Opioid addiction

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Learning Objectives

1. Describe the concepts of prescription drug abuse, misuse, addiction, and diversion, including their recognition, risk factors, and prevention.

2. Explain the guidelines pertaining to the prescribing of controlled substances and North Carolina-specific regulations.

3. Discuss the treatment of pain, including evaluation, treatment, and medications.

4. Describe steps to take to ensure safe and effective prescribing of controlled substances.
PAIN CRISES

- Over 100 million Americans affected
- Pain accounts for 20% of all clinic visits
- Analgesics = 12% of all prescriptions (# 2)
- $600 billion dollars/yr in health care and loss of productivity costs
- Leading cause of work loss & disability

Stewart WF et al JAMA 2003; 290:2443-2454
What is the Addiction Risk?

- Published rates of abuse and/or addiction in chronic pain populations are 3-19%.
- Suggests that known risk factors for abuse or addiction in the general population would be good predictors for problematic prescription opioid use:
  - Past alcohol or drug use
  - Family history of substance abuse, a history of legal problems and drug and alcohol abuse
  - Heavy tobacco use
  - History of psychiatric disorders (depression or anxiety)

1. Ives T et al. BMC Health Services Research 2006
2. Reid MC et al JGIM 2002
3. Michna E el al. JPSM 2004
4. Akbik H et al. JPSM 2006
Opioid use disorder (DSM-V)

- Taken in larger amounts or for longer periods
- Persistent desire/unsuccessful efforts to reduce usage
- Great deal of time spent obtaining/using opioids
- Craving, or strong desire to use opioids
- Failure to fulfill work/home obligations due to opioid use
- Lack of concern for problems due to recurrent opioid use
- Lack of interest in activities that used to be important
- Recurrent use of opioids despite hazards
- Continued use despite known problems due to opioid use
Opioid use disorder (DSM-V)

- **Tolerance** (except for those under medical supervision)
  - Markedly increased amounts to achieve desired effect
  - Markedly diminished effect with continued use at same amount

- **Withdrawal** (except for those under medical supervision)
  - Characteristic opioid withdrawal syndrome
  - Opioids are taken to relieve or avoid withdrawal syndrome

Mild OUD: 2-3 Criteria
Moderate OUD: 4-5 Criteria
Severe OUD: >6 Criteria

DSM 5 American Psychiatric Association
Opioid overdoses
Unintentional opioid deaths have increased more than 10 fold. Heroin or other synthetic narcotics are now involved in over 50% of deaths.

Unintentional medication/drug (X40-X44) with specific T-codes by drug type, Commonly Prescribed Opioid Medications=T40.2 or T40.3; Heroin and/or Other Synthetic Narcotics=T40.1 or T40.4.

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Analysis by Injury Epidemiology and Surveillance Unit
Substances* Contributing to Unintentional Medication or Drug Overdose Deaths, North Carolina Residents, 1999-2015

*These counts are not mutually exclusive. If the death involved multiple drugs it can be counted on multiple lines.

Analysis by Injury Epidemiology and Surveillance Unit
Rates of Unintentional/Undetermined Prescription Opioid Overdose Deaths & Outpatient Opioid Analgesic Prescriptions Dispensed

Average mortality rate: 6.4 per 100,000 persons
Average dispensing rate: 82.9 Rx per 100 persons

Analysis: Injury and Epidemiology Surveillance Unit
**Heroin, Fentanyl, and Fentanyl Analogues Detected in Toxicology Testing**, Office of Chief Medical Examiner Investigated Deaths

2016 – Fentanyl & Fentanyl Analogues detected in a larger proportion of death investigations by the OCME

Source: N.C. Office of the Chief Medical Examiner (OCME) and the OCME Toxicology Laboratory.

*Data for 2016 is considered provisional and is current as of Feb. 2017.

**Fentanyl analogues include: Acetyl fentanyl, Butrylfentanyl, Furanylfentanyl, Fluorofentanyl, Acrylfentanyl, Fluoroisobutrylfentanyl, Beta-Hydroxythiofentanyl, Carfentanil. The presence of a drug does not necessarily indicate that it was attributed to the cause of death
In 2014, for every 1 opioid overdose death, there were just under 3 hospitalizations and nearly 4 ED visits due to medication or drug overdose.

Analysis by Injury Epidemiology and Surveillance Unit

2004 to 2015 893% increase

*2014 data structure changed to include up to 95 diagnosis codes. It is unclear the overall impact of this change.
**2015 ICD 9 CM coding system transitioned to ICD10 CM. Impact unclear.

