Soothing the Savage Beast: Vignettes in Complicated Pain Management

Case Study

Past Medical History

MD is a 52 y/o female with chronic pain from TMJ, fibromyalgia and ruptured L4-L5 disc. She is a former high school teacher. MD is currently on disability due to PTSD from a student assault she suffered that happened to her when she was teaching in another state 25 years ago. The events of this episode are sketchy at best. She states she tries to eat right and exercise, however her height is 5 ft. 2 in and her weight 230 lbs. Her BMI is 42.1. In her chart it states she has borderline personality; however when asked about this she defensively states, “They always get it wrong! I don’t have borderline personality. In fact those psychiatrists were so bad they fired me, twice!!” When asked about sleep, she states she does snore and often wakes with a wet pillow case. She also states she has nightmares, and they center on her father. She states the oxycodone IR works better than the oxycodone (Oxycontin®) and she would like to stop the Oxycontin® and have all her oxycodone as the IR form and would also like to increase her total daily amount of IR oxycodone. In addition, patient states would like a refill on her carisoprodol (Soma®), as that is the only muscle relaxer that works for her and all her other doctors have given her this without any problems.

Case Study Continued

- Her current medications include:
  - Oxycodone (Oxycontin®) 40mg tid
  - Oxycodone IR 15mg qid
  - Diazepam 10mg hs for sleep
- She has failed:
  - Gabapentin: “gave me seizures”
  - Pregabalin (Lyrica®): “I try to watch my weight and don’t want to gain weight”
  - Topiramate (Topamax®): “I couldn’t think”
  - Pregabalin (Lyrica®): “I had no energy to do my daily chores”
  - NSAIDs: “I have an ulcer and they upset my stomach”
  - All muscle relaxers except Soma: “They knocked me out”

Case Study Continued

- Her current lab values are:
  - TSH: 13.00
  - Free testosterone: < 0.01
  - Total testosterone: < 0.01

Comorbidities, Pain and Opioid Therapy

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Nothing to Disclose

Mary Lynn McPherson has no relevant financial relationships to report

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Opioid Adverse Effects

- Constipation
- Nausea/vomiting
- Anorexia
- Sweating
- Dysphoria/delirium
- Pruritus/urticaria
- Hormonal changes
- Bladder dysfunction
- Cardiac effects
- Opioid-induced hyperalgesia
- Tolerance
- Physical dependence
- Addiction
- Diversion/unintentional death
- Sleep disturbances
- Psychomotor impairment
- Clouded vision
- Respiratory depression

What's the big deal?

- Prescription drug use AND abuse has increased significantly over the past decade.
- (Opium) has kept, and does now keep down the population: the women have fewer children than those of other countries…the feble opium-smokers of Assam…are more effeminate than women.”  Charles Alexander Bruce, 1839

Opioids and Hormonal Changes

- 100 million people in the US suffer from chronic pain
- Opioids are increasingly used to manage pain
- Opioids can suppress serum testosterone levels in animals and humans
  - Heroin users
  - High-dose methadone
  - Intrathecal opioid therapy
  - More recently seen with oral and transdermal opioid therapy
- Unrecognized and undertreated

Hypotestosteronemia

- Role of testosterone
  - More than a "sex hormone"
  - Intrauterine development → advanced age
  - Important contributor to the robust metabolic functioning of multiple body systems
    - Stimulation of muscle mass increase and strength
    - Linear growth and maturation of bone
    - Mood and cognition centers in the brain
    - Neuroactive steroids with a neuroprotective role

Opioid-Induced Modulation of Gonadal Function

- Primarily by acting on opioid receptors in the hypothalamus
  - Decreased release or disruption of the normal plasticity of GnRh secretion
  - Results in reduction of the release of LH and FSH from pituitary gland and of testosterone or estradiol from the gonads
- May have a direct effect on the pituitary gland and the testes


Specific Effects in Women

- Decline in LH, FSH, E2, testosterone and progesterone
  - Affects menstruation
- Long-term intrathecal opioid administration
  - 70% premenopausal women developed amenorrhea
  - 30% developed irregularities in menstruation
- Chronic use of SR opioids in women
  - Profound inhibition of ovarian sex hormone and adrenal androgen production
  - Important consequences on menstrual flow and reduced fertility
  - Significantly increased opioid-associated depression, osteoporosis, hyperalgesia


