Controlled Substance Monitoring in the Age of the Opioid Epidemic

Paul E. Hilliard, MS, MD
Hospital Pain Committee Chair
Department of Anesthesiology
CME housekeeping

• I have no financial disclosures
  – AKA, I have not made it far enough in my career yet to be courted by industry
Clinical Practice Guidelines for Opioid Prescribing

- CDC Guidelines
- Society Guidelines
- NIH workshop
- National and state legislation
Best Practices for Opioid Prescribing

• Controlled Substance (CS) agreement
• Comes with some terms and conditions
What is controlled substance monitoring?

- Traditionally used by prescribing physicians to follow patient activity and behavior when they have a CS agreement.
How can you use this?

- Helps the Anesthesiologist determine what a patient is getting and what is in their system.
- Two main ways to do this:
  1. Prescription Drug Monitoring Programs
  2. Urine toxicology
How can you use this?

• Helps the Anesthesiologist determine what a patient is getting and what is in their system

• Two main ways to do this:
  1. Prescription Drug Monitoring Programs
  2. Urine toxicology
Overview: Prescription Drug Monitoring Programs

- What are Prescription Drug Monitoring Programs (PDMPs)
  - Electronic record of controlled medication
  - Prescriptions entered at dispensing by the pharmacy
  - Reporting of all Schedule II-V drugs
DEA Schedule

• Based on accepted medical use and abuse potential
• Schedule I: no accepted medical use, high abuse potential causing severe psychological or physical harm
• https://www.dea.gov/druginfo/ds.shtml
# Drug Scheduling Guide

## United States

<table>
<thead>
<tr>
<th>Schedule</th>
<th>Description</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ⅰ</td>
<td>Most potential for abuse and dependence</td>
<td>Heroin, LSD, Marijuana, Ecstasy, Peyote</td>
</tr>
<tr>
<td>Ⅱ</td>
<td>High potential for abuse and dependence</td>
<td>Vicodin, Cocaine, Meth, OxyContin, Adderall</td>
</tr>
<tr>
<td>Ⅲ</td>
<td>Moderate potential for abuse/dependence</td>
<td>Tylenol with Codeine, Ketamine, Steroids, Testosterone</td>
</tr>
<tr>
<td>Ⅳ</td>
<td>Low potential for abuse and dependence</td>
<td>Xanax, Darvon, Valium, Ativan, Ambien, Tramadol</td>
</tr>
<tr>
<td>Ⅴ</td>
<td>Lowest potential for abuse/dependence</td>
<td>Robitussin AC, Lomotil, Motofen, Lyrica</td>
</tr>
</tbody>
</table>

Source: United States Drug Enforcement Agency
PDMP

• Exists in 50 states plus Guam and DC
• Missouri 7/18/17 Governor Eric Greitens by executive order will implement one as well
History

• First PDMP 1991 in Oklahoma
• Started as a law enforcement tool
• Evolved into a clinical tool
• In Michigan: Official Prescription Program (OPP) started in 2003
• Requested report by fax
• Manual query – about two weeks for a report
• 2005, moved online with 48 hr. turn around
History

• April 2007 – full automation, took several minutes
• April 2017 – upgraded version (PMP Aware), 0.6 seconds.
• 43 states use same software
• 120 million records maintained up to 5 years
• Prescribers can run self reports
To Register

• DEA #
• License #
• Controlled Substance ID #
• NPI
# Drug Scheduling Guide

## United States

<table>
<thead>
<tr>
<th>Schedule</th>
<th>Description</th>
<th>Medicinal Qualities</th>
<th>Prescriptions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Schedule I</strong></td>
<td>Most potential for abuse and dependence</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>No medicinal qualities</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Heroin, LSD, Marijuana Ecstasy, Peyote</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Schedule II</strong></td>
<td>High potential for abuse and dependence</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Some medicinal qualities</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Vicodin, Cocaine, Meth, OxyContin, Adderall</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Schedule III</strong></td>
<td>Moderate potential for abuse/dependence</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Acceptable medicinal qualities</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Doctor’s prescription required</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tylenol with Codeine, Ketamine, Steroids, Testosterone</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Schedule IV</strong></td>
<td>Low potential for abuse and dependence</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Acceptable medicinal qualities</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Prescription required - fewer refill regulations</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Xanax, Darvon, Valium, Ativan, Ambien, Tramadol</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Schedule V</strong></td>
<td>Lowest potential for abuse/dependence</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Acceptable medicinal qualities</td>
<td></td>
<td></td>
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<td></td>
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Source: United States Drug Enforcement Agency
Who runs it (PDMP) depends on where you live

