Integration of Opioid Prescribing Guidelines in Primary Care to Improve Quality and Safety

Conflict of Interest Disclosure
Author’s conflicts of interest:
- Peggy Lutz, no conflict of interest

Objectives
• Identify strategies to positively influence culture related to managing chronic non-cancer pain.
• Identify innovative communication strategies to disseminate clinical information and best practice expectations to providers and leaders.
• Identify "outside the box" clinical resource tools to support best practices related to management of chronic non-cancer pain or chronic opioid therapy.
• Discuss potential ethical considerations with violation of a controlled substance treatment agreement and termination from care.
Ascension Wisconsin

Ministry Health Care
- 13 hospitals
- 45 primary care clinics
- 10,000 associates
- 400 medical group physicians

Ascension Wisconsin
- 22 hospitals
- 114 clinics
- 23,500 associates
- 1,000 medical group clinicians

In Wisconsin, It's the LAW!
HOPE Legislation (2013): series of legislative bills to combat the heroin and prescription drug abuse and increase treatment options for addiction
- Requires a prescriber to review a patient’s PDMP record prior to prescribing controlled substances, with limited exceptions.
- Changes pharmacy requirement to submit information to the PDMP from 7 days to 24 hours.
- Requires law enforcement to report controlled substance violations to PDMP with notification to the physician
- Expands access to naloxone (Narcan®) by offering the drug for purchase from certain pharmacies without a prescription via standing order
- Allows regulatory bodies to develop best practice guidelines

Guidelines, Guidelines, and MORE Guidelines
Guidelines for Prescribing Opioids for Chronic Pain
www.cdc.gov
ICSI Institute for Clinical Systems Improvement
Intermountain Healthcare
Wisconsin Medical Examining Board
American Pain Society
American Academy of Pain Management
Current State

- Lack of standardization – multiple treatment agreements options
  - “contracts” with punitive language
- Expired controlled substance prescribing policy
- Knowledge deficit and cost issues with UDT
- Clinical metrics
  - Concurrent use of opioids and benzodiazepines/sedatives – 32%
  - Use of a controlled substance treatment agreement – 19%
  - Patients prescribed opioids with a UDT in the past 12 months – 10%

Negative Attitudes and Clinical Challenges Abound

- “I'd rather drain 4 perirectal abscesses than manage one patient with chronic pain.”
- “Sometimes it's just easier to write the prescription than taking the time to sort through all these issues with chronic pain.”
- “I do not prescribe narcotics of any kind for chronic pain.”
- “I'm not going to follow the guidelines until I’m told I absolutely have to do so.”
- “Need more time at appointments. While I know what I need to do at each visit for chronic pain, I usually have 2-3 more concerns to also address in a 15 min appointment.”
- “How much extra staff are you willing to hire to do all the things listed above?”

Project Team

- Lisa Benson, MD
  - Chief Quality Officer
  - Executive Sponsor
- Maria Hoertz, MD
  - Medical Director, Internal Medicine
- Nicole Brady, MD
  - Regional VP, Internal Medicine
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- Mitch Campbell, RN
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- Kathryn Olson, DNP
  - Nursing Administration
- Peggy Lutz, NP
  - Pain Management Director
- Robert Sedlacek, MD
  - Physician Champion, Family Medicine
- Risk Management, Quality Council, Education, Clinical Informatics, Pharmacy, Lab Services
Project Objectives

- Adopt the Wisconsin Medical Examining Board Opioid Prescribing Guideline as the framework for safe and responsible prescribing of opioid analgesics for chronic non-cancer pain.
- Integrate EBP for the assessment and management of chronic non-cancer pain into clinical practice.
- Reduce the potential for misuse, abuse, and diversion of controlled substances.
"I learned that we can do anything, but we can't do everything... at least not at the same time. So think of your priorities not in terms of what activities you do, but when you do them. Timing is everything."

Dan Millman
Patient Communication

- Providers did not feel comfortable having “difficult conversations” with patients
  - Patient handout on overall philosophy on management of chronic pain
  - Patient letter to raise awareness of changes in monitoring for patients on chronic opioid therapy
  - Weekly update segment on patient education and communication

What additional strategies could you utilize to communicate clinical information and expectations to providers and leaders?
A provider’s story:

- “Many of those medications were prescribed by well meaning, but undereducated providers. I know this because I was one of those providers who didn’t know what I didn’t know about chronic pain, opioids, substance use disorders, and the complex interplay of psychology with human biology.”
- The local hospital emergency department calls a patient’s primary care provider for all unexpected patient deaths. I received that phone call one night about a 35-year-old mother who had established with me the year before.”

A Patient’s Story...

“Trying to get pain under control is hard. When you are on narcotics, you are often treated like a second-class citizen, a drug seeker. One of the most disappointing things about having pain is the feeling of being judged, as if any normal person would want pain or to have the need to take pain medicine. It is important to treat pain acutely, and recognize how much psychological and emotional pain there is in that situation. Having a caring provider definitely is good for the soul of the patient, which in turn helps with pain and anxiety that come with chronic pain.”

