Long term Complications of Opioid Therapy

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Disclosures

- Speaker- Lilly Pharmaceutical
- Pain Management Medical Advisory Board-General Electric
Objective

- Evaluate potential side effects of long term opioid therapy
- Overview monitoring and treatment strategies

Introduction

- What do we know?
- How can we screen or monitor our patients?
- How can we prevent, manage/treat complications?
Why Do We Prescribe Opioids?

- Acute pain
  - Medical conditions
  - Perioperatively
  - Exacerbation of chronic pain conditions
- Cancer pain
  - Cancer
  - Complications of treatment
    - Chemotherapy or radiation induced neuropathy
- Chronic pain
  - Chronic medical conditions
  - Post surgical
  - Idiopathic
  - Goals
    - Pain reduction
    - Functional improvement
    - Continued participation in society

Long term Opioid Treatment Controversial

- Limited long term studies for opioid therapy in chronic pain not related to cancer
  - Long term analgesic efficacy is unclear
- Dropout rates in various clinical studies is relatively high (20 to 40%)
  - Due to lack of analgesia and/or high side effect profile of opioid analgesics
- Complications
  - Dependency/abuse
  - Immune dysfunction
  - Hormonal dysfunction
  - OIH
  - Death
Experiences

- The good, the bad, and the ugly
  - Many of us have patients who (as far as we know) are doing well with chronic opioid maintenance treatment
  - Many of us have patients who struggle with efficacy or side effects with this treatment modality
  - Many of us struggle with patients who do not appear to be responsive to treatment or who raise concerns related to dependency and/or diversion

ARE OPIOIDS IN CHRONIC PAIN ABSOLUTELY NEEDED?
Long term Opioids

- Variable pain and function impact >6 mos
  - Weak evidence for some SR prep (TD fentanyl and SR morphine II-2)
  - II-3 for hydrocodone and III for methadone
- Minimal impact on pain, or social functioning.
- Association with increased medical costs, surgery and prolonged disability

Trescott et al. Pain Physician 2008
Abuse

- 18-41% in patient receiving opioids for chronic pain
- Lifetime substance use disorders 36-56% (43% current)
- Aberrant medication behavior 5-24%

Trescott et al. Pain Physician 2008

Abuse

- Illicit drug use is significant in chronic pain patients
  - Similar with IR and SR opioids
- Lead to increase ED visits
- Opioid related deaths have overshadowed MVA deaths (esp Methadone)

Manchikanti et al. Pain Physician 2011
Compared 39 high dose opioid patients (methadone mean dose 111-133 mg daily (range 30-320 mg) to 20 control chronic pain patients intermittent (not daily) short acting opioid.

- QoL
- Side effects
- Function of hormonal axes

Quality of Life

WHAT ABOUT SIDE EFFECTS OF LONG TERM THERAPY?
Opioid Complications and Side Effects

- Acute
  - Respiratory depression
  - Sedation/cognitive impairment
  - Constipation
  - Dependence
    - Tolerance
    - Physical/psychological dependence
    - Addiction
  - Morbidity/mortality
    - Abuse/diversion
    - Overdose (accidental or intentional)
    - Drug/drug interactions
    - Direct medication side effects
    - Accidents
      - Home/Work related
      - Motor vehicle
Chronic

- Immune dysfunction
- Hormonal dysfunction
- Hypogonadism
- Dependence
  - Tolerance
  - Physical/psychological dependence
  - Addiction
- Neuroplasticity
  - Opioid induced hyperalgesia (OIH)
  - The Brain
    - Opioid exposure causes structural and functional changes in reward- and affect-processing circuitry.
    - Morphologic changes occur rapidly in humans during new exposure to prescription opioid analgesics.
- Morbidity/mortality
  - Abuse/diversion
  - Overdose (accidental or intentional)
  - Drug/drug interactions
  - Direct medication side effects
  - Accidents
    - Home/Work related
    - Motor vehicle
    - Reports can be unreliable (reporting bias)

Opioid Side Effects

- Immune dysfunction
- Hormonal dysfunction
- Opioid induced hyperalgesia (OIH)
- Morphologic/functional changes
- Death
Immune dysfunction

- Opioid use affects both innate immunity and adaptive immunity.

- Chronic opioids decreases the proliferative capacity of macrophage progenitor cells and lymphocytes.

- Differentiated function of immune cells is significantly affected by opioids
  - mediated by either a direct action of opioids on the target cells or
  - indirect centrally mediated pathways.