- Law enforcement
- State Government
- Licensing Boards
PDMP Mandatory Query by Prescribers and Dispensers

(Listing of the specific conditions for mandatory query)

- Prescribers and Dispensers (14)
- Prescribers Only (24)
- No Mandatory Query (14)

Research is current as of August 24, 2017

*Missouri does not have a state-wide PDMP*
• Mandatory reporting by pharmacy (and veterinarians)
• Mandatory use – many states have this
• Michigan senate bill 166 (mandatory use) and bill 167 (bill for sanctions)
• January 2020 if it passes
• Update: June 2018!!
How does it help?

• Take Ohio as an example
Chart #2 - Opioid Prescriptions Dispensed to Ohio Patients, by Year

- 2011: 12.5
- 2012: 12.6
- 2013: 12.4
- 2014: 12.2
- 2015: 11.2
- 2016: 10.1

# of Rx in Millions
Chart #3 - Benzodiazepine Solid Doses Dispensed to Ohio Patients, by Year

- 2011: 296
- 2012: 297
- 2013: 294
- 2014: 287
- 2015: 275
- 2016: 254

# of Solid Oral Doses in Millions

Year
Reduces “Doctor Shopping”

• Doctor Shopping – generally accepted definition is receiving a prescription for a controlled substance from 5 or more providers in a calendar month
Chart #6 - Total Doctor Shoppers*, by Year

*In this chart, a doctor shopper is defined as an individual receiving a prescription for a controlled substance from five or more prescribers in one calendar month.
Barriers to using PDMP

- Unreimbursed time
- Burdensome to enroll
- Cumbersome system
- Lack of clinical guidance
APPRISS

- PDMP software used in 43 states
- https://apprisshealth.com/
NARX SCORES

<table>
<thead>
<tr>
<th>Narcotic</th>
<th>Sedative</th>
<th>Stimulant</th>
</tr>
</thead>
<tbody>
<tr>
<td>541</td>
<td>531</td>
<td>301</td>
</tr>
</tbody>
</table>

OVERDOSE RISK SCORE

- 560 (range 0.000)

ADDITIONAL RISK INDICATORS (2)

1. 4 opioid or sedative dispensing pharmacies in any 90 day period in the last 2 years
2. ≥ 100 MME total and ≥ 40 MME/day average

*This NarxCare report is based on search criteria supplied and the data entered by the dispensing pharmacy. For more information about any prescription, please contact the dispensing pharmacy or the prescriber. NarxCare scores and reports are intended to aid and assist medical decision making. None of the information presented should be used as sole justification for providing or refusing to provide medications. The information on this report is not warranted as accurate or complete.*
**NARX SCORING**

<table>
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<th>Sedative</th>
<th>Stimulant</th>
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<td>531</td>
<td>301</td>
</tr>
</tbody>
</table>

**OVERDOSE RISK SCORE**

560 (range 0-999)

**ADDITIONAL RISK INDICATORS (2)**

1. >= 4 narcotic or sedative dispensing pharmacies in any 90 day period in the last 2 years
2. >= 100 MME total and 40 MME/day average
Additional Risk Factors

- >= 4 opioid or sedative dispensing pharmacies in the last 2 years
- > 100 MEM total and > 40 MEM per day
NARX SCORES

- Narcotic: 541
- Sedative: 531
- Stimulant: 301

OVERDOSE RISK SCORE: 560 (76.2% probability)

ADDITIONAL RISK INDICATORS:
1. ≥4 opioid or sedative dispensing pharmacies in any 90 day period in the past 2 years
2. ≥100 MME total and 40 MME/day average

Graphs:
- RX GRAPH
- All Prescribers
- Prescribers by 4-3-2-1

Per CDC guidance, the conversion factors and associated daily morphine milligram equivalents for drugs prescribed as part of medication assisted treatment for opioid use disorder should not be used to benchmark against dosage thresholds meant for opioids prescribed for pain.
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• Can do bulk patient search
• Can run self reports
How can you use this?

