Case Study
Mary Williams: 42 year old female

**Past Medical History**
- Type 2 diabetes mellitus x 8 years
- Painful diabetic neuropathy x 2 years
- Hypertension
- Chronic low back pain
- Tobacco dependence
- Alcohol dependence (in recovery 10 yrs)
- Obesity
Case Study
Mary Williams

Current Medications
- Metformin 1000 mg 2x/day
- Lisinopril 10 mg 1x/day
- Hydrochlorothiazide 12.5 mg 1x/day
- Aspirin 81 mg 1x/day

Current Pain Medications
- Oxycodone/APAP 5mg/325 mg
  1-2 tablets every 4-6 hours
- Gabapentin 300 mg 3x/day

Case Study
Mary Williams

Previous Pain Medications
- NSAIDs
  Inadequate pain relief and upset stomach
- Acetaminophen
  Inadequate pain relief
- Tricyclic antidepressants
  Inadequate pain relief and dry mouth
- Tramadol
  Inadequate pain relief
- Acetaminophen with codeine
  Inadequate pain relief
Case Study
Mary Williams

Social History

- **Receptionist**
  Law office 20 hours/week

- **Married**
  Husband manages hardware store

- **Children**
  Ages 6, 12 and 15 years

Case Study
Mary Williams

Substance Use History

- **Alcohol dependence**
  In recovery for past 10 years

- **Tried marijuana in high school**

- **No recent history of illicit drug use**

- **Smokes tobacco**
  1 pack per day for the past 25 years

Family History

- **Family history of substance abuse**
  Mother died from complications of alcoholic cirrhosis
Assessing Chronic Pain and Opioid Misuse Risk

Learning Objectives: Essential Content 1

- Discuss prevalence of chronic pain in the US
- Discuss prevalence of the use and misuse of opioid analgesics
- Describe the pharmacology, efficacy and safety of opioid analgesics
- Describe the components of a thorough opioid misuse risk assessment for a potential candidate for chronic opioid therapy
Case Study
Mary Williams

- Visiting provider for first time
- Previous PCP moved out of state

- Takes 4 to 8 oxycodone/ APAP tablets per day for chronic pain
  - Makes it possible for her to go to work
- Best pain relief 8 tablets per day
  - Previous PCP limit of 150 tablets per month
  - Afraid she would become “addicted”
- She hopes to get enough medication to consistently take 8 tablets per day

Case Study
Mary Williams

- Visiting provider for first time
- Previous PCP moved out of state

- Very careful not to run out early
  - Gets anxious if supply runs out early in month
- Nausea, vomiting and diarrhea upon running out
- Has enough medication to last one week
  - Brought in her previous medical records
Case Study
Mary Williams

Pain Assessment
- Severe pain in feet
  - Burning, numbness and tingling
- Trouble sleeping and “depressed” because of her chronic pain
- Pain worse at night
- Due to only taking 3-4 tablets/day because it is end of month

On a scale of 1-10 states pain is “20”

Assessing Pain
Building Trust

Patient Issues

Patients will assume that you don’t believe their pain complaints

Often demonstrated by exaggerating pain scores

Building Trust

Patient Issues

Some patients with adequate pain relief believe it is not in their best interest to report pain relief

Fear that medication will be reduced

Fear that physician may decrease efforts to diagnose problem

Building Trust

Provider Issues

- Assume patient fears you think pain is not real or not very severe
- After you take a through pain history...