A Model of Person-centered Pain Care

“We must see in all of our patients the person with pain, rather than the painful patient, and work to meet them where they are, addressing all of their issues”

Robert Sedlacek, MD, Family Medicine, Ascension Medical Group – Merrill Clinic.
Provider Data

- Baseline data by clinic and by individual provider
- Shared with providers by Medical Directors

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<tr>
<th>Clinic Location</th>
<th>Providers</th>
<th>New to Clinic</th>
<th>Patients on</th>
<th>Patients not on</th>
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<th>Patients not on due to high risk and no STNTU</th>
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Provider Survey

\[
\text{Limitations: Small sample size, Margin of error 20% reported to show opportunities for improvement.}
\]

What strategies can you suggest to positively influence culture related to managing chronic non-cancer pain?
Clinical Resources
- Review of opioid risk assessment tools
- MME calculators
- Standardized controlled substance treatment agreement
- Guide to managing violations of the treatment agreement
- Guidelines and tools for tapering opioid analgesics
- Guidelines for prescribing naloxone
- Comprehensive pain evaluation checklist
- UDT interpretation guidelines
- Holistic chronic pain treatment template

Controlled Substance Treatment Agreement
Before
- Numerous agreements
- Incorrectly used as an informed consent
- Viewed as a “contract”
- Violation of agreement could lead to termination from clinician’s practice and medical clinic

After
- One standard agreement for all clinics
- Patient information sheets on opioids, benzodiazepines, stimulants, and sedatives to assist with informed consent
- Resource guide on how to appropriately manage violations of the treatment agreement

Urine Drug Testing
Before
- Variable patient cost; for many, cost prohibitive
- Use of tests that are not clinically relevant to pain management monitoring
- Knowledge deficit by clinicians on what test to order and how to interpret results

After
- Price adjustment, uniform patient cost in progress
- Standardization of drug test panels across clinics/hospital labs
- Expand use of point of care testing in clinics without lab services on site
- Increase clinician knowledge TBD
Controlled Substance Policy

Before

- Owned by Risk Management
- Statutory nature
- Provider protection versus clinical relevance
- Focused on “contracts” and termination procedures
- Detailed list and descriptions of “Drug Seeking Behavior”

After

- Owned by clinical leaders
- Plain language
- Clear expectations
- Clinically relevant covering treatment agreements, UDT, ePOMD, office visits, and prescribing guidelines
- Not prescriptive but outlines best practices.

Training

WI Medical Examining Board and WI Board of Nursing requires 2 hours of continuing education on responsible opioid prescribing for license/APRN certification renewal

- Internal online program free to all Ascension WI clinicians
- Regional live CME events
- Clinic patient care staff mandatory in-services
- Weekly pain updates archived
- Informal teaching opportunities

What training strategies can you suggest to hardwire practice changes?
Post-implementation data pending

Limited by:
- Change in EHR conversion mid-project.
- Limited IT resources to write reports in new platform; resources primarily allocated to support current and upcoming EHR conversions

What metrics would you suggest to monitor progress with integrating best practices for chronic pain management?

Lessons Learned
What went well...
- Greater awareness of opioid safety and management of chronic pain
- Pain leadership established system-wide
- Standardization
- Usable resources available to support clinical practice
- Defined policy with clear expectations for practice
- Beginning to change the larger culture

Would have been better with...
- Greater availability of IT resources to get data to support workflow and drive practice change
- Less disruption from change in EHR
- Defined leadership structure within Ascension WI medical groups
- “Inertia” – clinician burnout from amount of change
What's Next?

More of the same to hardwire best practices
Data, data, and more data
- Follow-up on defined metrics
- ePDMP compliance and prescriber practice data

EHR updates to support workflow
- Pain care plan summary – historical snapshot
- ePDMP and EHR integration to streamline access
  and ability to audit compliance

Expand work of Ministry Health Care to all of Ascension Wisconsin
- Controlled substance policy
- Treatment agreement
- State-wide Pain Council

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MINISTRY MEDICAL GROUP – Managing Pain, Improving Lives

The complexities of chronic pain require a comprehensive treatment approach using a multidisciplinary care team. Larger emphasis should be placed on use of non-pharmacologic strategies to improve function and quality of life. Multiple factors can impact treatment planning including:

- Patient’s current functional status,
- Pain diagnosis and mechanism of pain,
- Presence of physical and/or behavioral comorbidities,
- Individualized pain treatment goals,
- Availability of therapy options, and
- Potential barriers to treatment e.g., financial, transportation, employment, support network, etc.

GENERAL TREATMENT STRATEGIES FOR CHRONIC PAIN:

- Treat the underlying cause of pain.
- Patients must take an active role in managing his or her pain.
- All patients should engage in self-management strategies including tobacco avoidance/cessation, sleep hygiene, weight loss/management, exercise, meditation and relaxation.

