Assessing Safety, Efficacy and Misuse of Opioid Therapy for Chronic Pain

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Disclosures

The views expressed in this presentation are those of the author and do not necessarily reflect positions or policies of the Veterans Health Administration.

Dr. Fiellin has received honoraria from Pinney Associates for serving on an external advisory board reviewing the diversion and misuse of buprenorphine.
Learning Objectives

• Describe consensus recommendations for opioid monitoring

• Describe steps/tools for monitoring safety, efficacy and misuse

• Understand strengths, limitations and practical tips to use of these tools
Outline

• Guidelines:
  - American Pain Society (APS) - American Academy of Pain Medicine (AAPM)
  - Federation of State Medical Boards (FSMB)

• Monitoring tools: Strengths, limitations and practical tips
Clinicians should reassess patients on opioids periodically and as warranted by changing circumstances *(strong recommendation, low quality evidence)*:

- Documentation of pain intensity and level of functioning
- Assessments of progress toward achieving therapeutic goals
- Presence of adverse events
- Adherence to prescribed therapies

In patients at high risk or who have engaged in aberrant behaviors, clinicians should periodically obtain urine drug screens or other information to confirm adherence to the plan of care *(strong recommendation, low-quality evidence)*.
In patients not at high risk and not known to have engaged in aberrant behaviors, clinicians should consider periodically obtaining urine drug screens or other information to confirm adherence to the plan of care (weak recommendation, low-quality evidence).

Because patient self-report may be unreliable for determining amount of opioid use, functionality, or aberrant drug-related behaviors, pill counts, urine drug screening, family member or caregiver interviews, and use of prescription monitoring program data can be useful supplements.
Although evidence is lacking on the accuracy and effects on clinical outcomes of formal screening instruments for identification of aberrant drug-related behaviors, use of tools with strong content, face and construct validity, such as the Pain Assessment and Documentation Tool (PADT) and Current Opioid Misuse Measure (COMM) are recommended.
The revised Model Policy (July 2013) identifies the following as departures from accepted best clinical practices:

- Inadequate monitoring during the use of potentially abusible medications: Opioids may be associated with addiction, drug abuse, aberrant behaviors, chemical coping and other dysfunctional behavioral problems, and some patients may benefit from opioid dose reductions or tapering or weaning off the opioid.

- Not making use of available tools for risk mitigation: When available, the state prescription drug monitoring program should be checked in advance of prescribing opioids and should be available for ongoing monitoring.

*Consensus guidelines without reference to levels of evidence
FSMB: Ongoing Monitoring

• The physician should regularly review the patient’s progress, including any new information about
  - Etiology of the pain or the patient’s overall health
  - Level of function.

• When possible, collateral information about the patient’s response to opioid therapy should be obtained from family members or other close contacts, and the state prescription drug monitoring program (PDMP).
• The patient should be seen more frequently while the treatment plan is being initiated and the opioid dose adjusted. As the patient is stabilized in the treatment regimen, follow-up visits may be scheduled less frequently.

• However, if the patient is seen less than monthly and an opioid is prescribed, arrangements must be made for the patient to obtain a refill or new prescription when needed.
At each visit, the results of chronic opioid therapy should be monitored by assessing what have been called the “5As” of chronic pain management:

- Analgesia: 11-point Numerical Rating Scale
- Activities of daily living (function): “Your goal was to get back in your walking routine. How is it going?”
- Adverse effects: detailed questions → sedation, constipation, dizziness, falls, etc
- Adherence to the treatment agreement: Is the patient no-showing appointments? Is the patient adhering to monitoring?
Urine Drug Testing

- Performs better than physician impression

- Inconsistent benefit demonstrated in generally poor quality studies

- Take home: learn how to order and interpret first; *then*, incorporate into clinical practice

Goals of Urine Drug Testing

• Improve Patient Care and Safety
  - Facilitate doctor-patient communication
  - Provide objective information
  - Diagnostic tool for drug misuse or addiction

Rationale for Urine Drug Testing

• Supplements patient report and behavioral monitoring:
  
  - Confirm use of prescribed medication: Adherence testing
  
  - Confirm lack of use of non-prescribed medications and illicit drugs

A Proposed Urine Drug Testing Approach

• **Who?**
  - All patients prescribed opioids/controlled substances.

• **What?**
  - Cocaine, Amphetamines/Methamphetamines, Opiates, Methadone, Benzodiazepines, Marijuana, Barbiturates, PCP; *synthetic opioids (oxycodone, fentanyl, buprenorphine) require separate test*

• **When?**
  - Routinely and randomly as part of treatment agreement.
  - Also: initiation of treatment; changes in regimen; functionality declines.