Analysis by Injury Epidemiology and Surveillance Unit
Increase in Acute Hepatitis C Cases
North Carolina, 2000–2016*

2009 to 2016*
Reported Hep C cases increased more than 500%
Opioid Overdose Reversals with Naloxone Reported by NC Law Enforcement Agencies, 1/1/2015-7/31/2017

Yearly Reversal Totals
2015: 36
2016: 318
2017 YTD: 255
TOTAL: 609

165 Law Enforcement Agencies carrying naloxone, covering 72 counties

Source: North Carolina Harm Reduction Coalition (NCHRC), August 2017
Analysis by Injury Epidemiology and Surveillance Unit
Federal and State guidelines for opioid prescribing
<table>
<thead>
<tr>
<th></th>
<th>CDC guidelines for opioid use in chronic pain</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>Consider non-opioid medications &amp; behavioral interventions first.</td>
</tr>
<tr>
<td>2</td>
<td>Establish &amp; measure goals for function and pain</td>
</tr>
<tr>
<td>3</td>
<td>Discuss risks &amp; benefits before &amp; during opioid therapy. Use strategies to reduce risk including offering naloxone.</td>
</tr>
<tr>
<td>4</td>
<td>Use immediate release opioids while starting opioids for chronic pain</td>
</tr>
<tr>
<td>5</td>
<td>‘Start low &amp; go slow’, reassess if dose ≥ 50 MME /day. Avoid opioid doses ≥ 90 MME/day</td>
</tr>
<tr>
<td>6</td>
<td>Prescribe short duration (3 days, maximum 7 days) for acute pain</td>
</tr>
<tr>
<td>7</td>
<td>Evaluate risk factors for opioid related harms &amp; avoid benzodiazepines</td>
</tr>
<tr>
<td>8</td>
<td>Check State Prescription Drug Monitoring Programs database</td>
</tr>
<tr>
<td>9</td>
<td>Use periodic urine drug screens to monitor misuse &amp; adherence</td>
</tr>
<tr>
<td>10</td>
<td>Arrange treatment of Opioid Use Disorder if needed</td>
</tr>
</tbody>
</table>
NCMB New CME requirement

- Effective July 1, 2017
- **Who must comply?** Physicians and PAs who prescribe ANY controlled substances (even non-opioids). Residents are exempt.
- **MDs/DOs:** Three hours of relevant CME during each three year CME cycle
- **PAs/NPs:** Two hours of relevant CME in each two year CME cycle
STOP (Strengthen Opioid Misuse Prevention) Act

- Targets Schedule II and III opioids
- Limits first-time prescriptions of opioids for acute pain to ≤5 days (≤7 days after surgery)
- Allows follow-up prescriptions for pain
- Limit does not apply to controlled substances administered in a hospital, nursing home
- Requires Controlled Substance Reporting System (CSRS) check first time & every 90 days for opioid Rx & documentation

Effective January 1, 2018
Addiction Treatment

- Behavioral Treatments
- Medications
- Self Help Groups

Setting:
- Outpatient/Intensive Outpatient
- Partial Hospital
- Inpatient/Residential
- Detoxification (inpatient or outpatient)
ADDITION IS A DISEASE OF THE BRAIN
As other diseases, it affects tissue function

Decreased Brain Metabolism in Drug Abuse Patient

Decreased Heart Metabolism in Heart Disease Patient

Sources: From the laboratories of Drs. N. Volkow and H. Schelbert
Chronic Opioid Use Changes Brain Structure and Function

Potential physiologic mechanisms of tolerance and dependence include

- Changes in dopamine reward circuitry including decreased D₂ receptors (figure)¹
- Opioid receptor desensitization and downregulation²
- Decreased synthesis of endogenous opioids²
- Increased neuronal excitability when opioids are withdrawn²

Behavioral/cognitive changes

- Craving induced by drug cues³
- Loss of control over drug seeking behavior³

NIDA Principles of Effective Treatment

#7 Medications are important, especially when combined with behavioral therapies.

#8 Substance abuse and coexisting mental disorders should receive integrated care.