Show empathy for patient experience

Educate patient about need for accurate pain scores to monitor therapy

Validate that you believe pain is real

Discuss factors which worsen pain and limit treatment (i.e. substance abuse, mental health)

Believing a patient’s pain complaint does not mean opioids are indicated

Pain Assessment

- Pain scales
  - Numeric rating
  - Visual analog
  - Faces scale

- Multidimensional instruments
  - McGill Pain Questionnaire
  - Brief Pain Inventory (BPI)
  - Pain, Enjoyment, General activity (PEG) scale

Case Study
Mary Williams

PEG Scale Assessment
In the past week:

- Pain on average?
  - No pain
  - As bad as you can imagine

- Pain interfered with enjoyment of life?
  - Does not interfere
  - Completely interferes

- Pain interfered with general activity?
  - Does not interfere
  - Completely interferes

Physical
- Normal vital signs
- Weight 220 lbs (BMI 32 = obese)
- No acute distress
- Normal cardiopulmonary exam
- Spine normal alignment, negative straight leg test
- No Achilles tendon reflex bilaterally
- Diabetic foot exam:
  - No lesions/ulcerations
  - Palpable pulses
  - Monofilament testing bilaterally 4/5
**Scope of the Problem**

100 Million in U.S. with Chronic Pain

- 42% with pain lasting over one year
- 33% report pain as disabling
- 63% have seen primary care physician for help

$600 Billion Annual Costs

- Healthcare expenses
- Lost income
- Lost productivity

**Chronic Pain is Complex**

**Genetic Predispositions**

- Structure and function of the nervous system
- Molecular basis for response to pain and/or analgesia

**Environmental Stressor Effects**

- Work, home

**Social Effects**

- Socially determined constructs of pain, suffering and disability
- Beliefs about pain treatment

American Academy of Pain Medicine www.painmed.org
Institute of Medicine. 2011 Relieving Pain in America. Washington D.C.
## Psychiatric Co-Morbidities

<table>
<thead>
<tr>
<th>Condition</th>
<th>Incidence Chronic Pain Patients</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression</td>
<td>33 - 54%</td>
<td>Cheatle M, Gallagher R, 2006</td>
</tr>
<tr>
<td>Anxiety Disorders</td>
<td>16.5 - 50%</td>
<td>Dersh J., et al., 2002</td>
</tr>
<tr>
<td>Personality Disorders</td>
<td>31 - 81%</td>
<td>Knaster P, et al., 2012</td>
</tr>
<tr>
<td>PTSD</td>
<td>49% veterans 2% civilians</td>
<td>Otis J., et al., 2010</td>
</tr>
<tr>
<td>Substance Use Disorders</td>
<td>15 - 28%</td>
<td>Polatin PB, et al. 1992</td>
</tr>
</tbody>
</table>

## Chronic Pain is Complex

![Diagram illustrating various factors affecting patients A and B](Gatchel_RJ_Am_Psychol_2004_Nov_59(8):795-805.png)
Screening for Unhealthy Substance Use

**Alcohol**

“Do you sometimes drink beer, wine, or other alcoholic beverages?”

“How many times in the past year have you had 5 (4 for women) or more drinks in a day?”

(+ answer: > 0)

**Drugs**

“How many times in the past year have you used an illegal drug or used a prescription medication for non-medical reasons?”

(+ answer: > 0)

---

Screening for Mental Illness

**Patient Health Questionnaire (PHQ 2, PHQ 9)**

**Other psychiatric history – anxiety, PTSD**

**Suicidal, homicidal**

**Mental status and competency**

---

**Screening for Depression**

**PHQ2**

<table>
<thead>
<tr>
<th>Over the last 2 weeks, how often have you been bothered by any of the following problems?</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Little interest or pleasure in doing things</td>
</tr>
<tr>
<td>2. Feeling down, depressed, or hopeless</td>
</tr>
</tbody>
</table>

**Scoring:**

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Not at all</td>
</tr>
<tr>
<td>1</td>
<td>Several days</td>
</tr>
<tr>
<td>2</td>
<td>More than half the days</td>
</tr>
<tr>
<td>3</td>
<td>Nearly every day</td>
</tr>
</tbody>
</table>

- **Interpretation**
  - Positive if 3 or more points

- **Administer PHQ9 if positive**

- **Efficacy**
  - Test Sensitivity: 83%
  - Test Specificity: 92%

---

**Case Study**

**Mary Williams**

**Screening Results**

- Screened negative for unhealthy substance use and depression
Pain is moderate to severe
Pain has significant impact on function
Pain has significant impact on quality of life
Non-opioid pharmacotherapy has failed
If already on opioids, is there documented benefit
Opioids