• **How?**
  - Patient-centered approach.
  - Complete documentation, including history of last med intake.

How to Discuss UDT

- New patient initiating on opioids: (as part of treatment agreement discussion)
  - “This is our routine practice as a patient safety issue.”

- Patient who has been on opioids for a while:
  - “Why now?” → “New clinic policy started recently”

- Patient says: “But I’m not a drug addict”:  
  - “Routine testing…not singling anyone out.”

- Patient says: “I refuse”:
  - “We can’t prescribe if we’re unable to do the routine safety monitoring discussed in the treatment agreement.”

Laboratory Testing Procedures

- **Screening:**
  - Enzyme-Mediated Immunoassay (EIA)

- **Confirmatory:**
  - Gas Chromatography/ Mass Spectrometry

Screening: Enzyme-mediated Immunoassay (EIA)

**PROS**

- Sensitive
- Inexpensive
- Requires small urine sample
- Rapid turnaround
- Can do point of care testing

**CONS**

- Qualitative analysis only
- Subject to cross-reactivity
- Variable sensitivity/specificity
- **Does not reliably detect semisynthetic/synthetic opioids including oxycodone, fentanyl**

## EIA Interpretation

<table>
<thead>
<tr>
<th>Substance</th>
<th>Shows up as</th>
<th>Duration of detection (outer limit)</th>
<th>Sources of false positivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphetamine</td>
<td>Amphetamine</td>
<td>~48 hours</td>
<td>PPA, ephedrine, L-methamphetamine</td>
</tr>
<tr>
<td>Barbiturate</td>
<td>Barbiturate</td>
<td>24 hours/3 weeks</td>
<td>-</td>
</tr>
<tr>
<td>Benzodiazepine</td>
<td>Benzodiazepine</td>
<td>~72 hours</td>
<td>-</td>
</tr>
<tr>
<td>Cannabis</td>
<td>Cannabinoid</td>
<td>4 weeks*</td>
<td>-</td>
</tr>
<tr>
<td>Cocaine</td>
<td>Cocaine</td>
<td>~96 hours/3 weeks*</td>
<td>-</td>
</tr>
<tr>
<td>Fentanyl/bup</td>
<td>[need separate assay]</td>
<td>[need separate assay]</td>
<td>-</td>
</tr>
<tr>
<td>Methadone</td>
<td>Methadone</td>
<td>~72 hours</td>
<td>-</td>
</tr>
<tr>
<td>Codeine</td>
<td>Opiate</td>
<td>~72 hours</td>
<td>Other opiates</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>Opiate</td>
<td>~72 hours</td>
<td>-</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>Opiate</td>
<td>~72 hours</td>
<td>-</td>
</tr>
<tr>
<td>Morphine</td>
<td>Opiate</td>
<td>~72 hours</td>
<td>-</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>Oxycodone**</td>
<td>~72 hours</td>
<td>naloxone</td>
</tr>
</tbody>
</table>

*in heavy users  **often not part of standard EIA so may need separate assay
Next Steps with Unexpected (+) EIA

<table>
<thead>
<tr>
<th>IF EIA IS POSITIVE FOR:</th>
<th>SPECIFIC ENOUGH TO MAKE CLINICAL DECISIONS WITHOUT CONFIRMATORY TEST?</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMPHETAMINES</td>
<td>NO → send GC/MS if not on other likely cross reactors</td>
</tr>
<tr>
<td>BARBITURATES</td>
<td>YES</td>
</tr>
<tr>
<td>BENZODIAZEPINES</td>
<td>YES</td>
</tr>
<tr>
<td>CANNABINOIDS</td>
<td>YES</td>
</tr>
<tr>
<td>COCAINE</td>
<td>YES</td>
</tr>
<tr>
<td>METHADONE</td>
<td>YES</td>
</tr>
<tr>
<td>OPIATES</td>
<td>NO → send GC/MS</td>
</tr>
<tr>
<td>OXYCODONE</td>
<td>NO → send GC/MS</td>
</tr>
</tbody>
</table>
# Confirmatory: Gas Chromatography/Mass Spectrometry

**PROS**
- Quantitative
- Highly specific and sensitive
- Few false results

**CONS**
- Relatively expensive
- Limited by laboratory services and quality

In general, if the substance in the GC/MS is a small fraction of the parent compound (<30%), it is likely to be a metabolite. If it is a large fraction of the parent compound (>50%), it is likely to have been taken exogenously.
## RESULTS

