics System, DEA’s Automation of Reports and Consolidated Orders System
Role of Prescribing Opioids and Overdose Deaths

Nearly 2M Americans, aged 12 or older, either abused or were dependent on prescription opioids in 2014.
Challenges

• While there were 16,235 deaths involving prescription opioids in 2013, an increase of 1% from 2012, the number of deaths involving heroin increased dramatically. There were 8,257 heroin-related deaths in 2013, up 39% from 2012. Total drug overdose deaths in 2013 hit 43,982, up 6% from 2012.

• There were 59,000 overdose deaths in 2016 and it is estimated that over 69,000 will die in 2017. This number of deaths is only surpassed by lung cancer deaths but it is greater than the individual death rates of bladder, breast, colon-rectal, endometrial, kidney/pelvis, leukemia, liver and intrahepatic bile duct, melanoma, non-hodgkin lymphoma, pancreatic, prostate, and thyroid cancers.
Opioids: Double-edged sword

Cornerstone of pain management

Mood altering properties
Dynorphin, Dysphoria, and Dependence: the Stress of Addiction

Charles Chavkin and George F Koob

The hypothesis that the dynorphin-kappa opioid receptor system may be a key component of the neuroplasticity associated with stress-induced mood disorders and the ‘dark side’ of addiction (withdrawal-negative affect stage) continues to gain preclinical and clinical experimental support. The endogenous kappa opioid peptides derived from prodynorphin encode the dysphoric, anxiogenic, and cognitive disrupting responses to behavioral stress exposure.

(Bruchas et al, 2010; Carroll and Carlezon, 2013)

*Neuropsychopharmacology* 41, 373-374 (January 2016) | doi:10.1038/npp.2015.258.
Opiates (Natural Alkaloids)

Natural alkaloids
- morphine
- codeine
- thebaine

Semi-synthetics
- heroin
- oxycodone
- hydrocodone
- buprenorphine
- naloxone
Morphine, Heroin or Codeine: It does not make any difference

Morphine can arise in the blood and urine through the administration of morphine itself or through the metabolism of heroin or codeine.

Opioid Use (Addiction) Changes the following:

- Opioid Receptors (mu, kappa, delta)- euphoria
- The Endogenous Opioid Peptide System (Endorphins/Dynorphins)
- Cellular Membrane Action- down regulation of GTP to GDP (conversion of release of arrestin)
- Dopamine Pathways- decreased production, storage, and transport
Opioid Receptors (Euphoria Receptors)

- **µ (mu):**
  - Activated by morphine: Analgesia
  - Primary action site of all opioids
  - Distribution: primarily in CNS and also GI
  - Linked to substance use disorders

- **δ (delta):** Duloxetine, Gabapentin??? for endogenous peptides (endorphins)- Nerve Conduction- slows pain signal between the peripheral nervous system and the central nervous system (brain, hypothalamus, spinal cord)

- **κ (kappa):** Cannabinoids ??? analgesia, endocrine changes and dysphoria (brain-amygdala, spinal cord) [dynorphins] Stress Reduction
Opioid Receptors

- Five classes of opioid receptor
  - Mu(µ), Delta(δ), Kappa(κ) Nociceptin Subtypes (σ, ε receptors)
- Subtype of µ, δ, κ receptor
- Structural characteristics** (The more characteristics, the higher addiction liability)
  - Typical G-protein-coupled receptor
    - Seven hydrophobic region
    - Three intracellular loops
    - Three extracellular loops
    - Intracellular carboxy-terminal tail
    - Extracellular amino-terminal tail
Fig. 1. The opioid receptor is illustrated. More detailed description is given in the text.
The “Dynamite” of Opioids

- Aspirin (1 stick)
- Codeine (1 stick)
- Hydrocodone (3 sticks)
- Morphine (4 sticks)
- Fentanyl (21 sticks)
Opiates/Opioids

Pure agonists
- FULL
  - Morphine
  - Heroin
  - oxycodone
  - Fentanyl
- PARTIAL
  - butorphanol
  - pentazocine

Antagonists
- PURE
  - naloxone
  - naltrexone

Mixed agonists/antagonists
- buprenorphine
- nalbuphine

Others
- tramadol
In 1874, English chemist C.R. Wright ventured out into making a non-addictive form of codeine and morphine. In doing so he combined anhydrous morphine alkaloid and acetic anhydride (Hodgson). This produced what is known as diacetylmorphine (Hodgson). In short diacetylmorphine is an acetylated version of morphine.
Opioid Addiction is Greater Than a Mother’s Love (Dynorphin)

- The reason for the that addicts can not stop using is once the dopaminergic system is deactivated (depleted) due to multiple neurobiological reasons- the reinforcing effects of the drug becomes more powerful than a mother’s love for her children. In 2016, the potencies of most street drugs (marijuana/heroin) have increased. This increased potency creates the increased reinforcing effects of dopamine thus increasing the addiction liability of the drug on the brain.
Dopamine

Primary chemical in the brain responsible for activating the reward pathway

During the preoccupation phase of addiction, dopamine is being released stimulating desire for a drug.

During the intoxication phase, all the dopamine in the brain is released giving the user a euphoric feeling.