- Clinical impact yet to be clearly elucidated
HORMONAL DYSFUNCTION

- Modulate gonadal function primarily by acting on opioid receptors in the hypothalamus
  - Decr release of luteinizing hormone and follicle stimulating hormone from the pituitary gland, and of testosterone or estradiol from the gonads.
Effects

Men
- Erectile dysfunction
- Impotence
- Decreased muscle mass

Women
- Menstrual disorders
  - Irregular menstrual cycle
  - Oligomenorrhoea
  - Amenorrhea

Both
- Loss of libido
- Depression/anxiety
- Low energy
- Infertility
- Osteoporosis/fracture
**Monitoring/Management**

- History
- Laboratory
  - Luteinizing hormone, follicle stimulating hormone, and testosterone or estradiol
  - Monitoring of bone density
- Management
  - Reducing the dose, or eliminating opioids
  - Hormone replacement therapy
    - Referral to Endocrinology


**OPIOID INDUCED HYPERALGESIA (OIH)**
Opioid-induced Hyperalgesia in Humans
Molecular Mechanisms and Clinical Considerations

Larry F. Chu, MD, MS (BCHM), MS (Epidemiology),* Martin S. Angst, MD,*
and David Clark, MD, PhD* i

Clin J Pain • Volume 24, Number 6, July/August 2008

- Long term use
- High dose (oral) or intrathecal opioids
- Ultra low dose opioids

Opioid Induced Hyperalgesia (OIH)

- Proposed mechanisms
  - Metabolite effect (ie morphine 3-glucuronide (M3G))
  - GABA neuron cell apoptosis (opioid induced)
  - NMDA receptor agonism
OIH Possible Mechanisms

1. Sensitization of primary afferent neurons
2. Incr excitatory neurotransmitter production and decr reuptake
3. Sensitization of second order neurons to excitatory neurotransmitters
4. Neuroplastic changes in rostral ventromedial medulla leading to incr spinal dynorphin and incr primary afferent activity and pain


Treatment

- Opioid weaning
- Opioid Rotation
  - Methadone (weak NMDA antagonism)
    - Caution with transition
    - May increase nociception
- NMDA antagonists
  - Ketamine
  - Dextramethorphan
Opioids and the Brain

- Imaging study 19 patients
  - 10 given oral morphine SR vs 9 patient with placebo
  - Brain MR at Baseline, one month and average 4.7 months after discontinuation of medication


- Demonstrated volume changes in the morphine group
  - Increased volume- right hypothalamus, left inferior frontal gyrus, right ventral posterior cingulate, and right caudal pons
  - Decreased volume- amygdala
  - Volume changes correlated with morphine dose
  - Many changes were persistent over time
  - ?related to positive or negative effect

Opioids and the Brain

- Longer duration of prescription opioid exposure was associated with greater changes in functional connectivity.

Alterations in brain structure and functional connectivity in prescription opioid-dependent patients.
Upadhyay J - Brain - 01-Jul-2010; 133(Pt 7): 2098-114

Opioids and the Brain

- Changes in amygdala functional connectivity were observed
  - prescription opioid dependence is associated with structural and functional changes in brain regions
    - implicated in the regulation of affect and impulse control
    - reward and motivational functions.

Alterations in brain structure and functional connectivity in prescription opioid-dependent patients.
Upadhyay J - Brain - 01-Jul-2010; 133(Pt 7): 2098-114
Drug overdose deaths increasing problem

The number of drug overdose deaths in Ohio from prescription and illicit drugs increased by more than 350 percent between 1999 and 2008—a much greater rate than by suicide or traffic accidents.

Ohio deaths, by year


KEN MARSHALL / THE PLAIN DEALER
Prevention and Management Strategies

- Patient selection and good H&P
- Patient education and re-education
- Prescription monitoring and urine toxicology
- Frequent office visits and assessment
- Collateral interview
- Psychological assessment

Prevention and Management Strategies

- Vigilance
  - Know what to look for
- Monitor
  - Ask the right questions
  - Consider laboratory evaluation as appropriate
- Treat
  - Reduce or eliminate opioid analgesics
  - Consider adjuncts (to reduce opioid dose)
  - Referral - endocrinologist
Summary

- We discussed issues we and our patients encounter when opioids are utilized long term
- Objectives
  - Discussed current information regarding complications of long term opioid therapy.
  - Discussed monitoring and treatment strategies
- What We Know
  - Complications are common to chronic opioid therapy
  - We Can Monitor, Manage Or Treat Many Of These Complications

Do This!

- Be aware and vigilant
- Informed consent, Patient education
- Monitor, treat and monitor
Thank You!