The Use of Opioids for Non-malignant pain

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Objectives

- State of opioid prescribing
- Efficacy for chronic non-cancer pain (CNCP) & side effects
- Addiction: definitions
- Opioid risk stratification & monitoring
Nomenclature

- **Opium**: dried powdered mixture of 20 alkaloids from the seed capsules of the poppy
- **Opiate**: any agent derived from opium (really only 3: codeine, morphine, thebaine)
- **Opioid**: all substances with morphine like properties
We are a culture of pill takers....

- Americans are only ~5% of the world’s population, yet we use 80% of the world’s opioid supply, 99% of the world’s hydrocodone supply and 66% of the world’s illicit drugs.¹

Opioid use - statistics

- 15% of chronic pain patients not treated with opioids had illicit drug use vs. 34% illicit drug use in patients treated with opioids.¹
  - Patients with substance abuse are more likely to request & be prescribed opioids?
  - Patients prescribed opioids are more likely to develop co-morbid substance abuse issues?

Opioid overdose

- From 2004 to 2008 the estimated number of emergency department visits linked to the nonmedical use of prescription pain relievers rose from 144,644 visits to 305,885 visits a year.¹

- Methadone was 2% of painkiller prescriptions in the United States in 2009, but was involved in >30% of prescription painkiller overdose deaths.²
  - 4/10 overdose deaths from a single prescription painkiller involved methadone
  - 6x as many people died of methadone overdoses in 2009 vs 1999

¹ http://www.cdc.gov/media/pressrel/2010/r100617.htm
² http://www.cdc.gov/media/releases/2012/p0703_methadone.html
Unintentional Drug Overdose Deaths
United States, 1970-2007

In 2007, there were 9.18 deaths per 100,000 population due to unintentional drug overdose, based on 27,658 deaths.

Source: Centers for Disease Control and Prevention. Unintentional Drug Poisoning in the United States (July 2010).
Drug-Induced Deaths Second Only to Motor Vehicle Fatalities, 1999–2007

Tremendous increase in prescribing

- From 1997 to 2007, the milligram-per-person use of prescription opioids in the U.S. increased from 74 milligrams to 369 milligrams
  - ↑ 402%

- In 2000, retail pharmacies dispensed 174 million prescriptions for opioids; by 2009, 257 million prescriptions were dispensed
  - ↑ 48%

http://www.whitehouse.gov/ondcp/prescription-drug-abuse
Who is prescribing these meds?

- 90% of patients are on opioids prior to presenting to a pain center.¹
- Main prescribers of opioid analgesics are PCPs, followed by dentists and orthopedic surgeons. The main prescribers for patients age 10-19 are dentists.²

PCP prescribing habits

- A 2012 study on PCP prescribing (N=61 PCPs) of pain meds to high risk patients showed that most reported low confidence and satisfaction levels in treating chronic pain.
  - Despite this fact the majority (67.2%) were “highly likely” to prescribe opioids to patients with active substance use.

PCP prescribing habits

- In a 2012 study of 38 PCPS who treat high-risk patients, only 42.9% used an opioid agreement when prescribing to patients with a history of substance abuse.

PCP prescribing habits

- PCPs assessed regarding following of nationally accepted pain treatment guidelines before and after 2-hour intervention
- What % of PCPs discussed....

<table>
<thead>
<tr>
<th></th>
<th>Before</th>
<th>After</th>
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</thead>
<tbody>
<tr>
<td>Comorbid depression</td>
<td>35%</td>
<td>44%</td>
</tr>
<tr>
<td>Functional status</td>
<td>38%</td>
<td>49%</td>
</tr>
<tr>
<td>Substance use</td>
<td>25%</td>
<td>34%</td>
</tr>
<tr>
<td>Side effects</td>
<td>14%</td>
<td>20%</td>
</tr>
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</table>

OPIOIDS FOR PAIN
Whatever they’re called, at least they work...