During the withdrawal phase, the brain has run out of dopamine and cannot function properly until more is made.
Fig. 8

1.) Behaviors - Pleasure
2.) Euphoria - Addiction
3.) Movement - Parkinson’s Disease - EPS
4.) Perception - Psychosis

Dopamine Neural Pathways

- Mesocortical pathway
- Mesolimbic pathway
- Nigrostriatal pathway
- Tuberoinfundibular pathway
MESOLIMBIC DOPAMINE SYSTEM

- **Circuit #1 Mu: Use-Dopamine**
  - Relief/Like
    - Pleasure/Pain circuit
    - Meso-accumbens

- **Circuit #2 Delta: Abuse-Endorphins**
  - Repeat/Want
    - Desire and urge circuit
    - Basolateral n. of amygdala

- **Circuit #3 Kappa:Addiction-Dynorphin A/B**
  - Need/Craving
    - Pathologic desire & demand circuit
      - Periaquedical gray of brain stem
      - Stimulation of the periaqueductal gray matter of the midbrain activates enkephalin-releasing neurons that project to the raphe nuclei in the brainstem.
      - Enkephalin (endogenous opioid neurotransmitter), binds to mu opioid receptors.
Consequences
Overdosing- #1 Issue

In the events of a opioid overdose, medical professionals and in some cases law enforcement administer naloxone, commonly referred to as naloxone.

Naloxone acts as an antagonist and reverses the traumatic effects of a heroin overdose by competing with morphine for the opiate receptors (mostly the mu receptors) and binding to them therefore reversing the effects of heroin overdosing such as respiratory depression and sedation.

It is administered via nasal, I.V., I.M. or S.C. and is excreted through the urine within 72 hours.

One down fall to the usage of naloxone is the onset of withdrawal symptoms for the opioid user.

• CDC Morbidity and Mortality Weekly report for June 19 2015 states that over 27,000 lives has been saved by Naloxone since 1999
Contents Of Narcotic Overdose Kit
Withdrawal # 2 Issue

The onset of withdrawal symptoms vary among users. Typically those who use heroin once a day experience peak withdrawal effects within 36-48 hours of their last administered dose.

Symptoms such as pain, restlessness and vomiting go away within 7-10 days.

Medication assisted treatments (MAT) is recommended by SAMHSA for withdrawal.
What Is MAT?

MAT is any treatment for opioid addiction that includes a medication (e.g., methadone, buprenorphine, naltrexone, naloxone) approved by the U.S. Food and Drug Administration (FDA) for opioid addiction detoxification or maintenance treatment. MAT may be provided in an OTP or an OTP medication unit (e.g., pharmacy, physician’s office) or, for buprenorphine, a physician’s office or other health care setting. Comprehensive maintenance, medical maintenance, interim maintenance, detoxification, and medically supervised withdrawal are types of MAT.

Outcome Challenge: The Treatment Gap: DATA 2000 Waiver

• Waiver Authority for Physicians Who Dispense or Prescribe Certain Narcotic Drugs for maintenance or detoxification treatments:
  o # of Physicians in the U.S. = 916,264
  o # of DATA Certified Physicians = 33,806

• This comes out to only 3.7% of physicians being DATA Certified, left to treat 1.9 million opioid addicted patients in the US.

  One physician for 55,800 opioid addicted patients

Cravings # 3 Issue

- Craving: memory of rewarding aspects of drug use superimposed on a negative emotional state
  - Compels drug-seeking in dependent individuals

- 3 Types of Cravings
  - Withdrawal induced
  - Cue-induced
  - Drug-induced
Options of Pharmacological Treatment

1. Methadone
   - Full \( \mu \) agonists
   - Once/day dosed
   - 40-60 mg/d: sufficient to block withdrawal symptoms

2. Buprenorphine and Buprenorphine/Naloxone
   - \( \mu \) Receptor partial agonist
   - Kappa receptor partial antagonist
   - 12-16 mg/d
   - Combination ↓ risk of diversion

3. Naltrexone
   - Opioid antagonist
   - Oral or injectable
   - This extended-release injectable medication is the most recent drug, approved in October of 2010, for the treatment of opioid addiction.

4. Naloxone- Overdose Prevention-Training required for all practitioners who are prescribing opioids to patients
Components of Comprehensive Drug Addiction Treatment
GUIDELINE FOR PRESCRIBING OPIOIDS FOR CHRONIC PAIN
Purpose, Use, and Primary Audience

- **Primary Care Providers**
  - Family medicine, Internal medicine
  - Physicians, nurse practitioners, physician assistants

- **Treating patients >18 years with chronic pain**
  - Pain longer than 3 months or past time of normal tissue healing

- **Outpatient settings**

- **Does not include active cancer treatment, palliative care, and end-of-life care**
National Comprehensive Cancer Network Guidelines Adult Cancer Pain Concerning Substance Use Disorders

- Physicians and other oncology practitioners be aware of the range of opioid use patterns to detect any potential aberrant behaviors:
- Potential Risk Factors for Misuse/Abuse/Use Disorders include:
  - History of substance use disorder;
  - History of binge drinking;
  - Family History of addiction;
  - Family History of mental illness;
  - Family History of Trauma (physical, emotional, sexual)
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Tools and Materials

- **Provider and patient materials**
  - Checklist for prescribing opioids for chronic pain
  - Fact sheets
  - Posters
  - Web banners and badges
  - Social media web buttons and infographics

- **CDC Opioid Overdose Website**
  [www.cdc.gov/drugoverdose/index.html](http://www.cdc.gov/drugoverdose/index.html)
For more information please contact Centers for Disease Control and Prevention

1600 Clifton Road NE, Atlanta, GA 30333
Telephone: 1-800-CDC-INFO (232-4636)/TTY: 1-888-232-6348
Visit: www.cdc.gov | Contact CDC at: 1-800-CDC-INFO or www.cdc.gov/info

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.