TREATMENT OPTIONS BASED ON SELECT MECHANISMS OF PAIN: (ICSI, 2016; AMDG, 2015)

- **Arthritis**: aerobic and strengthening exercise, aquatic therapy, intra-articular injections
- **Chronic musculoskeletal pain**: exercise, manual therapies (neck and back pain), aquatic therapy, TENS, ultrasound, mindfulness-based stress reduction, cognitive behavioral therapy (CBT), yoga, acupuncture
- **Fibromyalgia and diffuse non-specific myalgias**: graded aerobic exercise, heated aquatic therapy, relaxation, CBT, massage, hypnosis, acupuncture, biopsychosocial interdisciplinary team approach
- **Headache**: biofeedback, relaxation, CBT, therapeutic injections, acupuncture
- **Nerve compression / radicular pain**: physical therapy, therapeutic injections, interventional procedures, surgical intervention
- **Chronic neuropathy**: TENS

OVERVIEW OF SELECT TREATMENT STRATEGIES:

- **Psychological modalities**: A variety of psychotherapeutic interventions are available to help patients problem solve to replace maladaptive thoughts, behaviors, and coping strategies with more adaptive strategies. Consider referral to Behavioral Health or Pain Psychology.
- **Physical rehabilitation modalities**: Active therapies such as strength training and/or conditioning exercise should be the mainstay of treatment; passive therapies should be in addition to and not a substitute for active participation in an exercise program. A graded exercise program is recommended to overcome deconditioning often seen with chronic pain. Consider referral to Physical or Occupational Therapy.
- **Interventional treatment**: Patients who have failed conservative treatment should be referred for potential interventional options. Diagnostic injections can help confirm the pain generator; therapeutic injections are available for spinal, visceral, and peripheral pain conditions.
- **Advanced interventional therapies**: Spinal cord stimulation may be an option for refractory radicular spinal pain; intrathecal pumps may be an option for intractable cancer-related pain and spasticity.
This information is not intended to be an exhaustive review of non-pharmacologic treatment of chronic pain conditions. If the patient has tried first line therapy and is not meeting their treatment goals, consider referral to specialty care for assistance in clarifying the pain source or developing the treatment plan.

A [Holistic Chronic Pain Treatment Plan](#) summary is available. This summary puts the treatment goals and plan in writing, and serves as a visible reminder to patients of the role they have in the success of their treatment.

For questions, contact Peggy Lutz, Service Line Director, Pain Management [peggy.lutz@ascension.org](mailto:peggy.lutz@ascension.org) or Robert Sedlacek, MD, Family Medicine, Merrill [robert.sedlacek@ascension.org](mailto:robert.sedlacek@ascension.org)

References:


Chronic pain, for many, is a problem that eludes an easy fix. The challenge of finding an adequate treatment, even for common types of pain, underscores the role that psychosocial variables play in causing, maintaining, exacerbating, and mitigating pain symptoms, pain severity, and physical functioning. These factors, more than the pain source or type, affect coping and adaptation, resilience, and emotional responses. Psychosocial factors also play a role in a patient’s openness to treatments and compliance with treatment plans.

- Bob was injured in an industrial explosion and suffered numerous injuries resulting in the amputation of both legs just above the knee.
- Lori’s parachute malfunctioned, and she fell 10,000 feet with minimal chute support, landing in a deeply plowed soybean field. She broke her back at L1-L2.
- Kelly has migraines of increasing frequency and intensity such that she misses 5-10 days of work per month.
- Jim is 70 and reports severe knee and ankle pain.

All of these patients have debilitating pain. Those in a clinical role will understand immediately that the pain management plans for each of these patients will be different, dictated by not only their pain complaints but by the psychosocial context of their pain. Consider the difference it makes in the conceptualization of a pain plan to know that Bob was newly married when his accident occurred at age 48, that he suffers from serious PTSD and anxiety. Lori was 16 when she suffered her injuries, later traveled widely in Europe, married, has a child but is now debilitated by episodes of paroxysmal pain. Kelly is the single mother of two children under the age of 10, the first of her siblings to graduate from college. She is proud, independent, and prefers natural therapies. Jim is a POW Viet Nam veteran who has been disabled with depression. He currently abuses alcohol. The clinician’s assessment of pain will be influenced further by knowing each patient’s history of trauma, examples of resilience or self-discipline in their past, personal loss histories, future goals, and family coping patterns.

Louis Gifford, an internationally renowned expert in pain treatment and management, succinctly described the importance of acknowledging and assessing the psychosocial complexities of pain:

“A clinician unacquainted with the complexity of the pain experience will regard painful conditions as either psychological or pathological; a more informed clinician will unconsciously ascribe a percentage to each area; but an enlightened clinician will see pain as a dynamic interaction between a multitude of influences and manage it accordingly and appropriately.”

A few thoughts in summary:

- Pain is a complex, multidimensional sensory experience that varies in quality, strength, duration, location, and unpleasantness.
- The severity or unpleasantness of pain is not directly related to the nature and extent of tissue damage. It’s not that simple.
- Psychological factors, such as the situational and emotional factors that exist when we experience pain, can profoundly alter pain perceptions.
• Health care clinicians’ beliefs about pain bias their assessments of pain patients and their selection of treatment methods.
• If you need assistance in assessing a patient with complex psychosocial contributors, consider referring your patient for a psychological assessment. Psychological evaluations focus on the emotional distress and maladaptive behaviors that accompany chronic pain; they also provide the clinician and the patient with individualized cognitive and behavioral self-management strategies that may reduce their perceptions of pain and related disability and enhance their self-efficacy. As a result, psychological assessments have become standard in chronic pain treatment.
• Consider referring your patients for behavioral health interventions. Two strategies have demonstrated efficacy in pain patients, especially in tandem with other wellness strategies – diet and appropriate medication. These two strategies are 1) cognitive behavioral therapy and 2) mindfulness. Mindfulness for pain patients is appropriate as a recommendation for most patients. This compassionate programming teaches patients how to manage the suffering, fear, and despair associated with pain, and how to reclaim a full, rich life.