Management of Opioid-Induced Hypogonadism

- Consider nonopioid pain management options
  - TENS, behavioral therapies, injections, radiofrequency, nerve stimulation, nonopioid drugs
- Consider opioid rotation
- Consider strategies that allow opioid dose reduction
  - Concomitant nonopioid analgesics
  - Nonpharmacologic modalities
- Testosterone supplementation (men)
  - Consider consultation with an endocrinologist
  - Choose formulation and dose
    - Transdermal gel
    - Transdermal patch
    - Intramuscular injection
  - Monitor prostate-specific antigen and prostate examination in men
  - Monitor clinical and laboratory results


Testosterone Replacement in Women

- Diagnosis of androgen deficiency in women is difficult
  - Common tests for measuring circulating testosterone are not precise or accurate for physiologically low female testosterone concentrations
- Transdermal patch is the only formulation approved for women
- Designed to deliver 300 mcg/d to achieve testosterone concentrations compatible with premenopausal levels
  - Steady-state serum concentrations achieved after application of second patch


Testosterone Replacement in Women
Hypothyroidism-Induced Pain

- Can cause a variety of muscle or joint-related symptoms
- General muscular weakness and pain, including cramps, and stiffness
- Myopathies (skeletal muscle)
- Carpal Tunnel Syndrome
- Tarsal Tunnel syndrome
- General joint pain, aching, stiffness, known as "arthropathy"
- Tendonitis in the arms and legs

Vitamin D and Chronic Pain

- Inadequacies in Vitamin D have been linked to:
  - Chronic musculoskeletal pain
  - Muscle weakness or fatigue
  - Fibromyalgia syndrome
  - Rheumatic disorders
  - Osteoarthritis
  - Hyperesthesia
  - Migraine headaches
  - Other chronic somatic complaints
  - Mood disturbance of chronic fatigue syndrome
  - Seasonal affective disorder

Vitamin D Supplementation

- In patients with chronic, nonspecific musculoskeletal pain and fatigue syndromes:
  - Vitamin D may be inadequate and concentrations of serum 25(OH)D may be insufficient or deficient.
  - All patients should take a multivitamin to assure at least minimal daily values of essential nutrients, including calcium and 400-800 IU of vitamin D.
  - Recommend a daily 2000 IU vitamin D3 supplement
    - May require extra calcium
Vitamin D Supplementation

- Monitor patient compliance and results for up to 3 months.
  - Other therapies for pain already in progress are generally not discontinued
- If results are still lacking after 3 months, or a persistent 25(OH)D deficiency or osteomalacia is verified, consider a brief course of prescribed high-dose vitamin D3, with or without calcium.

The Effect of PTSD on Chronic Non Cancer Pain

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Disclosure

Ernest J. Dole reports no relevant financial relationships.

Objectives

- Describe the prevalence of co-morbidity of PTSD and chronic non-cancer pain (CNCP)
- List the common symptoms of PTSD & CNCP and the impact that co-morbidity can have on symptoms of both conditions
- Describe the different theoretical models used to describe the co-morbid condition of PTSD & CNCP
- Describe the implications for assessment of therapy for patients with both PTSD & CNCP
- Describe the implications for implementations of therapy for patients with PTSD & CNCP

Setting the Stage

- Definition of Post-Traumatic Stress Disorder (PTSD)
  - an individual must have been exposed to a traumatic event
  - have at least one re-experiencing, three avoidance, and two hyperarousal phenomena
  - have had the symptoms for at least 1 month
  - and the symptoms must cause clinically important distress or reduced day-to-day functioning.
  - It is labeled as acute for the first 3 months and chronic if it lasts beyond 3 months
  - People with sub-syndromal PTSD have all the criteria for PTSD except one of the re-experiencing, avoidance, or hyperarousal phenomena


Case Study Focus

- MD is a 52 y/o female with chronic pain from TMJ, fibromyalgia and ruptured L4-L5 disc.
- She is a former high school teacher.
- MD is currently on disability due to PTSD from a student assault she suffered that happened to her when she was teaching in another state 25 years ago.
- What risk factors does MD have for the development of PTSD?
- What questions could/should be asked that are not in the case?
### Setting the Stage

#### Wretched Statistics
- Every 9 seconds in the US a woman is assaulted or beaten.
- Domestic violence is the leading cause of injury to women—more than car accidents, muggings, and rape combined.
- One in every four women will experience domestic violence in her lifetime.
- An estimated 1.3 million women are victims of physical assault by an intimate partner each year.
- Females who are 20-24 years of age are at the greatest risk of nonfatal intimate partner violence.
- Most cases of domestic violence are never reported to the police.