Natural (Opiates) and Semisynthetic

Synthetic

Opioid Chemical Classes with Examples

- Phenathrenes prototypical opioids
  - Morphine, Codeine, Hydromorphone, Hydrocodone, Oxymorphone, Buprenorphine

- Benzomorphans
  - Pentazocine

- Phenylpiperidines
  - Fentanyl

- Diphenylheptanes
  - Methadone

Activation of Mu Receptors

**Opioid Pharmacodynamics**

- Turn on descending inhibitory systems in the midbrain
- Prevent ascending transmission of pain signal
- Inhibit terminals of C-fibers in the spinal cord
- Inhibit activation of peripheral nociceptors

Image source: www.mayo.edu/proceedings

How Good are Opioids for Chronic Pain?

- Most literature: surveys and uncontrolled case series
- RCTs are short duration <8 months with small samples <300 patients
- Mostly pharmaceutical company sponsored
- Outcomes
  - Better analgesia with opioids vs. placebo
  - Pain relief modest
  - Mixed reports on function
  - Addiction not assessed

Variable Response to Opioids

Not all patients respond to the same opioid in the same way

Not all pain responds to the same opioid in the same way

Variable Response to Opioids

Mu Receptor

- G protein-coupled receptor family, signal via second messenger (cAMP)
- >100 polymorphisms in the human MOR gene
- Mu receptor subtypes

Variable Response to Opioids

**Opioid Pharmacokinetics**

- Opioid metabolism differs by individual opioid and by individual patient
- Most opioids are metabolized by the cytochrome P450 (CYP) system
  - Codeine may be ineffective in ~10% of Caucasians due to genetic polymorphisms in CYP2D6
- Trial of several opioids may be needed to find acceptable balance between analgesia and tolerability


---

**Opioid Choices with Examples**

- **Full mu agonists**
  - Morphine, Oxycodone, Hydrocodone, Hydromorphone, Fentanyl, Methadone, Oxymorphone
- **Partial mu agonist**
  - Buprenorphine
- **Dual mechanism**
  - Tramadol, Tapentadol
- **Mixed agonist/antagonists**
  - Pentazocine
Opioid Formulations and Routes

Transdermal

- Immediate release (IR/SA)
- Extended release / Long acting (ER/LA)
- Fentanyl
- Buprenorphine

Buprenorphine off-label use for pain

Oral

Sublingual

Transdermal Preparations

- Fentanyl and Buprenorphine
- Convenient dosing
  - Fentanyl every 72 hours
  - Buprenorphine every 7 days
- Slow onset and delayed offset
- Requires predictable blood flow and adequate subcutaneous fat
- Absorption is altered with fever, broken skin, edema
- Some with metal foil backing and not compatible with MRI
## Opioid Choice

<table>
<thead>
<tr>
<th>Immediate Release (IR/SA)</th>
<th>Extended Release / Long-acting (ER/LA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Morphine</td>
<td>• Morphine</td>
</tr>
<tr>
<td>• Hydrocodone</td>
<td>• Hydrocodone</td>
</tr>
<tr>
<td>• Hydromorphone</td>
<td>• Hydromorphone</td>
</tr>
<tr>
<td>• Oxycodone</td>
<td>• Oxycodone</td>
</tr>
<tr>
<td>• Oxymorphone</td>
<td>• Oxymorphone</td>
</tr>
<tr>
<td>• Tramadol</td>
<td>• Tramadol</td>
</tr>
<tr>
<td>• Tapentadol</td>
<td>• Tapentadol</td>
</tr>
<tr>
<td>• Codeine</td>
<td>• Methadone</td>
</tr>
<tr>
<td></td>
<td>• Fentanyl transdermal</td>
</tr>
<tr>
<td></td>
<td>• Buprenorphine transdermal</td>
</tr>
</tbody>
</table>