For additional information, contact your local behavioral health/behavioral medicine services.

Submitted by: Gina Koeppl, PhD, Director, Behavioral Health – North Region

For questions, contact Peggy Lutz, Service Line Director, Pain Management peggy.lutz@ascension.org or Robert Sedlacek, MD, Family Medicine, Merrill robert.sedlacek@ascension.org
Testing Methods for Urine Drug Screening for Pain Management  (April 6, 2017)

Urine drug screening (UDS) is an important safe prescribing practice for all controlled substances. For patients with chronic pain and chronic opioid therapy, UDS is one component of the initial and ongoing risk assessment. UDS does not diagnose substance use disorders; unexpected results require further evaluation of the patient.

The Wisconsin Medical Examining Board (MEB) opioid prescribing guideline recommends a UDS prior to initiating chronic opioid therapy and at minimum once yearly; more frequent UDS is recommended for higher risk patients.

There is opportunity to improve UDS monitoring within Ministry Health Care. Among patients receiving opioids, only 10% received a UDS within the past year. Clinicians cite lack of understanding of available tests, what test to order, and how to interpret the test result as barriers to use of UDS. Over the next few weeks, basic concepts related to UDS, information on how to interpret results and clinical application of result findings will be covered.

**METHODS OF TESTING**

**Immunooassay (IA)** urine drug tests are **qualitative screening** tests that identify presence or absence of drug classes. IA tests rely on the binding of an antibody designed to detect a specific chemical or group of closely related chemicals. IA tests can be performed in a lab or as a point of care test.

Variables that can influence the test result include test specific drug cutoff levels (minimum concentration of a drug or metabolite that must be present to produce a positive result), cross-reactivity within the drug class of interest, cross-reactivity of unrelated drugs, drug dose, dosing frequency and timing related to testing, metabolism (patient pharmacokinetics), urine dilution and urine pH.

**Advantages of IA:**
- Simultaneously screen for multiple drugs
- Fast results, inexpensive

**Disadvantages of IA:**
- In general, specific drugs are not detected within a drug class (for example opioid IA test detects several opioids in the class, not just morphine, codeine, etc)
- Variable sensitivity and specificity by test manufacturer; review of product insert is helpful
- A drug with concentration below the drug class cutoff will be reported as negative (the drug or metabolite in the class is present, just not detected); a false negative test if the goal is to detect presence of any concentration of drug in the class
- Polypharmacy may not be detected (for example morphine and hydromorphone are prescription drugs that could be taken, yet not separately identified by any opiate IA drug test)

**Gas Chromatography and Liquid Chromatography-Mass Spectrometry (GC-MS/LC-MS)** urine drug tests are **quantitative, confirmatory tests** identifying specific drugs and their metabolites and their respective concentrations.
Advantages of GC-MS/LC-MS:

- Highly specific (few false-positives); highly sensitive (few false-negatives) due to lower cutoff levels for detection
- Results are definitive for specific measurable substances
- Can detect multiple drugs within the drug classes, assisting interpretation (many drugs within a class, such as opioids will be reported if detected above the measuring limit)

Disadvantages of GC-MS/LC-MS:

- Results take 2-3 days; the test is typically run at an outside lab due to the need for specialized equipment
- More expensive (but may be more cost effective depending on the drug information needed)

Managing Unexpected UDS results – Part I (April 13, 2017)

Urine drug testing (UDT) is required for all patients receiving chronic opioid therapy. The Wisconsin Medical Examining Board (MEB) opioid prescribing guideline recommends a UDT prior to initiating chronic opioid therapy and at minimum once yearly; more frequent UDT is recommended for higher risk patients.

Why urine drug testing:

- Provides objective data regarding compliance with the pain treatment plan
- Aids in the evaluation of aberrant behaviors, unexplained symptoms, or unexpected responses to treatment. Is the patient taking illicit drugs? Is the patient taking prescribing medications from other sources? Has the patient stopped taking their medication?
- Improves patient safety by identifying dangerous medication combinations from non-prescribed sources that can increase the risk of overdose
- Important note: A positive drug test will not provide a diagnosis of a substance use disorder nor does a negative test result rule out a substance use disorder.

Patient Preparation and Education:

- Use a controlled substance treatment agreement (CSTA) that explicitly outlines expectation for UDT.
- Explain to patient that UDT is part of universal precautions. Patients are more likely to accept UDT as part of the treatment plan when they know they are not being signaled out or suspected of abusing drugs.
- Patient education tip: “[Controlled substances] are dangerous medication when not used appropriately. In order to provide you safe and effective treatment for your chronic pain, I am required to conduct UDT periodically. This is done for all patients receiving long-term opioid medication.”
Understanding test results:

Interpretation of immunoassay (IA) results requires an understanding of which drugs are included in the drug test panel, test specific drug cutoff levels, which drugs or drug metabolites will be detected, window of detection, and potential cross-reactivities for specific drugs. Clinicians should have access to a copy of the lab manual for the drug test panel(s) used in their clinic.