### Setting the Stage

#### Co-Morbidity of PTSD & CNCP

- Prevalence of CNCP within trauma samples ranged from 20%-80%.
- Prevalence of PTSD within CNCP samples ranged from 10%-50%.
- 24%-47% of fibromyalgia patients attribute the onset of their symptoms to a physical injury associated with an trauma such as MVA.
- In one study 57% of patients with fibromyalgia had clinically significant levels of PTSD sx.

### Co-Morbidity of PTSD & CNCP

- In a sample of PTSD patients reporting physical symptoms, CNCP was the most common physical complaint (45% back pain and 34% headaches).
- PTSD & CNCP share common symptoms of anxiety & depression, hyperarousal, fear & avoidance behavior, reduced activity levels.
- Evolving of PTSD & CNCP symptoms tend to develop in a parallel fashion.
- Studies suggest that the presence of both PTSD and chronic pain can increase the symptom severity of either condition.

### Setting the Stage

#### A prime cause of PTSD is childhood sexual abuse.
- About 16% of American women (about 40 million) are sexually abused (including rape, attempted rape, or other form of molestation) before they reach their 18th birthday.


### Theoretical Models

#### Mutual Maintenance Model

- Attentional bias may be present in chronic pain and PTSD patients such that they attend to threatening or painful stimuli.
- Anxiety sensitivity (AS) may contribute toward a vulnerability to catastrophize.
- Pain may be a reminder of the traumatic event, triggering an emotional response, avoidance of the cause of pain, and any memories of the trauma.
- In both disorders, avoidance may be adopted as a means to minimize pain and disturbing thoughts.
- Fatigue and lethargy associated with depression may contribute to both disorders.
- General anxiety may contribute to both disorders.
- Cognitive demands from symptoms of pain and PTSD limit the use of adaptive coping strategies.

### Co-Morbidity of PTSD & CNCP

- Prevalence of CNCP within trauma samples ranged from 20%-80%.
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### Setting the Stage

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Theoretical Models

• Shared Vulnerability Model
  - Anxiety sensitivity is a predisposing factor contributing to the development of both PTSD and CNCP.
  - AS enhances the perceived sense of alarm during a traumatic event, this increases awareness of psychological threat and physical injury. The increased sensitivity is thought to exacerbate overall emotionality and increase the risk for development of PTSD.
  - For PTSD, the degree of alarm caused by the stressor is combined with the alarm of physiological sensations to further exacerbate the emotional reaction, increasing the risk of developing PTSD.
  - For chronic pain, anxiety sensitivity heightens fear and avoidance of activities that may induce pain, which further increases the chances that pain will be maintained over time.


• Triple Vulnerability
  - An integrated set of triple vulnerabilities needs to be present for developing PTSD: a generalized biological vulnerability, a generalized psychological vulnerability in which one learns to focus anxiety on specific situations.
  - A true or false alarm develops during exposure to situations that symbolize or resemble an aspect of a traumatic event.
  - To develop PTSD, there must be development of anxiety or the sense that these events, including individual emotional reactions to them, are preceding in an unpredictable and uncontrollable manner; that is, when negative affect and a sense of emotional disorganization becomes settled on a belief of threat and not a belief of threat or safety.
  - To develop chronic pain, this model also relates to the development of chronic pain; for development of a chronic pain condition, there must also be development of a belief that the pain is preceding in an unpredictable and uncontrollable manner.


Implications for Therapy for Patients with Co-Morbid PTSD & CNCP

• Assessment
  - CNCP
    - McGill Pain Questionnaire
  - PTSD
    - Posttraumatic stress disorder checklist (PCL) (for a diagnosis of PTSD).