### Screening Test Results (EIA)

<table>
<thead>
<tr>
<th>DRUGS TAKEN</th>
<th>Screening Test Results (EIA)</th>
<th>Confirmatory Test Results (GCMS)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prescription Opioids</strong></td>
<td>- Buprenorphine</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>+ Codeine</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>+ Fentanyl</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>+ Hydrocodone</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>+ Hydromorphone</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>+ Meperidine</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>+ Methadone</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>+ Morphine</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>+ Oxycodone</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>+ Oxymorphone</td>
<td>+</td>
</tr>
<tr>
<td><strong>Illicit Drugs</strong></td>
<td>+ Amphetamines</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>+ Barbiturates</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>+ Benzodiazepines</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>+ Cocaine</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>+ Heroin</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>+ PCP</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>+ Cannabis</td>
<td></td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td>+ Poppy seeds*</td>
<td>F</td>
</tr>
<tr>
<td></td>
<td>F Other medications*</td>
<td>F</td>
</tr>
</tbody>
</table>

### Notes:

1. Oxycodeone, hydrocodeone, or hydromorphone may + opiate screen, esp. high dose, varies by lab—order confirmatory test.
2. Chronic use may result in longer detection times.
3. Benzodiazepine screen likely positive if alprazolam or diazepam taken, negative if clonazepam, lorazepam.
4. Heavy poppy seed ingestion (3+ bagels) may test positive for opiates—repeat off poppy seeds.
5. Some commonly used medications reported to cause false + results on screening assays are below—order confirmatory test.

- **Amphetamines**: bupropion, chlorpromazine, mezilene, pseudoephedrine, nasal decongestants, ranitidine, SSRIs, trazodone.
- **Barbiturates**: ibuprofen, naproxen, phenytion.
- **Benzodiazepines**: sertraline, oxaprazin.
- **Buprenorphine**: tramadol, other opioids.
- **Methadone**: diphenhydramine, doxylamine, cinnamamine, chlorpromazine, quetiapine, thioridazine, tramadol, verapamil.
- **Opiates**: dextromethorphan, diphenhydramine, ibuprofen, tramadol, verapamil.
- **Oxycodone**: naloxone, see list for “opiates.”
- **PCP**: dextromethorphan, diphenhydramine, ibuprofen, tramadol, venlafaxine.
- **Cannabis**: dronabinol, NSAIDS, PPIs.

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*Courtesy of Joanna L. Starrels, MD, MS*
What to do with Negative Result

- On immunoassay (screening test) can call lab for a ‘semi-quantitative’ meaning they can tell you if some medication was present but that it was below threshold.

- Can do a GC/MS on a negative result but will require a phone call to the lab and a separate order.

- Repeat test and make sure to document when patient says they last took the medication.

- Check urine concentration based on specific gravity or creatinine.
Differential for Findings

- Negative Urine Test
  - Decreased or irregular use of medication
  - Diverted medication
  - False negative
    - Lab threshold
    - Metabolism
    - Adulterated sample
    - Wrong test
    - Physiological dilution

- Positive Urine Test
  - Misuse of prescription medication
  - Recreational or moderate use of illicit substance
  - Substance abuse or dependence
  - False positive

Prescription Drug Monitoring Programs

- Vary by state
- Typically a listing of all controlled substances filled by patient; generally, pharmacy reporting can be state law
- Usually a lag time
- Allows prescribers to track multiple fills or “doctor shopping”
- In some you can also query yourself (as prescriber)
  - To detect misuse of your DEA registration number
- Population-level data equivocal on benefit
- Prescriber level qualitative data → increased provider comfort and confidence
Instruments for Patient Reported Safety, Efficacy, Misuse of Opioids

- Variety of instruments developed
  - Prescribed Opioids Difficulties Scale (PODS)
  - Pain Assessment and Documentation Tool (PADT)
  - Current Opioid Misuse Measure (COMM)
  - Prescription Drug Use Questionnaire (PDUQ)
  - Modified Pain Medication Questionnaire (mMPQ)
  - Prescription Opioid Misuse Index (POMI)
  - Bowel Function Index (BFI)
  - Patient Assessment of Constipation (PAC-SYM)
  - Bowel Function Diary (BF-Diary)
Systematic Review of Instruments of Safety, Efficacy, Misuse of Opioids

• Assessed the quality of the studies and instruments across 5 criteria:
  - Psychometric testing performed across all studies of each instrument
  - Reliability and validity testing
  - Risk of bias
  - Generalizability to general medical settings
  - Clinical utility