-Detoxification alone is not sufficient treatment & has to be followed by continuing care

Source: NIDA Principle of effective Treatment: A research based guide, 1999
Medications for Opioid Dependence

- Methadone (opioid agonist)
- Buprenorphine/naloxone (Suboxone®): opioid partial agonist
- Naltrexone (Vivitrol®) opioid antagonist
<table>
<thead>
<tr>
<th>Drug</th>
<th>Indication</th>
<th>strength</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buprenorphine (Subutex®)</td>
<td>Opioid dependence</td>
<td>2mg and 8 mg SL</td>
</tr>
<tr>
<td>Buprenorphine + naloxone</td>
<td>Opioid dependence</td>
<td>2 mg/0.5 mg and 8 mg/2 mg SL</td>
</tr>
<tr>
<td>Suboxone® film &amp; tablet</td>
<td></td>
<td>5.7 mg/1.4 mg sl</td>
</tr>
<tr>
<td>Zubsolv® tablet</td>
<td></td>
<td>4.2/0.7 mg buccal</td>
</tr>
<tr>
<td>Bunavail® buccal film</td>
<td></td>
<td>8-24 mg</td>
</tr>
<tr>
<td>Buprenorphine implant (Probufine®)</td>
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</table>
Probuphine: An implantable formulation of buprenorphine for the long-term treatment of opioid dependence
Monthly Buprenorphine injections (Sublocade)
Buprenorphine: evidence

• Is superior to clonidine and comparable to methadone for opiate withdrawal

• Is safer and less euphoric than methadone

• Is comparable to methadone for maintenance, retention may be better with high dose methadone.

• Recent data suggest buprenorphine may have superior benefits for neonate abstinence syndrome than methadone

BMJ 2005;331:1352-1353
Safety of buprenorphine

Opioid Overdose Deaths Decline 79% After Introduction of Buprenorphine in France

- French primary care MDs permitted to prescribe without special education or licensing since 1995
- Extensive certification requirements and practice limits continue in force in the U.S.

NALTREXONE

- Pure mu opioid antagonist approved to treat opioid and alcohol dependence.
  - Oral- ReVia®, now generic
  - Injectable- Vivitrol®
  - Implant- not FDA approved
Naltrexone: evidence

- Oral effective dose 50-100 mg/day, blocks 90% of effects of 25 mg i.v. heroin.
- Less effective than bup or methadone (Ahmadi et al, 2003).
- Poor compliance: < 5% at 9 months.
- Vivitrol® (injectable naltrexone) is a 4 week extended release formulation to address compliance (Comer et al, 2006).

Methadone: summary of evidence

• Trend toward ↑ doses: In 1988, 80% received < 60 mg/day, in 2011, 23% took <60 mg/day.

• Individual factors predict over 40% of variance in methadone dose.

• Methadone is potentially long term treatment requiring counseling and monitoring.

• Overdose. Methadone is one of the most common drugs involved in opioid overdose deaths.

## Behavioral Therapies

<table>
<thead>
<tr>
<th>Treatment Intervention</th>
<th>Primary Target Population(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>High-risk users</td>
</tr>
<tr>
<td>Brief intervention</td>
<td>✓</td>
</tr>
<tr>
<td>Motivational enhancement therapy</td>
<td></td>
</tr>
<tr>
<td>Cognitive behavioral therapy</td>
<td></td>
</tr>
<tr>
<td>Relapse prevention</td>
<td></td>
</tr>
<tr>
<td>Self Help</td>
<td></td>
</tr>
</tbody>
</table>


Slide courtesy: Dr T.K. Li, Director, NIAAA
NALOXONE PRESCRIPTION: WHO AND WHEN?

Option: Prescribe for patients at *increased risk*, including both:

- Those in treatment for opioid abuse or addiction
- Those in treatment for chronic pain

Addiction treatment populations:
- Anyone identified as abusing opioids (dependence not necessary)
- During MAT induction (methadone > buprenorphine)
- During tapering or after discharge from MAT
- Following involuntary d/c of MAT (e.g. incarceration, inpatient rehab)
Reversal of opioid overdoses Naloxone HCL (Narcan®)

• Mu-opioid receptor antagonist
• Can’t get ‘high’ from it (no potential for abuse)
• Uses: anesthesia & emergency
• Rapid acting (< 10 minutes)
• Delivered via injection (IM, SC, IV) or nasal
• In NC, available without prescription through a standing order
Naloxone to reverse opioid overdoses

naloxone injectable

naloxone nasal spray
EMS administered Naloxone more than **13,000** times in 2016

1ICD9 to ICD10 coding changed in October 2015. Impact on surveillance is unclear. Naloxone administration alone by EMS does not necessarily equate to an opioid overdose.