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Implications for Therapy in Patients with Co-Morbid PTSD & CNCP

Assessment
- Co-morbidity of PTSD w/ CNCP has been associated w/ prior opioid use when compared w/ patients w/ CNCP but no PTSD
- Advocate to screen for PTSD in all patients w/ PTSD and CNCP

National Institute on Drug Abuse

Implications for Therapy in Patients with Co-Morbid PTSD & CNCP

Treatment
- Eye Movement Desensitization & Reprocessing (EMDR)
  - Per recent review judged to be "beneficial"
- Basic Cognitive Behavioral Therapy (CBT)
  - Per recent review judged to be "beneficial"
- Hypnosis
  - Percent review effectiveness is "unknown"
- Group CBT
  - Percent review effectiveness is "unknown"
- Relaxation therapy
  - Percent review effectiveness is "unknown"


Implications for Therapy in Patients with Co-Morbid PTSD & CNCP

Pharmacotherapeutic Options
- TCA
  - Few tolerate amitriptyline
    - Per recent review effectiveness is "unknown"
  - Use nortriptyline; desipramine
    - Good for sleep
  - Mirtazapine
    - 15-30mg hs
    - Per recent review effectiveness is "unknown"


Implications for Therapy in Patients with Co-Morbid PTSD & CNCP

Pharmacotherapeutic Options
- Dual Acting Agents
  - Duloxetine (Cymbalta®)
    - Dose: 20 mg/day up to 120 mg/day
    - Caution/ADR: liver dysfunction; bleeding disorders
  - Milnacipran (Savella®)
    - 25 mg/day to 100 mg/day
    - 1st agent w/ more NE activity than serotonin
  - Venlafaxine (Effexor®)
    - May need to get to 300 mg/day
    - 1:30 NE:serotonin
    - Per recent review, "unlikely to be beneficial"


Implications for Therapy in Patients with Co-Morbid PTSD & CNCP

Pharmacotherapeutic Options
- Alpha Adrenergic Blocking Agents
  - Phazacin
  - May help w/ nightmares during sleep
    - 1mg-5mg hs; may go as high as 15mg hs
  - NMDA Receptor Antagonists
    - Memantine: 10 mg bid
    - Amanitine: 100mg bid
  - Dextromethorphan: 30mg bid
  - Central Alpha-2 Adrenergic Agonists
    - Clonidine: 0.1mg bid
    - Guanfacine: 0.03mg-1.5mg q day
    - Tizanidine: 2mg-8mg q 8 hours


Implications for Therapy

Pharmacotherapeutic Options
- Low Dose Naltrexone (LDN)
  - 4.5mg 1 hour before sleep
  - Safe and few ADRs; but must be willing to DC opiates
  - May work on microglia cells, increase endorphin concentrations; increase endorphin receptor numbers

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Impact of PTSD on CNCP

- Conclusion
  - Both conditions co-occur in patients frequently; therefore screening for PTSD in CNCP patients routinely may improve outcomes
  - There are simultaneous trajectories of CNCP and PTSD; therefore simultaneous treatment PTSD in CNCP patients routinely may improve outcomes
  - CBT, EMDR therapy may help patients w/ both co-morbidities
  - The ORT is only risk for aberrant assessment tool that asks about sexual abuse (PTSD)
  - The use of SNRIs, with the possible exception of venlafaxine, central acting alpha-2 adrenergic agents, & alpha adrenergic blocking agents may be helpful for patients w/ both CNCP & PTSD
  - LDN may hold promise in treatment of patients w/ both conditions

Sleep Apnea and Opioids

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Disclosure

Chris Herndon reports no relevant financial relationships.

Objectives

- Describe the pathophysiologic process and differences of central, obstructive, and mixed sleep apneas
- Explain the process in which opioids effect respiratory drive
- Discuss recent studies suggesting increased risk of opioid use in those with sleep apnea
- Formulate a plan to incorporate screening tools into current health-systems practice

Back to the Case

- MD is morbidly obese and snores
- She is on opioids and a benzodiazepine
- What questions do we need to ask that is not in the case?
- What is MD at risk for?

Regulation of Ventilation
Regulation of Ventilation
- PaCO₂, PaO₂, and pH stimulate ventilation
  - More sensitive to rise in PaCO₂ than drop in PO₂
- Respiratory center (pons and medulla) responds to neural and chemical input
  - Upper airway patency
  - Thoracic musculature control
- Thoracic neural receptors
  - Stretch fibers respond to lung volume
  - Irritant receptors respond to lung volume
- Peripheral and central chemoreceptors
  - Peripheral: aortic and carotid bodies (primarily PaO₂)
  - Central: ventral surface of medulla (primarily PaCO₂ and pH)

Types of Sleep Apnea
- Obstructive Sleep Apnea
  - Absent airflow with continued ventilatory effort
- Central Sleep Apnea
  - Absent airflow AND absent ventilatory effort
    - 5 subtypes, one being opioid-mediated and other depressants
- Mixed
  - Periods of absent ventilatory effort followed by obstructed airflow with ventilatory effort
- Hypopnea
  - Reduction in airflow not sufficient to meet diagnostic criteria for apnea