• Helps the Anesthesiologist determine what a patient is getting and what is in their system

• Two main ways to do this:
  
  1. Prescription Drug Monitoring Programs
  2. Urine toxicology
"You're fired, Jack. The lab results just came back, and you tested positive for Coke."
Drug Testing

- Urine is preferred, difficult to detect drugs in serum due to low concentration
Drug Testing

• Two types of urine drug tests exist
  – Screening: Immunoassay
  – Confirmatory: GC/MS
Immunoassay

Pro
• Cheap
• Quick
• Portable

Con
• Relies on interpretation of the reader
• High Rate of False Positives
Immunoassays

- Proprietary antibody screens
- Examples: EMIT II, KIMS, CEDIA, DRI, AxSYM
- Know which screen is being used
  - Sensitivity and specificity vary
<table>
<thead>
<tr>
<th>Drug</th>
<th>Federal Immunoassay cutoff (ng/mL)</th>
<th>Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphetamine (misuse)</td>
<td>1000</td>
<td>&lt;=5</td>
</tr>
<tr>
<td>Cannabinoids, 1 cigarette Chronic Smoker</td>
<td>50</td>
<td>2-4, &lt;=30</td>
</tr>
<tr>
<td>Benzoylecgonine after street dose of cocaine</td>
<td>300</td>
<td>1-2</td>
</tr>
<tr>
<td>Opiates (morphine, codeine)</td>
<td>2000</td>
<td>1-2</td>
</tr>
<tr>
<td>Phencyclidone -chronic user</td>
<td>25</td>
<td>8, &lt;=30</td>
</tr>
</tbody>
</table>
GC/MS

**Pro**
- Highly accurate and rarely give false positives
- You have to tell the lab what you are looking for

**Con**
- Expensive
- Takes longer to get results
- Chain of custody may be lost
• Both can have false negatives
• Both can miss same day drug use
This screen indicates a positive result for opiates and marijuana.
ELISA

- Specificity
- Poor = FALSE negative results
- Good (for wrong drug) = FALSE positive results
Substances with “poor” cross-reactivity
Possible FALSE negative

Drug Class
• Marijuana
• Amphetamines
• Benzodiazepines
• Opiates

Compound not detected
• Spice, KD
• Methylphenidate
• Clonazepam, Zolpidem
• Fentanyl, Tramadol, Buprenorphine, Methadone
Substances with “good” cross-reactivity Possible FALSE positive

**Drug class**
- Cannabinoids
- Opioids
- Benzodiazepine
- Methadone
- PCP
- Amphetamines

**Compounds detected**
- NSAIDS, Pantoprazole, diltiazem
- Chlorpromazine, fluoroquinolones
- Oxaprozin, sertraline
- Propoxyphene, seroquel
- Dextromethorphan, Meperidine
- Vicks, desipramine, Trazodone, Metoprolol
Alcohol use: Ethyl Glucuronide
False positive
Reasons for a negative result

- Drug was not taken/administered
- Drug was taken incorrectly (less than prescribed or less frequently)
- Drug delivery was variable
- Drug was not absorbed
- Specimen was collected too late
- Specimen was dilute, or adulterated
- Clinic or lab mix up
If tampering suspected, check

- Temp 90-100 degrees F
- Creatinine >20 mg/dL
- pH 4.5-8.0
- Color
Reasons for a positive result

- Drug was taken/administered
- Drug detected is an expected metabolite of a prescribed drug
- Drug detected is a process impurity
- Incorrect prescription filled
- Non-prescribed drug was used
- Drug was added to urine after collection
- Clinic or lab mix-up
- Result is a false positive (e.g. test specificity)
Reasons for a positive result

• Drug was taken/administered
• Drug detected is an expected metabolite of a prescribed drug
• Drug detected is a process impurity
• Incorrect prescription filled
• Non-prescribed drug was used
• Drug was added to urine after collection
• Clinic or lab mix-up
• Result is a false positive (e.g. test specificity)
Morphine

- Metabolized to hydromorphone (minor pathway, <3% expected)
- Thresholds for independent use of hydromorphone are not well established
Simplified opioid metabolism, poppy seeds and heroin not specifically detected by most ELISA assays