- In a large epidemiologic study in Denmark, chronic pain patients using opioids had worse pain, higher health care utilization and lower activity levels than matched chronic pain patients not using opioids.¹

- Opioid use may go against important principles of chronic pain management including increased self-efficacy, reduced reliance on the health care system, reinforcement of pain behavior, and passivity and loss of autonomy by externalization of the locus of control.²

...or maybe not.

- A systematic review of randomized trials for multiple opioids utilized for managing various chronic pain conditions, showed fair evidence for tramadol in managing osteoarthritis. For all other conditions and all other drugs excluding tramadol, the *evidence was poor* based on either weak positive evidence or indeterminate or negative evidence.

<table>
<thead>
<tr>
<th>Myth:</th>
<th>Fact:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic opioid therapy is supported by strong evidence</td>
<td>Evidence of long-term efficacy is limited and of low quality</td>
</tr>
<tr>
<td>Physical dependence only occurs with high doses over months</td>
<td>With daily use, dependence can occur in days or weeks</td>
</tr>
<tr>
<td>High dose (≥120 mg of morphine/day) therapy is supported by strong evidence</td>
<td>No randomized trials show long-term effectiveness in CNCP</td>
</tr>
</tbody>
</table>
Opioids – side effects

- Opioid-induced constipation is the most common side effect occurring in 40-95% of patients.¹

- Nausea occurs in 25% (less common in men), sedation in 20-60% and pruritus in 2-10%.²

- Opioids decrease total sleep time, sleep efficiency, delta sleep, REM sleep and increase time spent in light sleep.¹

Opioids & immunosupression

- Opioid use in >65 is associated with 3x ↑ risk of pneumonia.¹
- With the exception of methadone and tramadol, opioids have been shown to be immunosuppressive.²
- Opioids exacerbate immunosuppression in persons with HIV and may increase viral load.³

Opioid-induced Endocrinopathy (OIE)

- Hypothalamic-pituitary-gonadal Axis
  - Hypothalamus $\rightarrow$ GNRH $\rightarrow$ anterior pituitary $\rightarrow$ FSH & LH $\rightarrow$ gonads (testes/ovaries) $\rightarrow$ testosterone & estradiol

- Opioids bind in the hypothalamus $\downarrow$ pulsatile release of GNRH $\rightarrow$ $\downarrow$ LH & FSH

- Signs/symptoms of hypogonadism
  - Decreased libido, fatigue, depressed mood, hot flashes, loss of muscle mass, infertility, osteoporosis, erectile dysfunction, abnormal menses
Study: 88 males with CNCP on opioid medications, 44% had osteopenic or osteoporotic bone density and 27% were hypogonadal. ¹

Study: 54 males with CNCP on long-acting opioids vs 27 healthy controls, total testosterone was low in 74% of the opioid group. ²

- Of men who reported normal erectile function before opioid use, 87% had severe erectile dysfunction

Opioid-induced Hyperalgesia (OIH)

- The condition in which opioids result in increased pain levels
- OIH was first recognized in the 1800s, and that fact that morphine could result in increased pain was observed by Albutt in 1870.¹
- OIH typically produces diffuse pain, less defined in quality, that extends beyond areas of pre-existing pain. It is worsened with increasing opioid doses.

Patients with chronic low back pain treated with long-acting morphine developed hyperalgesia within 1 month of starting treatment.\(^1\)

Observational study in patients taking methadone or morphine for CNCP, both groups developed hyperalgesia.\(^2\)

Patients on opioids who were scheduled for an interventional treatment reported more than those not on opioids.\(^3\)

How are opioids addicting?