Epidemiology of Obstructive Sleep Apnea (OSA)
- 26% of adults are estimated to be at risk for obstructive sleep apnea
- African Americans effected more commonly than caucasians
- Prevalence increases linearly from age 18 to 55
- Men > women

Pathophysiology of OSA
- Upper airway obstruction
  - Pharyngeal wall changes
  - Nasal congestion
  - Tonsillar hypertrophy
  - Surrounding tissue changes due to obesity
  - Direct trauma and inflammation (i.e., intubation)
- Neuronal contribution
  - Visceral fat mediated leptin resistance
  - Upper airway preparation and patency
  - Dilator muscle innervation
- Medication effects on upper airway patency and drive

Clinical Features of OSA
- More suggestive
  - Witnessed apneas by bed partner
  - Awakening with choking
  - Obesity
  - Large neck circumference
  - Daytime sleepiness
  - Snoring
- Less suggestive
  - Morning headaches
  - Nocturnal restlessness
  - Non-restorative sleep
  - Hypertension

Diagnosis of OSA
- Testing
  - Polysomnography
  - Portable monitoring
- Events
  - Apnea – less than 20% of baseline for > 10 seconds / episode
  - Hypopnea – not apnea but reduced airflow for > 10 seconds / episode
  - Respiratory effort related arousals - awakening but not apnea or hypopnea
  - Hypoventilation – increase of PaCO₂ 10 mmHg > 25% of total sleep time
- Indexes
  - Apnea Hypopnea Index (events / hour)
  - Respiratory Disturbance Index (events / hour)
- Diagnosis
  - AHI or RDI > 15 AND asymptomatic
  - AHI or RDI > 5 AND symptomatic (disturbed sleep, snoring, fatigue)
Is opioid induced sleep disordered breathing clinically relevant?

Walker JM, et al.
- Retrospective cohort (n = 120)
  - 60 pts on chronic opioid therapy matched with 60 controls
  - Matched for age, sex, and BMI
  - Exclusion criteria: age < 18, CHF, stroke, neurologic disease, prior use of O₂, lack of opioid dosing info
  - Results from polysomnography data
    - AHI score greater in opioid vs. non-opioid group (43.5/h vs. 30.2/h; p < .001)
    - CSA events greater in opioid vs. non-opioid group (12.8/h vs. 2.1/h; p<.001)
    - Arterial oxygen saturation less in opioid vs. non-opioid group (-2.1%; p<.001)
    - Dose response relationship in all events

Dose correlation Walker et al

Jungquist CR, et al.
- Cross-section descriptive study of referrals to sleep clinic meeting criteria for sleep-disordered breathing (AHI >5)
  - Study arms include no pain (n=171), pain-no opioid (n=187), and pain-opioid (n=61)
  - Exclusion criteria: < 21 yrs, acute pain, methadone use for addiction, surgical trachea correction, narcolepsy
  - Results
    - No difference in Central Apnea Index (CAI) between no-pain and pain-no opioids (p = 0.28)
    - No difference in Obstructive Apnea Index (OAI)
    - Significant difference in CAI between pain-no opioids and pain-opioids study arms (p < 0.001)
    - Significant correlation R pain intensity in OAI and CAI (p=0.021 and p=0.009, respectively)
    - Dose correlation with CAI (p < 0.001), but not OAI

Opioid Effects on Sleep

Walker JM, et al.
- Ataxic (Briot) Breathing
  - Inhibition of central chemoreceptors
  - Typically associated with neurologic disease
  - Irregular and variable respiratory rate and effort
- Obstructive Sleep Apnea
  - Increased accessory muscle rigidity
  - Decreased airway patency via neuronal inhibition
- Central Sleep Apnea
  - Blunted response to hypoxemic respiratory drive via peripheral chemoreceptors
  - Blunted compensatory response to airway resistance or loading

Treatments

- Continuous positive airway pressure (CPAP)
  - Usually reserved for OSA
  - May worsen opioid-associated CSA
- Bi-level positive airway pressure (BiPAP)
- BiPAP with backup rate control
  - Superior to CPAP for opioid-associated sleep disordered breathing
- Adaptservo Ventilation (ASV)
  - Variance of ventilatory support which adapts to breathing pattern
  - Emerging data to suggest superiority over other modalities

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CSA treatment in chronic opioid use

STOP Bang Screening for Sleep Apnea
1. Do you snore loudly?
2. Do you often feel tired, fatigued, or sleepy during the daytime?
3. Has anyone observed you stop breathing during sleep?
4. Do you have or are you being treated for high blood pressure?
5. Body Mass Index > 35?
6. Age over 50 yrs?
7. Neck circumference greater than 40cm (15.5 in)?
8. Male?