- Poppy seeds
  - codeine
  - hydrocodone
- Morphine
  - hydromorphone
- Heroin
  - 6-monoacetyl morphine
  - morphine
Metabolism interpretation of Immunoassay Screens

• 6-MAM by GC/MS is absolute proof of heroin use
• Morphine from poppy seeds addressed by cutoff change from 300 to 2000 ng/mL
The States Where It's Legal To Smoke Marijuana

Laws on recreational and medical marijuana use in the US*

- [ ] Legalized for recreational & medical use
- [ ] Medical use only

Legalized for recreational & medical use
- Washington
- Washington D.C.
- Oregon
- Alaska
- Colorado
- California
- Massachusetts
- Nevada
- Maine

* As of Nov 10, 2016 - laws in some states have not yet taken effect.
Some states not highlighted allow limited medical marijuana access

Source: NY Times
False Positive Possibilities and Myths: Marijuana

• NSAIDS-yes
• Proton Pump Inhibitors-yes
• Hemp Food Products – no
• Passive Smoke Inhalation - no
Extreme Exposure Experiment
Extreme Exposure Experiment
Drug Detection Times in Different Matrices

- **Urine**
- **Oral Fluid**
- **Blood**
- **Sweat**
- **Hair**

**Concentration** vs. **Time**

- Minutes
- Hours
- Days
- Weeks
- Months

**Cutoff**
### Length of time specific drugs are detected in urine

<table>
<thead>
<tr>
<th>Drug</th>
<th>Time of detection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol</td>
<td>7 – 12 hours</td>
</tr>
<tr>
<td>Amphetamines</td>
<td>48 hours</td>
</tr>
<tr>
<td>Barbiturates</td>
<td>Short: 24 -48 hours, Long: up to 3 weeks</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>Short: 3 days, Long: up to 30 days</td>
</tr>
<tr>
<td>Cocaine</td>
<td>2 – 4 days</td>
</tr>
<tr>
<td>Marijuana</td>
<td>3 – 30 days</td>
</tr>
<tr>
<td>Methamphetamines</td>
<td>3 – 5 days</td>
</tr>
<tr>
<td>MDMA</td>
<td>48 hours</td>
</tr>
<tr>
<td>Opioids</td>
<td>Depends on drug/metabolite</td>
</tr>
<tr>
<td>PCP</td>
<td>8 days</td>
</tr>
</tbody>
</table>
Length of detection - Marijuana

• Marijuana use
  – Single use
  – Moderate use (4xwk)
  – Daily use
  – Heavy use

• Time of detection
  – 3 days
  – 5 – 7 days
  – 10 -15 days
  – > 30 days
Length of detection - opioids

• Specific drug
  – Codeine
  – Heroin
  – Hydromorphone
  – Methadone
  – Morphine
  – Oxycodone
  – propoxyphene

• Time of detection
  – 48 hours
  – 48 hours
  – 2-4 days
  – 3 days or longer
  – 48-72 hours
  – 2-4 days
  – 6-48 hours
What drugs can we test for?

- "SAMHSA Five"
  - Marijuana, Cocaine, Amphetamines, Opiates, PCP
Point of care testing

- Amphetamines, Barbiturates, Benzodiazepines, Cannabinoid, Cocaine, Methamphetamines, Methadone, MDMA, Opioids, Oxycodone, PCP, Propoxyphene
## Opioid Process Impurities

MRO Alert XXI, No. 3, 2010

<table>
<thead>
<tr>
<th>Active pharmaceutical compound</th>
<th>Process impurities</th>
<th>Allowable pharmaceutical impurity limit (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Codeine</td>
<td>Morphine</td>
<td>0.15</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>Codeine</td>
<td>0.15</td>
</tr>
<tr>
<td>Hydromorphine</td>
<td>Morphine , Hydrocodone</td>
<td>0.15 , 0.1</td>
</tr>
<tr>
<td>Morphine</td>
<td>Codeine</td>
<td>0.5</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>Hydrocodone</td>
<td>1.0</td>
</tr>
<tr>
<td>Oxymorphone</td>
<td>Hydromorphone, Oxycodone</td>
<td>0.15 , 0.5</td>
</tr>
</tbody>
</table>
Urine Drug Testing cannot reliably evaluate dosing
Amphetamines