- Opioids activate pre-synaptic GABA neurons in the ventral tegmental area of the midbrain, inhibiting the release of GABA.
- This dis-inhibits (GABA tonically inhibits dopamine release here) dopaminergic neurons allowing extra dopamine in the nucleus accumbens stimulating the reinforcing effects.
Addiction

- In CNCP, rates were believed to be 2-18%.
- July 2011 study assessed rates of opioid abuse/dependence using both DSM-IV and proposed DSM-V criteria in CNCP:

35%

Tolerance

- Two forms:
  - Increased amount of substance to achieve the same effect
  - Decreased effect with the same amount of substance used over a period of time

- May be positive or negative

- *Tachyphylaxis*: an acute (sudden) decrease in the response to a drug after its administration
  - EX: LSD
Withdrawal

- Development of a set of symptoms when the substance is removed (usually acutely) or prevented from being used.
- Withdrawal symptoms do not indicate tolerance and do not indicate addiction.
  - SSRIs – widely known not to be associated with tolerance or addiction
Addiction (ASAM)

- Addiction is a primary, chronic disease of brain reward, motivation, memory and related circuitry.
- Dysfunction in these circuits leads to characteristic biological, psychological, social and spiritual manifestations.
- This is reflected in an individual pathologically pursuing reward and/or relief by substance use and other behaviors.
ABCDE’s of Addiction

- Inability to completely **Abstain**
- Impairment in **Behavioral** control
- **Craving**
- **Diminished** recognition of significant problems
- A dysfunctional **Emotional** response
4 C’s of Addiction

- Loss of Control over use
- Continued use despite negative Consequences
- Compulsive use
- Craving
Substance Abuse

- A maladaptive pattern of substance use $\geq 1$ within a 12-month period:
  - Failure to fulfill major role obligations
  - Recurrent use in conditions which are physically hazardous
  - Substance-related legal problems
  - Continued use despite social/interpersonal problems
Substance Dependence

- A maladaptive pattern of substance use $\geq 3$ within a 12-month period:
  - Tolerance
  - Withdrawal
  - Taking substance in larger amounts or for longer periods than intended
  - Persistent desire or unsuccessful efforts to cut down
  - Great deal of time spent obtaining, using or recovering from substance
  - Social/recreational/occupational activities are given up
  - Continued use despite knowing it is a problem
Pseudo-addiction

- A state in which the patient displays drug-seeking behavior due to an untreated or poorly treated underlying condition. When appropriate treatment is given, drug-seeking behaviors resolve
  - Opioid seeking for true untreated pain
  - Benzo seeking for anxiety
    - Ex: 49 yo WF with Stage IV squamous cell carcinoma of tongue. Using ativan 1mg 6x/day
Assessing Addiction Risk

- Evaluation should be done before a patient is prescribed any opioids
- Understand general risk factors
- Understand aberrant behaviors
- Utilize a validated tool (Opioid Risk Tool)
- Render recommendation for treatment type and monitoring
Risk factors for Opioid abuse

- Family history of alcohol, illicit or prescription drug abuse
- History or preadolescent sexual abuse
- History of mental illness
- Legal/arrest history
- Personal history of alcohol, illicit or prescription drug abuse
- Psychological stressors (relationship issues, financial difficulties)
- Tobacco abuse
- Unrealistic expectations from opioid use (100% pain relief, resumption of all life activities without modification)
- Younger age
Aberrant behaviors

- Increasing dose of medication without clinician recommendation
- Abnormal results on UDS
- Injecting oral medications
- Selling medications
- Forgery to obtain medications
- Simultaneously obtaining controlled medications from multiple providers
Aberrant behaviors (cont.)

- Going to ER for opioid medication refills
- Requesting early refills
- Reporting lost or stolen prescriptions
- Not following up with appointments that do not involve dispensing opioids
- Motor vehicle accidents or arrests
- Abuse of illicit substances
- Reporting relief only from opioid medications
Aberrant Behavior