“Yes” to three or more of the eight questions indicates high risk for OSA

Conclusions
- Opioid related sleep disorder breathing may present as both obstructive and central sleep apneas (CSA > OSA)
- Treatment of OSA with CPAP may worsen underlying opioid associated CSA
- Severity of CSA associated with chronic opioid use is dose related
- Concurrent OSA and CSA results in significant hypoxemia
- Sleep disordered breathing implicated in part of growing national problem of opioid overdose deaths

High-Dose Opioids for CNCP: Should the Sky be the Limit?

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Disclosure
Michele L. Matthews reports no relevant financial relationships.

Learning Objectives
At the end of this program, the participant will be able to:
- Analyze the risk of overdose in patients receiving high dose opioids
What is High-Dose Opioid Use?

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<tbody>
<tr>
<td>Morphine Milligram Equivalents</td>
<td>≥ 120</td>
<td>≥ 200</td>
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Veterans Affairs/DoD Chronic Opioid Therapy Guidelines. Available at: http://www.healthquality.va.gov/Chronic_Opioid_Therapy_COT.asp
Canadian Guidelines on COT in CNCP. Available at: http://nationalpaincentre.mcmaster.ca/opioid/

Who Gets High-Dose Opioid Therapy?

- **TROUP Study (2008)**
  - Population
    - Arkansas residents with CNCP
  - Correlates
    - Age between 41-60 years
    - Medicaid
    - Multiple pain diagnoses
    - Mental health diagnosis
    - Concomitant sedative-hypnotic

- **Morasco et al (2010)**
  - Population
    - Military veterans in the Pacific Northwest
  - Correlates
    - Male gender
    - Multiple pain diagnoses
    - Multiple comorbidities
    - Mental health diagnosis
    - Concomitant sedative-hypnotic
    - Nicotine dependence


Opioid Prescriptions and ED Visits

- **TROUP Study (2010)**
  - Highest rates of ED visits in:
    - Younger age
    - Females
    - Multiple comorbidities
    - Presence of back pain
    - Presence of headaches
  - Correlation with daily dose
    - Doses between 35 to 120 mg/day were significantly associated with ED visits in commercially-insured patients
    - Doses higher than 120 mg/day were not associated with ED visits but were associated with doubling of risk of adverse effects in all patients


Opioid Prescriptions and Risk of Overdose

- **CONSORT Study (2010)**
  - Overdose rates
    - 148 per 100,000 person-years (fatal and nonfatal combined)
    - 17 per 100,000 person-years (fatal alone)
  - Relationship between dose and overdose

<table>
<thead>
<tr>
<th>Daily Opioid Dose (MME)</th>
<th>Overdose Rate (95 CI) Per 100,000 Person-Years</th>
<th>Hazard Ratio for All Overdose Events (95 CI)</th>
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<tbody>
<tr>
<td>1 to &lt; 20</td>
<td>160 (100 – 233)</td>
<td>1.00</td>
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<td>20 to &lt; 50</td>
<td>260 (95 – 505)</td>
<td>1.44 (0.57 – 3.62)</td>
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<td>50 to &lt;100</td>
<td>677 (249 – 1377)</td>
<td>3.73 (1.47 – 9.50)</td>
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<tr>
<td>≥ 100</td>
<td>1791 (884 – 2995)</td>
<td>8.87 (3.96 – 19.72)</td>
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Opioid Prescriptions and Risk of Overdose (cont’d)

- **Bohnert et al (2011)**
  - Unadjusted rate of prescription opioid overdose death by opioid dose

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<tr>
<th>Daily Opioid Dose (MME)</th>
<th>Overdose Deaths</th>
<th>Person-Months</th>
<th>Overdose Death Rate per 1000 Person-Months (95%CI)</th>
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<td>0</td>
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<td>2,729,022.7</td>
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<td>1 - &lt; 20</td>
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<td>108</td>
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<td>125</td>
<td>100,479.3</td>
<td>1.24 (1.04-1.45)</td>
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Opioid Prescriptions and Risk of Overdose (cont'd)