This update focuses on unexpected positive results related to illicit drugs. See table Drugs of Abuse Testing – Illicit Drugs.

Definitions:

- “Expected” test result is positive for the patient’s prescribed medication, but negative for all other unexpected substances
- “Unexpected” test result could be negative for the prescribed medication, positive for unexpected substance(s), or both

Follow-up of unexpected positive results for illicit drugs:

- Avoid making significant treatment decisions based solely on UDT results. All unexpected results require further evaluation and can indicate a wide spectrum of aberrant behaviors from chemical coping to substance use disorder. Treatment decisions should be based on all relevant data including UDT, patient interview, ePDMP review, and the behavioral and physical assessment.
- IA positive results should be considered presumptive until confirmed by GC-MS/LC-MS, although it is not always necessary to confirm all positive results. Talk with the patient about possible cross-reactivities related to medications or food; send for confirmation if the patient’s self-report is not consistent with the test result.
- Discussing test results with a patient can be difficult. Patients need clear explanation of the test results in terms they can understand and what it means for them and the treatment plan. Straightforward, nonjudgmental communication is essential.
- Follow-up may include counseling, increased frequency of office visits and UDT, limiting quantity with opioid prescription, evaluation for mental health and substances use disorders with referral to Behavioral Health or Addiction Medicine as appropriate, and/or discontinuing the opioid medication.
- Consider referral to a comprehensive pain management specialist in the context of uncontrolled pain that is difficult to manage by the primary care provider, especially if the patient feels the need to seek outside substances to control pain. Patient should be advised that the purpose of the referral is to look at alternative treatment options that may or may not include prescribing of opioid analgesics.

Managing Unexpected UDT results – Part II  (April 20, 2017)

Last week’s pain update focused on managing unexpected positive urine drug test (UDT) results related to illicit drugs. This week, managing unexpected results, both positive and negative, for prescription medications will be covered.

Understanding test results:

Interpretation of immunoassay (IA) results requires an understanding of which drugs are included in the drug test panel, test specific drug cutoff levels, which drugs or drug metabolites will be detected, window of detection, and potential cross-reactivities for specific drugs. Contact the laboratory when looking for specific drugs to make sure the correct test is ordered. Clinicians should have access to a copy of the lab manual for the drug test panel(s) used in their clinic.

Opioid Metabolic Pathways

It is important to understand metabolism of opioids for accurate UDT interpretation. For example, codeine metabolizes to morphine and to a lesser extent hydrocodone, therefore, all three substances may be present in urine.

Responding to unexpected NEGATIVE results:

- Take a thorough medication history including date of last use and quantity of use during the preceding 2-3 days
  - Patients on low dose PRN medication may result negative
  - Did the patient run out of medication early due to increasing the dose or frequency of use? Rule out poorly controlled pain versus substance misuse/abuse.
  - Is the patient not taking the full prescribed dose? Rule out patient hoarding of drug for future use versus diversion?
- Is the testing outside the window of detection for the expected prescribed drug?
- Is the drug testing panel specific to the expected prescribed drug?
- Clinical conditions that could produce negative results:
  - Induced enzyme levels from smoking causing more rapid metabolism/elimination of the drug
  - Shortened GI tract from surgery reducing absorption of the drug
- Did the patient consume excessive fluids causing diluted urine? Check the specific gravity of the sample.
- Has the specimen been adulterated or substituted?
- Consider retesting; consider possibility of diversion or non-use of medication.
• The rate of false negative results with IA is rare; typically confirmatory testing is not needed for negative results. Consider confirmatory testing if the patient adamantly reports taking the medication in question.

Responding to unexpected POSITIVE results:
• Take a thorough medication history, including OTC medications, to assess for potential cross-reactivities; include in the history where medication was obtained to assess for non-prescribed source
• Review the PDMP to check for other sources of prescribed medication
• Some opioids are normally metabolized into other opioid substances. The presence of other opioid substances may indicate appropriate use of the prescribed opioid.
• Consider confirmation testing to rule out cross reactivity. See table Urine Drug Testing – Prescription Medications.

Treatment planning
• All unexpected results require further evaluation.
• IA positive results should be considered presumptive until confirmed by GC-MS/LC-MS.
• When in doubt, consult with a clinician knowledgeable in UDT interpretation e.g. pain management specialist or a colleague managing higher risk pain patients.
• Follow-up may include counseling, increased frequency of office visits and UDT, limiting quantity with opioid prescription, evaluation for mental health and substances use disorders with referral to Behavioral Health or Addiction Medicine as appropriate, and/or discontinuing the opioid medication.
• Consider referral to a comprehensive pain management specialist in the context of uncontrolled pain that is difficult to manage by the primary care provider, especially if the patient feels the need to seek outside substances to control pain. Patient should be advised that the purpose of the referral is to look at alternative treatment options that may or may not include prescribing of opioid analgesics.