## Selected Opioids With Unique Properties
**Methadone is Different**

**The problem...**
- Long, variable, unpredictable half-life
  - Analgesia 6-8 hours
  - Serum t½ 20-100 hours
- QTc prolongation, risk of torsade de points

**Some possible advantages...**
- Mu opioid agonist, NMDA receptor antagonist
  - Potentially less tolerance, better efficacy in neuropathic pain
- No active metabolites
- Inexpensive, small dosage units (5mg tablets)


## Dual Mechanism Opioids

<table>
<thead>
<tr>
<th>Tramadol</th>
<th>Tapentadol</th>
</tr>
</thead>
<tbody>
<tr>
<td>▪ Mu-opioid agonist and NE and serotonin reuptake inhibitor</td>
<td>▪ Mu-opioid agonist and NE reuptake inhibitor</td>
</tr>
<tr>
<td>▪ Seizure risk</td>
<td>▪ Seizure risk</td>
</tr>
<tr>
<td>▪ Physical dependence</td>
<td>▪ Physical dependence</td>
</tr>
<tr>
<td>▪ Not scheduled as controlled substance BUT has addiction potential</td>
<td>▪ Schedule II controlled substance with addiction potential</td>
</tr>
</tbody>
</table>

Medical Letter April 2010

## Resources on Specific Opioids

### Providers
- e.g., dosing, specific product risks, limitations for use in patients with gastrointestinal problems such as inability to swallow, feeding tubes or malabsorption issues
- [dailymed.nlm.nih.gov/dailymed](dailymed.nlm.nih.gov/dailymed)
- [accessdata.fda.gov/scripts/cder/drugsatfda/](accessdata.fda.gov/scripts/cder/drugsatfda/)
- Package inserts on ER/LA website
- Adverse events to be reported to FDA [fda.gov/Drugs/InformationOnDrugs/ucm135151.htm](fda.gov/Drugs/InformationOnDrugs/ucm135151.htm)

### Patients
- e.g., side effects, drug-drug interactions including CNS depressants, safe disposal
- Materials: [er-la-opioidrems.com/lfwUI/rem/products.action](er-la-opioidrems.com/lfwUI/rem/products.action)
- Medication guide given at the pharmacy
## Opioid Risks


## Issues Preventing Opioid Prescribing

<table>
<thead>
<tr>
<th>Issues</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potential for patients to become addicted</td>
<td>89%</td>
</tr>
<tr>
<td>Potential for patients to sell or divert</td>
<td>75%</td>
</tr>
<tr>
<td>Opioid side effects</td>
<td>53%</td>
</tr>
<tr>
<td>Regulatory/law enforcement monitoring</td>
<td>40%</td>
</tr>
<tr>
<td>Hassle and time required to track/refill</td>
<td>28%</td>
</tr>
</tbody>
</table>
Opioid Tolerance and Physical Dependence

Both tolerance and physical dependence are physiological adaptations to chronic opioid exposure.

**Tolerance:**
- Increased dosage needed to produce specific effect
  - Develops readily for CNS and respiratory depression
  - Less so for constipation
  - Unclear about analgesia

**Physical Dependence:**
- Signs and symptoms of withdrawal by abrupt opioid cessation, rapid dose reduction

Opioid Safety and Risks

<table>
<thead>
<tr>
<th>Allergies</th>
<th>Organ Toxicities</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rare</td>
<td>Suppression of hypothalamic-pituitary-gonadal axis</td>
<td>Nausea, sedation, constipation, urinary retention, sweating</td>
</tr>
<tr>
<td></td>
<td>&gt;50 mg (MSO₄ equivalents) associated with 2x increase fracture risk*</td>
<td>Pruritis (histamine release)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Respiratory depression – sleep apnea</td>
</tr>
</tbody>
</table>