*2016 data are preliminary and subject to change

Source: NC DETECT (statewide ED data), N.C. Division of Public Health and UNC Carolina Center for Health Informatics (CCHI); EMSpic- UNC Emergency Medicine Department, N.C. Office of Emergency Medical Services (OEMS)
We Need to Treat the Whole Person!
Drug Abuse Treatment Core Components and Comprehensive Services

- Medical
- Mental Health
- Vocational
- Educational
- Legal
- AIDS / HIV Risks
- Financial
- Housing & Transportation
- Child Care
- Family

Core Treatment
- Intake Assessment
- Treatment Plans
- Group/Individual Counseling
- Abstinence Based
- Pharmaco-therapy
- Self-Help (AA/NA)
- Urine Monitoring
- Case Management
- Continuing Care

Etheridge, Hubbard, Anderson, Craddock, & Flynn, 1997 (PAB)
What is Recovery in Addiction?

- Recovery from alcohol and drug problems is a process of change through which an individual achieves abstinence and improved health, wellness, and quality of life. (CSAT 2005 National Recovery Summit)

- How does one get there?
What percent of those who develop Alcohol Use Disorders eventually reach remission/recovery?

<table>
<thead>
<tr>
<th>Study</th>
<th>Remission rate in total population</th>
<th>Remission rate in those with lifetime SUD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dawson et al 2005</td>
<td>10.3% for alcohol dependence</td>
<td>47.7% in full remission for 1 year (18% full abstinence). 29% in remission for 5 years or more</td>
</tr>
<tr>
<td>Dawson et al, 2008</td>
<td>5.3% for AUD over 3 years</td>
<td>44% full remission</td>
</tr>
<tr>
<td>Hasin et al 1997</td>
<td>12.6% for AUD</td>
<td>61% alcohol abuse, 29% for alcohol dependence</td>
</tr>
</tbody>
</table>

Overall remission rate in Community samples is 43.5%. Only 18% did this through complete Abstinence. In community studies, high rate of non-abstinent remission. There are over 25 million people in US who are in remission from SUD.
What percent of those who develop Drug Use Disorders eventually reach remission/recovery?

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample</th>
<th>Follow up</th>
<th>Recovery rate in those with lifetime SUD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gossop (2002) UK</td>
<td>N=549, all drugs</td>
<td>1 &amp; 2 years</td>
<td>Year 1 35% for residential and 15% for outpatient</td>
</tr>
<tr>
<td>Hser, 2007</td>
<td>N=242, heroin</td>
<td>33 years</td>
<td>43%</td>
</tr>
<tr>
<td>Hser, 2006</td>
<td>N=321, cocaine</td>
<td>12 years</td>
<td>52%</td>
</tr>
<tr>
<td>McLellan</td>
<td>N=802, Physicians</td>
<td>5 years</td>
<td>81%</td>
</tr>
</tbody>
</table>

Average success rate across 78 trials is 57% (Prendergast, 2002)
Primary drug abstinence is often associated with continuing use of other drugs
Some studies suggest patients with primary mental health problems do better
Why do some feel that Rx does not work?

“I know someone who has been in and out of treatment a dozen times- it just doesn’t work!”

- Most Rx focused on a single episode of care. On average 3-4 Rx episodes are required for long term abstinence.
- Detoxification alone is not adequate Rx.
- Overall Rx approach should shift from acute intervention to long term management.
We Are Using Science to Develop Even Better Treatment
Precision medicine for psychopharmacology: a general introduction

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ABSTRACT

Introduction: Precision medicine is an emerging medical model that can provide accurate diagnoses and tailored therapeutic strategies for patients based on data pertaining to genes, microbiomes, environment, family history and lifestyle.

Areas covered: Here, we provide basic information about precision medicine and newly introduced concepts, such as the precision medicine ecosystem and big data processing, and omics technologies including pharmacogenomics, pharmaconometabolomics, pharmacoproteomics, pharmacoeuigenomics, connectomics and exposomics. The authors review the current state of omics in psychiatry and the future direction of psychopharmacology as it moves towards precision medicine.

Expert commentary: Advances in precision medicine have been facilitated by achievements in multiple fields, including large-scale biological databases, powerful methods for characterizing patients (such as genomics, proteomics, metabolomics, diverse cellular assays, and even social networks and mobile health technologies), and computer-based tools for analyzing large amounts of data.
Final Word

“I did then what I knew how to do; now that I know better, I do better.”

-Maya Angelou