Confirmatory Urine Drug Testing  (May 4, 2017)

Previous pain updates provided information on interpretation of immunoassay (IA) urine drug test results. You should recall that positive IA results should be considered presumptive until confirmed by gas or liquid chromatography-mass spectrometry (GC-MS/LC-MS), although it is not always necessary to confirm all positive results. GC/LC-MS provides highly-specific results through identification and quantification of the individual drugs or metabolites within a specimen. GC/LC-MS also provides highly sensitive results due to lower cutoff levels for detection. Refer to Testing Methods for Urine Drug Screening for an overview of GC/LC-MS testing.

Interpretation of confirmatory urine drug test results:
  1. Correct interpretation of confirmatory test results requires a basic understanding of metabolic pathways, particularly for opioids and benzodiazepines, in order to understand which
metabolites will be present and which metabolites should not be present, based on the patient’s prescribed medication.

**Opioid Metabolic Pathways:**

- **Benzodiazepine Metabolic Pathways:**

![Diagram of opioid metabolic pathways](image)


2. Metabolites should be present; absence suggests potential adulterated sample (SAMHSA, 2012; page 47-49)

3. Opioids are metabolized in a linear sequence
   a. Heroin is rapidly converted to 6-MAM and then to morphine; there is minimal metabolism to hydromorphone. Rarely will heroin or 6-MAM be present due to heroin’s very short half-life.
   b. Codeine is metabolized to morphine; therefore both substances may be present after codeine use.
      i. Codeine alone is possible because a small proportion of patients (<10% of Caucasians) lack the enzyme needed to convert codeine to morphine.
      ii. Codeine may be metabolized to small quantities (generally <15%) of hydrocodone; this should not be interpreted as hydrocodone use when high concentrations of codeine are present.
   c. Morphine is metabolized to 3-morphine-glucuronide and 6-morphine-glucuronide and to a small extent (< 5%) to hydromorphone.
      i. Morphine does not metabolize to codeine; presence of morphine only is consistent with use of morphine or heroin.
d. Hydrocodone may be metabolized to small quantities of hydromorphone; this should not be interpreted as hydromorphone use when high concentrations of hydrocodone are present.

e. Synthetic opioids e.g., oxycodone, methadone, and fentanyl, have limited metabolism.
   i. Oxycodone is metabolized to noroxycodone and oxymorphone. If the concentration of oxycodone is greater than oxymorphone, use of oxycodone is likely.
   ii. Oxymorphone does not produce any metabolites that could be mistaken for another opioid.

4. Benzodiazepine metabolism is complex; providers should refer to metabolic pathways for anticipated metabolites.

5. THCA quantification can demonstrate abstinence through decreasing levels.
   a. May be present in urine for more than 3 months in chronic high users
   b. Levels may increase if a patient has lost significant weight despite being abstinent
   c. Passive smoke inhalation does not produce appreciable amounts of THCA in a urine specimen to explain positive marijuana results

6. Amphetamines are minimally metabolized but frequently cross react; therefore, confirmatory testing is needed to identify which substances are present.

7. A methamphetamine positive result requires chiral analysis to differentiate between two isomers: $d$-methamphetamine and $l$-methamphetamine
   a. Any $d$-methamphetamine present is from an illicit source.
   b. If 100% of the isomer is $l$-methamphetamine (aka l-desoxyephedrine), the source is likely from a Vicks inhaler or a metabolite of selegiline.

8. Confirmatory tests provide quantitative concentrations of drugs and their metabolites; however, there is currently no broadly accepted, scientifically validated relationship between the concentrations reported in the urine and the doses taken of any drug.
   a. Interpretation of quantitative concentrations is difficult and requires more specialized training
   b. Providers with questions about interpretation should speak with a pain or addiction specialist experienced with interpretation.

9. Confirmation of all positive IA results is not clinically indicated and not cost effective.
   a. If a patient admits drug use when informed of a positive test result, a confirmatory test is generally not needed.
   b. If the IA test is highly specific to a drug with limited cross-reactivities e.g., cocaine, confirmation is generally not needed.
   c. Refer to the tables Drugs of Abuse Testing – Illicit Drugs and UDT – Prescribed Medications to help determine when confirmation is necessary.

Confirmatory testing with chromatography and spectrometry of positive urine drug testing by IA is complicated and contains many opportunities for miscommunication and misunderstanding. This guide is intended to provide a broad overview of the most common pitfalls that providers are likely to encounter. Refer back to this and the other articles in this series often to ensure a clear understanding of the test results when discussing them with patients. Any questions can be referred to a pain or addiction specialist experienced with interpretation and clinical application of findings.
References:


Substance Abuse and Mental Health Services Administration. (2012). *Clinical Drug Testing in Primary Care, Technical Assistance Publication (TAP) 32*. Retrieved from SAMHSA:

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## DRUGS OF ABUSE TESTING – ILLICIT DRUGS