Respiratory Depression

- Depression of the medullary respiratory center
- Decreased tidal volume and minute ventilation
- Right-shifted CO₂ response
- Hypercapnea, hypoxia and decreased oxygen saturation
- Various agonist-type opioids do appear to differ in potential for ventilatory depression in humans
- Immediately life threatening
- The key to remember is that sedation occurs before respiratory depression therefore it is a warning sign that the patient is overmedicated

Managing Opioid Adverse Effects

<table>
<thead>
<tr>
<th>Effect</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea and vomiting</td>
<td>Usually resolves in few days; antiemetics, switch opioids</td>
</tr>
<tr>
<td>Sedation</td>
<td>Decrease dose</td>
</tr>
<tr>
<td>Constipation</td>
<td>Senna laxatives, bowel stimulants, switch opioids; avoid bulking agents</td>
</tr>
<tr>
<td>Pruritis</td>
<td>Switch opioids, antihistamines</td>
</tr>
<tr>
<td>Urinary Retention</td>
<td>Switch opioids</td>
</tr>
</tbody>
</table>


Opioid Safety and Risks

Worsening Pain
- Withdrawal mediated pain
- Hyperalgesia in some patients

Addiction

Overdose
- At high doses (ER/LA formulations contain more opioid than IR/SA and increase overdose risk)
- When combined with other sedatives

Opioid Sales, Deaths and Substance Abuse Treatment Admissions

### New Users: Specific Illicit Drugs

![Bar chart showing new users of specific illicit drugs.](chart1)

* Includes pain relievers, tranquilizers, stimulants, and sedatives

SAMHSA, 2009 National Survey on Drug Use and Health (September 2010).

### Where Pain Relievers Were Obtained

![Pie chart showing sources of pain relievers.](chart2)

- **55%** Obtained free from friend or relative
- **17.3%** Prescribed by one doctor
- **7.1%** Other source
- **4.4%** Got from drug dealer or stranger
- **4.8%** Took from friend or relative without asking
- **11.4%** Bought from friend or relative

2010 National Survey on Drug Use and Health: SAMHSA, Office of Applied Studies; 2011
Collateral Opioid Risk

- **Risks**
  - Young children ingestion and overdose
  - Adolescents experimentation leading to overdose and addiction

- **Mitigating risk**
  - Safe storage and disposal
  - Educate family members
  - Have poison control number handy

Opioid Addiction Risk

- True incidence and prevalence of addiction in chronic pain populations prescribed opioids is unknown due to different criteria used to define addiction in different studies

- The range in prevalence reported is 0-50%

# Opioid Misuse Risk

## Known Risk Factors

### Good Predictors for Prescription Opioid Misuse

- Young age (less than 45 years)
- Personal history of substance abuse
  - Illicit, prescription, alcohol, nicotine
- Family history of substance abuse
- Legal history
  - DUI, incarceration
- Mental health problems
- History of sexual abuse

## Why Patients Become Addicted to Opioids

Opioids activate mu receptors in midbrain “reward pathway” causing euphoria

- Dopaminergic system that is very reinforcing
- Most rewarding are fast onset opioids
- ER/LA should be less rewarding if taken as prescribed but are very rewarding if adulterated (e.g., crushed, chewed)
Abuse Deterrent/Resistant Formulations

In Development

Physical Barriers
- Reducing Drug Rewards
- Agonist-antagonist Combinations
- Aversive Components
- Prodrugs

Currently there are NO PROVEN abuse deterrent/resistant opioids or formulations


Drug-Drug Interactions

Profiles Vary Among Different Opioids and Opioid Formulations

Central nervous system depressants (alcohol, sedatives, hypnotics, tricyclic antidepressants)
- Can have potentiating effect on sedation and respiratory depression caused by opioids

Some ER/LA opioid formulations
- May rapidly release opioid (dose dump) when exposed to alcohol
- Some drug levels may increase without dose dumping when exposed to alcohol

Diuretics
- Opioids can reduce efficacy by inducing release of antidiuretic hormone (ADH)

Some Opioids (methadone, buprenorphine)
- Can prolong the QTc interval

Concomitant drugs that act as inhibitors or inducers of various cytochrome P450 enzymes
- Can result in higher or lower than expected blood levels of some opioids