### Instruments Assessing Safety, Efficacy, Misuse of Opioids

<table>
<thead>
<tr>
<th>Instrument</th>
<th>Number of Safety Items</th>
<th>Number of Efficacy Items</th>
<th>Number of Misuse Items</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prescribed Opioids Difficulties Scale (PODS)</td>
<td>8</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>Pain Assessment and Documentation Tool (PADT)</td>
<td>12</td>
<td>12</td>
<td>17</td>
</tr>
<tr>
<td>Current Opioid Misuse Measure (COMM)</td>
<td>3</td>
<td>0</td>
<td>11</td>
</tr>
<tr>
<td>Prescription Drug Use Questionnaire (PDUQ)</td>
<td>0</td>
<td>2</td>
<td>15</td>
</tr>
<tr>
<td>Modified Pain Medication Questionnaire (mMPQ)</td>
<td>0</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Prescription Opioid Misuse Index (POMI)</td>
<td>0</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>Bowel Function Index (BFI)</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Patient Assessment of Constipation (PAC-SYM)</td>
<td>12</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Bowel Function Diary (BF-Diary)</td>
<td>9</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

## Instruments Assessing Safety, Efficacy, Misuse of Opioids

**Table 4**

<table>
<thead>
<tr>
<th>Instrument</th>
<th>Psychometric categories tested</th>
<th>Statistical significance of testing</th>
<th>Risk of bias in conduct/interpretation</th>
<th>Generalizability limitations</th>
<th>Clinical utility</th>
</tr>
</thead>
<tbody>
<tr>
<td>PODS</td>
<td>4</td>
<td>Robust</td>
<td>Low</td>
<td>None</td>
<td>Equivocal</td>
</tr>
<tr>
<td>PADT</td>
<td>2</td>
<td>Equivocal</td>
<td>High</td>
<td>Conduct of instrument</td>
<td>Equivocal</td>
</tr>
<tr>
<td>COMM</td>
<td>5</td>
<td>Robust</td>
<td>Low</td>
<td>None</td>
<td>Equivocal</td>
</tr>
<tr>
<td>PDUQ-p</td>
<td>5</td>
<td>Equivocal</td>
<td>Low</td>
<td>Patient selection</td>
<td>Equivocal</td>
</tr>
<tr>
<td>mPMQ</td>
<td>1</td>
<td>Robust</td>
<td>Low</td>
<td>None</td>
<td>Equivocal</td>
</tr>
<tr>
<td>POMI</td>
<td>2</td>
<td>Robust</td>
<td>Low</td>
<td>Patient selection</td>
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<tr>
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<tr>
<td>PAC-SYM</td>
<td>3</td>
<td>Equivocal</td>
<td>Low</td>
<td>Patient selection</td>
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</tr>
<tr>
<td>BF-Diary</td>
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<td>Robust</td>
<td>Low</td>
<td>Conduct of instrument</td>
<td>Equivocal</td>
</tr>
</tbody>
</table>

PODS, Prescribed Opioid Difficulties Scale; PADT, Pain Assessment and Documentation Tool; COMM, Current Opioid Misuse Measure; PDUQ-p, Prescription Drug Use Questionnaire-patient version; mPMQ, modified Pain Medication Questionnaire; POMI, Prescription Opioid Misuse Index; BFI, Bowel Function Index; PAC-SYM, Patient Assessment of Constipation Symptoms; BF-Diary, Bowel Function Diary.
Instruments Assessing Safety, Efficacy, Misuse of Opioids: Limitations for Clinical Practice

- None tested in clinical practice
- No evidence to support that their use is associated with improved clinical outcomes
- Length (number of items) may limit utility with patients, especially in non-specialty settings
- Most instruments tend to focus on a particular aspect, e.g. safety, efficacy or misuse but not all three
  - Most items focused on misuse
Summary

• APS-AAPM guidelines recommend structured monitoring

• New FSMB Model Policy cites specific monitoring techniques as standard of care

• Urine drug testing performs better than physician impression but only with adequate interpretation knowledge

• PDMPs are widespread; use of them improves provider confidence and is recommended by FSMB

• Instruments for patient reported safety, efficacy and misuse exist but have not been tested in clinical settings or for their impact on clinical outcomes
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Upon completion of the Post Test:

• You will receive an email detailing correct answers, explanations, and references for each question.

• You will be directed to a module evaluation, upon completion of which you will be emailed your module Certificate of Completion.

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