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<thead>
<tr>
<th>Suspected Drug of Abuse</th>
<th>Positive Result Findings by IA</th>
<th>Potential Cross-Reactivity</th>
<th>Approximate Window of Detection for Drugs in Urine</th>
<th>Next Steps</th>
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<tr>
<td><strong>Cocaine</strong></td>
<td>Benzoylcegonine</td>
<td>Coca leaf teas, Topical anesthetics containing cocaine</td>
<td>2-4 days&lt;br&gt;1,2</td>
<td><strong>Confirmatory testing not required.</strong> Cocaine’s primary metabolite, benzoylcegonine, has low cross-reactivity and is highly predictive of cocaine use.</td>
</tr>
<tr>
<td><strong>Heroin</strong></td>
<td>Opiates</td>
<td>Dextromethorphan, Diphenhydramine, Doxylamine, Opiates, Poppy seeds</td>
<td>1-3 days&lt;br&gt;1</td>
<td><strong>Send for confirmatory testing.</strong> Heroin rapidly metabolizes to morphine. 6-monoacetylmorphine (6-MAM) is an intermediate metabolite between heroin and morphine and is considered conclusive proof of heroin use.</td>
</tr>
<tr>
<td><strong>Methamphetamine</strong></td>
<td>d-methamphetamine</td>
<td>Bupropion, Chlorpromazine, Desipramine, Dextroamphetamine, Doxepin, Ephedrine, Fluoxetine, Labetalol, Methylphenidate, Phenylephrine, Pseudoephedrine, Ranitidine, Selegiline, Trazadone, Trazadone, Vick’s</td>
<td>3-4 days&lt;br&gt;2</td>
<td><strong>Send for confirmatory testing and chiral analysis.</strong> Chiral analysis will differentiate between two isomers: d-methamphetamine, which is considered a drug of abuse; and l-methamphetamine (aka l-desoxyephedrine), an active ingredient in Vicks inhalers and a metabolite of selegiline (anti-Parkinson drug).</td>
</tr>
<tr>
<td><strong>Marijuana</strong></td>
<td>11-nor-Δ9 tetrahydrocannabinol-9-carboxylic acid (THCA)</td>
<td>Dronabinol, Efavirenz, NSAIDs, PPIs, Promethazine</td>
<td>Single use – 3 days&lt;br&gt;Moderate use (4 times/week) - 5-7 days&lt;br&gt;Chronic daily use – 10-15 days&lt;br&gt;Chronic heavy smoker - &gt; 30 days</td>
<td>Positive IA is likely positive for use of marijuana. <strong>May send for confirmatory testing.</strong> Confirmation is helpful to quantify e.g., serial testing to confirm abstinence. IA does not distinguish between smoked marijuana and the synthetic preparation, dronabinol (Marinol®). Does not easily detect cannabidiol (CBD) at usual dosing levels.</td>
</tr>
<tr>
<td><strong>PCP</strong></td>
<td>Phencyclidine</td>
<td>Diphenhydramine, Dextromethorphan, Trazadone, Venlafaxine</td>
<td>8 days&lt;br&gt;3&lt;br&gt;Chronic use – several weeks&lt;br&gt;1</td>
<td><strong>Send for confirmatory testing.</strong></td>
</tr>
<tr>
<td><strong>Ecstasy</strong></td>
<td>3,4-Methylenedioxyamphetamine (MDMA)</td>
<td>Similar to the methamphetamine list</td>
<td>1-2 days&lt;br&gt;1</td>
<td><strong>Send for confirmatory testing.</strong> Requires 100 times as much d-methamphetamine to make this assay positive.</td>
</tr>
</tbody>
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REFERENCES


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<tr>
<th>Drug / Drug Category</th>
<th>Positive Result Findings by IA</th>
<th>Potential Cross-Reactivity</th>
<th>Approximate Window of Detection for Drugs in Urine*</th>
<th>Notes / Next Steps</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphetamines</td>
<td>d-Amphetamine</td>
<td>Bupropion, Desipramine, Dextroamphetamine, Doxepin, Ephedrine, Fluoxetine, Labetalol, Methylphenidate, Phenylephrine, Pseudoephedrine, Ranitidine, Selegiline, Trazadone, Vick's</td>
<td>1-3 days&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Highly cross-reactive with high rate of false positives. <strong>Note:</strong> The list of possible cross-reactants is not comprehensive; refer to drug test panel literature for test-specific cross-reactants. If IA positive for amphetamine and negative for methamphetamine, can reasonably exclude illicit use of methamphetamine. Will detect Adderall (amphetamine and dextroamphetamine); does not detect lisdexamfetamine (Vyvanse) or methylphenidate (Ritalin, Concerta).</td>
</tr>
<tr>
<td>Barbiturates</td>
<td>Secobarbital**, Butalbital**</td>
<td>Ibuprofen, Naproxen</td>
<td>1 day for short-acting&lt;sup&gt;2,3&lt;/sup&gt; 21 days for long-acting&lt;sup&gt;2,3&lt;/sup&gt;</td>
<td>For unexpected positive, send for confirmatory testing.</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>Oxazepam**, Nordiazepine**</td>
<td>Oxaprozin, Sertraline</td>
<td>3 days short-acting&lt;sup&gt;2,3&lt;/sup&gt; 30 days long-acting&lt;sup&gt;2,3&lt;/sup&gt;</td>
<td>For unexpected positive, send for confirmatory testing. May not detect alprazolam, clonazepam, and lorazepam. Clonazepam detection requires 23 times more drug than most other benzodiazepines and is not easily detected with this assay.</td>
</tr>
<tr>
<td>Codeine***</td>
<td>Morphine</td>
<td>Dextromethorphan, Fluoroquinolone, Levofoxacain</td>
<td>1-2 days&lt;sup&gt;1,3&lt;/sup&gt;</td>
<td>Codeine metabolizes to morphine and to a lesser extent hydrocodone, therefore, all three substances may be present in urine.</td>
</tr>
<tr>
<td>Morphine</td>
<td>Morphine</td>
<td></td>
<td>1-2 days&lt;sup&gt;1&lt;/sup&gt;</td>
<td>For unexpected positive, send for confirmatory testing.</td>
</tr>
<tr>
<td>Hydrocodone***</td>
<td>Morphine</td>
<td>Heroin, Oflaxacin, Poppy seeds / poppy oil, Rifampin, Quinine</td>
<td>1-2 days&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Hydrocodone is metabolized in small amounts to hydromorphone; both may be found in urine. Use of hydrocodone immediately before testing (&lt; 2 hours) may result in negative test as liver has not had time to metabolize enough to hydromorphone.</td>
</tr>
<tr>
<td>Hydromorphone***</td>
<td>Morphine</td>
<td></td>
<td>1-2 days&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Hydromorphone use does NOT result in positive screen for hydrocodone.</td>
</tr>
<tr>
<td>Methadone</td>
<td>Methadone</td>
<td></td>
<td>3-6 days&lt;sup&gt;2&lt;/sup&gt; Maintenance dose 3-11 days&lt;sup&gt;1&lt;/sup&gt;</td>
<td><strong>Confirmatory testing not required:</strong> test is specific for methadone.</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>Oxycodone</td>
<td>Immediate release 2-4 days&lt;sup&gt;1,2,3&lt;/sup&gt; Controlled release 1.5-3 days&lt;sup&gt;1&lt;/sup&gt;</td>
<td>1-2 days&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Oxycodone is metabolized to oxymorphone; both may be found in urine.</td>
</tr>
</tbody>
</table>