- Aberrant behaviors are found in up to 40% of patients prescribed opioid medications.
- The most predictive risk factor for abuse is a personal history of substance abuse.
| 1. Family History of Substance Abuse | Alcohol | [ ] | 1 | 3 |
|                                      | Illegal Drugs | [ ] | 2 | 3 |
|                                      | Prescription Drugs | [ ] | 4 | 4 |
| 2. Personal History of Substance Abuse | Alcohol | [ ] | 3 | 3 |
|                                      | Illegal Drugs | [ ] | 4 | 4 |
|                                      | Prescription Drugs | [ ] | 5 | 5 |
| 3. Age (Mark box if 16 – 45)          | [ ] | 1 | 1 |
| 4. History of Preadolescent Sexual Abuse | [ ] | 3 | 0 |
| 5. Psychological Disease              | Attention Deficit Disorder, Obsessive Compulsive Disorder, Bipolar, Schizophrenia | [ ] | 2 | 2 |
|                                      | Depression | [ ] | 1 | 1 |

**TOTAL**

<table>
<thead>
<tr>
<th></th>
<th>Item Score If Female</th>
<th>Item Score If Male</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td></td>
<td></td>
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</tbody>
</table>

Total Score Risk Category

- Low Risk: 0 – 3
- Moderate Risk: 4 – 7
- High Risk: ≥8
# Monitoring based on Risk Level

<table>
<thead>
<tr>
<th></th>
<th>Low</th>
<th>Moderate</th>
<th>High</th>
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<tbody>
<tr>
<td>Aberrant behavior?</td>
<td>5%</td>
<td>28%</td>
<td>90%</td>
</tr>
<tr>
<td>Frequency of visits</td>
<td>Monthly</td>
<td>Biweekly</td>
<td>Weekly</td>
</tr>
<tr>
<td>UDS at initiation?</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Other UDS</td>
<td>Randomly</td>
<td>Every visit</td>
<td>Every visit</td>
</tr>
<tr>
<td>Pill Counts?</td>
<td>No</td>
<td>Consider</td>
<td>Yes</td>
</tr>
<tr>
<td>Referral to psychiatry/addiction?</td>
<td>No</td>
<td>Consider</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Screener and Opioid Assessment for Patients with Pain-Revised (SOAPP-R)

- Predicts possible opioid abuse in chronic pain patients
- 5-10 minutes to administer (filled out by the patient)
- 24 items
- Free to use, comes with self-scoring
  - Add up the score of all items.
    - $\geq 22$ high risk
    - $10 - 21$ moderate risk
    - $< 9$ low risk
### Screener and Opioid Assessment for Patients with Pain-Revised (SOAPP®-R)

The following are some questions given to patients who are on or being considered for medication for their pain. Please answer each question as honestly as possible. There are no right or wrong answers.

<table>
<thead>
<tr>
<th>Question</th>
<th>Never</th>
<th>Seldom</th>
<th>Sometimes</th>
<th>Often</th>
<th>Very Often</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. How often do you have mood swings?</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>2. How often have you felt a need for higher doses of medication to treat your pain?</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>3. How often have you felt impatient with your doctors?</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>4. How often have you felt that things are just too overwhelming that you can't handle them?</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>5. How often is there tension in the home?</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>6. How often have you counted pain pills to see how many are remaining?</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>7. How often have you been concerned that people are taking your pills?</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
</tbody>
</table>
Which screening method to use?

- 2012 study compared psychologist screen vs ORT vs SOAPP-r at 1 year for patients who were subsequently discharged\(^1\)
  - Psychologist screen was most predictive of discharge and a combination of psychologist + screening method gave the best sensitivity/specificity.

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Tips: Outpatients

- Discuss openly the need for frequent visits
- Phrase it in terms of concern/safety
- Tell patients at the first visit use of urine drug screens
- Inform them that like all medications, use of opioids will be a trial.
- Determine your own threshold/end-point and discuss with the patient at the first visit.
- Document, document, document
Tips: Inpatient

- Less is more
- Inform the patient that if they do not agree with the treatment plan, there are other facilities they can freely choose
- Remember, YOU are in charge of treatment not the patient
So, for those on opioids

- Necessary to screen for mental illness
- Necessary to screen for substance use
- There are high rates of addiction (~1/3)
- There is lack of evidence for efficacy