- One of the most difficult assays to interpret
- Many drugs can cause false positive result
  - Amantadine
  - Bupropion
  - Chlorpromazine
  - Dextroamphetamine
  - Ephedrine
  - Labetalol
  - Methamphetamine
  - Phentermine
  - Pseudoephendrine
  - Ranitidine
  - Trazodone
A few more words about Marijuana

- Immunoassays test for THC - tetrahydrocannabinol
- THC is highly lipophilic and stored in fat tissues
- UDS negative for opioid but positive for THC = problem
- Confirmatory test is not GC/MS – more advanced immunoassay
Confirmatory Tests

• When in doubt, get a GC/MS
• You need to tell the lab what you are looking for
GC/MS of Oxycodone

SPEC: oxycodone 27-SEP-95 DERIVED SPECTRUM #9
Samp: Oxycodone Base, lot#0993112E
Comm: Syringe Pump, 5uL/min
Mode: ESI +Q1MS LMR AVER UP LR

Base: 316.0  Inten: 113056
Norm: 316.0  RIC : 318172
Peak: 1000.00  mmu
Data: 1/100

Oxycodone
C_{18}H_{21}NO_{4}
(M.W. 315.36)

(c) 2007, Purdue Pharma L.P. *Restricted use.
Questions

• Feel free to contact me:
• paulhill@med.umich.edu
Knowledge Check

• True or False, your state has a PDMP
Knowledge Check

• **True** or False, your state has a PDMP

• All 50 states have a PDMP or are building one including Guam and DC
Knowledge Check

Clinician use of PDMP is associated with all of the following, EXCEPT:

A. Decrease prescription of opioids
B. Decrease prescription of benzodiazepines
C. Reduced incidence of doctor shopping
D. Decrease in incidence of opioid overdose
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A. Decrease prescription of opioids
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D. Decrease in incidence of opioid overdose
Knowledge Check

• Which of the following indicate a urine sample has been tampered with:
  • A. Temp 90-100 degrees F
  • B. Creatinine >20 mg/dL
  • C. pH 4.5-8.0
  • D. Clear Color with very low specific gravity
Knowledge Check

Which of the following indicate a urine sample has been tampered with:

A. Temp 90-100 degrees F
B. Creatinine >20 mg/dL
C. pH 4.5-8.0
D. Clear Color with very low specific gravity
A patient prescribed codeine may have all of the following on UDS, except:

A. Codeine as well as morphine and hydrocodone
B. Codeine only if they lack the CYP450 2D6 enzyme
C. Codeine commonly causes a false positive for cannabis
D. None of the above
A patient prescribed codeine may have all of the following on UDS, except:

A. Codeine as well as morphine and hydrocodone
B. Codeine only if they lack the CYP450 2D6 enzyme
C. Codeine commonly causes a false positive for cannabis
D. None of the above
Knowledge Check

Your patient is prescribed a transdermal fentanyl patch. The POC UDS is negative for fentanyl, which is the next appropriate step?
A. Notify the prescribing physician that you suspect a CS violation, they are likely diverting patches
B. Send sample for GC/CS and ask that the sample be run against fentanyl metabolites
C. No further action required since fentanyl is often missed on POC testing
D. Only IV fentanyl is detected on POC UDS, so no further action is needed.
Knowledge Check

Your patient is prescribed a transdermal fentanyl patch. The POC UDS is negative for fentanyl, which is the next appropriate step?

A. Notify the prescribing physician that you suspect a CS violation, they are likely diverting patches

B. **Send sample for GC/CS and ask that the sample be run against fentanyl metabolites**

C. No further action required since fentanyl is often missed on POC testing

D. Only IV fentanyl is detected on POC UDS, so no further action is needed.
A 32 YO F with severe RA presents for pre op testing. Her POC UDS is positive for marijuana. Likely explanations for this include:
A. She may be on NSAID therapy
B. She may be using marijuana
C. She may have had second hand exposure
D. A and B
A 32 YO F with sever RA presents for pre op testing. Her POC UDS is positive for marijuana. Likely explanations for this include:

A. She may be on NSAID therapy
B. She may be using marijuana
C. She may have had second hand exposure
D. A and B