FDA Blueprint: www.fda.gov/downloads/drugs/drugsafety/informationbydrugclass/ucm277916.pdf
Important Resource: DailyMed

- Updated medication content and labeling
  - Search and download
- Reformatted drug labeling easier to read
- National Library of Medicine (NLM) provides as a public service; does not accept advertisements

Risk in Elderly

- Drug-drug interactions
- Drug-disease interactions
  - CHF, chronic liver and renal disease
  - Dementia
- Decline in therapeutic index
- Age-related predisposition to adverse drug effects
- Start low and go slow

Risk Assessment

Assess for Opioid Misuse Risk

Prior to Prescribing

- Validated questionnaire
- Urine drug testing
- Check state prescription drug monitoring program data (if available)
- Review old medical records
- Talk to previous provider (if possible)
Validated Questionnaires

ORT  Opioid Risk Tool
SOAPP  Screener & Opioid Assessment for Patients with Pain
STAR  Screening Tool for Addiction Risk
SISAP  Screening Instrument for Substance Abuse Potential
PDUQ  Prescription Drug Use Questionnaire

No “Gold Standard”
All lack rigorous testing

Case Study
Mary Williams

Opioid Risk Tool Score

<table>
<thead>
<tr>
<th></th>
<th>Female</th>
<th>Male</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Family history of substance abuse</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Illegal drugs</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Prescription drugs</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td><strong>Personal history of substance abuse</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Illegal drugs</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Prescription drugs</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td><strong>Age between 16-45 years</strong></td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td><strong>History of preadolescent sexual abuse</strong></td>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td><strong>Psychological disease</strong></td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>ADHD, OCD, bipolar, schizophrenia</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Depression</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

SCORING
0-3 Low Risk
4-7 Moderate Risk
>8 High Risk

**Opioid Misuse Risk Stratification**

**How should it be used?**

**Discuss level of concern with patient**
- “Despite being in recovery from alcoholism, you are at higher risk for developing problems with the opioid pain medication.”

**Level of monitoring that should be implemented**
- Frequency of visits, urine drug testing, etc.
- High risk patients may need to agree to random call-backs

**Need for pain and/or addiction consultant**
- If available

**Some patients may be too risky for opioids analgesics**
- e.g., patient with recent opioid addiction

---

**Prescription Drug Monitoring Programs**

Clinical tool that supports safe prescribing and dispensing

May help prevent or stop harm from drug diversion, misuse and abuse

Specifics vary from state to state

Can provide:
- Patient’s prescription history for Schedule II–V
- Solicited reports online; real time or delay of days to weeks
- Unsolicited reports on patients with “questionable activity”

---

Case Study
Mary Williams

Follow-up
- Patient agrees to return in one week
- Provider has time to check records and Prescription Drug Monitoring Program (PDMP)
- Patient has left a Urine Drug Test (UDT)

Summary Points: Essential Content 1

Opioids:
- Can be beneficial for some
- Side effects are common but can be managed
- Can be harmful for some
- Carry significant risk including overdose and addiction
- Misuse risk can be assessed using systematic approach which includes validated risk assessment questionnaires
Case Study
Mary Williams

Review of Medical Records

- Progress notes, medication lists are reconciled
- Radiology reports
  - Lumbar degenerative joint disease
  - Mild spinal stenosis
- No evidence of misuse of her opioid prescriptions
- Lack of adequate documentation about pain and functional benefits in her old record

Case Study
Mary Williams

Opioid Use Assessment

- Obtaining functional benefit (i.e., fully employed) on current medication regimen
- Moderate risk for prescription opioid misuse based on the Opioid Risk Tool score
Questions for Next Visit

Initiating Opioid Therapy Safely

Clinician Concerns:

- Should I change her opioid prescription?
- Should I change the opioid dose?
- What about any other adjuvant medications or therapies?
- What sort of treatment plan should I develop?