- Gomes et al (2011)
  - Association between opioid-related death and overdose

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<tr>
<th>Daily Opioid Dose (MME)</th>
<th>Cases (n/N)</th>
<th>Controls (n/N)</th>
<th>OR (95% CI)</th>
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<td>20 – 49</td>
<td>118/498</td>
<td>514/1714</td>
<td>1.32 (0.94-1.84)</td>
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<tr>
<td>50 – 99</td>
<td>97/498</td>
<td>273/1714</td>
<td>1.92 (1.30-2.85)</td>
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<tr>
<td>100 – 199</td>
<td>82/498</td>
<td>181/1714</td>
<td>2.04 (1.28-3.24)</td>
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<tr>
<td>≥ 200</td>
<td>116/498</td>
<td>223/1714</td>
<td>2.88 (1.79-4.63)</td>
</tr>
</tbody>
</table>


Risk of Unintentional Drug Overdose Death

- Paulozzi et al (2012)

<table>
<thead>
<tr>
<th>Daily Opioid Dose (MME)</th>
<th>Case Deaths (%)</th>
<th>Control Patients (%)</th>
<th>OR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single peak &gt; 40</td>
<td>54.7</td>
<td>26.6</td>
<td>3.3 (2.6-4.1)</td>
</tr>
<tr>
<td>Single peak &gt; 120</td>
<td>29.7</td>
<td>5.2</td>
<td>7.6 (5.8-10)</td>
</tr>
<tr>
<td>True peak &gt; 40</td>
<td>65.3</td>
<td>30</td>
<td>4.3 (3.4-5.5)</td>
</tr>
<tr>
<td>True peak &gt; 120</td>
<td>36.3</td>
<td>6.4</td>
<td>8.4 (6.5-10.8)</td>
</tr>
<tr>
<td>Average &gt; 40</td>
<td>34.3</td>
<td>4.3</td>
<td>12.2 (9.2-16)</td>
</tr>
<tr>
<td>Average &gt; 120</td>
<td>20</td>
<td>2.1</td>
<td>11.3 (8.1-15.8)</td>
</tr>
</tbody>
</table>


Percentage of Patients and Prescription Drug Overdoses, by Risk Group

- Rich and Webster (2011)

<table>
<thead>
<tr>
<th>Observation</th>
<th>N = 20 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MME &gt; 60</td>
<td>20 (100)</td>
</tr>
<tr>
<td>Last documented pain level &gt; 6/10 (NRS)</td>
<td>20 (100)</td>
</tr>
<tr>
<td>Taking opioids for &gt; 6 months</td>
<td>20 (100)</td>
</tr>
<tr>
<td>History of mental health disorder</td>
<td>14 (70)</td>
</tr>
<tr>
<td>History of snoring</td>
<td>12 (60)</td>
</tr>
<tr>
<td>Current or past substance abuse disorder</td>
<td>8 (40)</td>
</tr>
</tbody>
</table>


Malpractice Cases Involving Fatal Opioid Overdose

- Passik SD, Lowery A. Psychological variables potentially implicated in opioid-related mortality as observed in clinical practice. Pain Medicine 2011; 12: S36-S42.

Risk Factors Beyond Dose

- Provider error due to knowledge deficits
- Psychological variables
  - Catastrophizing
  - Impulsivity
  - Chemical coping
  - Lack of acceptance
  - Personality disorders
  - Demoralization and existential distress
  - Sensation seeking
  - Escapism

- Patient non-adherence
- Unanticipated comorbidities
- Presence of additional centrally-acting drugs

Clinical Implications

- Guidelines for COT in CNCP
- Risk Evaluation and Mitigation Strategies (REMS) for ER/LA opioids
- Prescription drug monitoring programs (PDMPs)
- Opioid overdose prevention initiatives
- Expansion of substance abuse resources
- Role of the insurer
- Does regulation mean education?
Summary

- Opioid dose has been correlated to increased risk of overdose in patients with CNCP
  - Limitations to available data
    - Need to identify better ways to gather data related to opioid-related overdose deaths
  - Need for balance between the “epidemics”
    - Underreatment of pain vs. risk of opioid misuse/abuse/overdose

Back to the Case

Is this patient at risk of opioid overdose?
If so, what are her risk factors?

What are your recommendations for safe and effective pain management?