<sup>1</sup> Includes previous day's dose
<sup>2</sup> Includes previous day's and half dose
<sup>3</sup> Includes previous day's and 1/3 dose
<table>
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<tr>
<th>Drug</th>
<th>Confirmation</th>
<th>Detection Time</th>
<th>Action</th>
</tr>
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<tr>
<td>Buprenorphine</td>
<td>Confirmatory testing not required; test is specific for buprenorphine.</td>
<td>Up to 4 days&lt;sup&gt;1&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Fentanyl***</td>
<td>Must order test specific to fentanyl to confirm use.</td>
<td>Up to 3 days</td>
<td></td>
</tr>
<tr>
<td>Oxymorphone***</td>
<td>Must order test specific to oxymorphone to confirm use.</td>
<td>Immediate release 1.5-2.5 days&lt;sup&gt;1&lt;/sup&gt; Extended release 1-4 days&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Oxymorphone use does NOT result in positive screen for oxycodone</td>
</tr>
<tr>
<td>Tramadol***</td>
<td>Must order test specific to tramadol to confirm use.</td>
<td>Up to 3-5 days</td>
<td></td>
</tr>
<tr>
<td>Tricyclic antidepressants</td>
<td>For unexpected positive, send for confirmatory testing. Most TCAs will be metabolized to a substrate for this assay.</td>
<td>Nortriptyline Carbamezapine Cyclobenzaprinee Diphenhydramine Hydroxyzine Quetiapine</td>
<td></td>
</tr>
</tbody>
</table>

* Higher doses and some pathologies may extend the window of detection  
** Results vary based on drug test panel  
*** Not included in standard opioid IA screen.

**Responding to UNEXPECTED NEGATIVE results:**

- Take a thorough medication history including date of last use and quantity of use during the preceding 2-3 days  
  - Patients on low dose PRN medication may result negative  
  - Did the patient run out of medication early due to increasing the dose or frequency of use? Rule out poorly controlled pain versus substance misuse/abuse.  
  - Is the patient not taking the full prescribed dose? Rule out patient hoarding of drug for future use versus diversion?
- Is the testing outside the window of detection for the expected prescribed drug?  
- Is the drug testing panel specific to the expected prescribed drug?  
- Clinical conditions that could produce negative results:  
  - Induced enzyme levels from smoking causing more rapid metabolism/elimination of the drug  
  - Shortened GI tract from surgery reducing absorption of the drug  
- Did the patient consume excessive fluids causing diluted urine? Check the specific gravity of the sample.  
- Has the specimen been adulterated or substituted?  
- Consider retesting; consider possibility of diversion or non-use of medication.  
- The rate of false negative results with IA is rare; typically confirmatory testing is not needed for negative results. Consider confirmation testing if the patient adamantly reports taking the medication in question.

**Responding to UNEXPECTED POSITIVE results:**

- Take a thorough medication history, including OTC medications, to assess for potential cross-reactivities; include in the history where medication was obtained to assess for non-prescribed source  
- Review the PDMP to check for other sources of prescribed medication  
- Some opioids are normally metabolized into other opioid substances. The presence of other opioid substances may indicate appropriate use of the prescribed opioid.
URINE DRUG TESTING – PRESCRIPTION MEDICATIONS

REFERENCES


