

Drug Testing Guide for Chronic Pain Management Services
ARUP Clinical Drug Abuse Testing
March 2007

Gwen McMillin, Ph.D., Medical Director, Clinical Drug Abuse Testing
Fran Urry, Ph.D., Assistant Medical Director, Clinical Drug Abuse Testing

A. OBJECTIVE AND CONTRIBUTIONS

Objective:

- to provide a working knowledge of drug testing, its contributions, processes, options, limitations, and interpretation/application in chronic pain management services, for physicians and associated health care staff.

Contributions:

- evidence that the patient is taking the medication prescribed by the pain management service (compliance).
- evidence that the patient is not taking the medication prescribed by the pain management service (diversion, or non-compliance).
- evidence that the patient is abusing a controlled substance, or other drug not prescribed by the pain management service (e.g., amphetamines, cocaine, marijuana, heroin, and other opiates, etc.), and may be subject to dismissal from the program.

B. ANALYTICAL ASPECTS

Specimen choices:

- **Urine** is generally the specimen of choice in pain management services. Drugs are present at higher concentrations and for longer periods of time in urine than in serum/plasma, facilitating a higher likelihood to detect compliance, non-compliance, and drug abuse; urine is also non-invasive.
- **Serum/plasma** is the most appropriate alternative to urine, when the donor is a dialysis patient, or is otherwise unable to provide a urine specimen. Serum/plasma is the specimen of choice if evaluating patient pharmacokinetics or therapeutic drug monitoring.
- Whichever specimen is chosen, **care and caution must be implemented in labeling the specimen such that the specimen is attributed to the right patient, and the appropriate test is selected.**

Analyses:

- Panels may be selected, which include the initial screen by immunoassay and confirmation of presumptive positives by mass spectrometry. **Note: a positive immunoassay screen alone lacks the essential qualitative accuracy necessary for the clinician to take action against the patient (e.g. dismissal from the program); in contrast, a mass spectrometric confirmation is highly accurate in qualitative identification and must be performed when important decisions are made regarding the patient.** See list of panels at end of this document.
- If interested in a single drug or drug class only, a direct confirmation without a screen can be selected. See list of individual drug tests by mass spectrometry at end of this document.
- For both the screen and confirmation, a cutoff concentration is validated in the laboratory. A **cutoff concentration** is the threshold used to define a positive result; a result at or above the cutoff concentration is defined as positive, whereas a result below the cutoff is defined as negative. See Table for drugs/drug classes covered in urine, their screen and confirmation cutoff concentrations, and detection times.
- **Issue related to screen cutoffs:** The screen cutoffs are defined by the reagent manufacturer, usually with a single cutoff, occasionally with a choice of two cutoffs; ARUP selects the lowest screen cutoff. ARUP confirmation cutoffs are always lower than the screen cutoffs. As a result, a specimen that contains a prescribed drug(s) may test as negative on the screen, therefore not taken to confirmation, and reported as negative. If a positive result is expected for a particular drug(s), **the client may add the following comment to the test requisition: If the screen is negative for drug X, reflex to confirmation.** If the confirmation is positive, the quantitative result will be reported. If the confirmation fails to confirm drug X, the laboratory will enter the comment: "Drug X in this specimen failed to confirm."
- **Issue related to confirmation cutoffs:** Laboratories performing drug abuse confirmations can measure concentrations that fall below the cutoff concentration. Two terms are commonly used: LOQ and LOD. A **limit of quantitation (LOQ)** is the lowest concentration at which the laboratory can meet all qualitative criteria for the drug's presence, and can quantitate within defined limits of accuracy and precision. At ARUP, the LOQ is synonymous with the cutoff concentration. The **limit of detection (LOD)** is the lowest concentration at which the laboratory can meet all qualitative criteria for the presence of the drug, but for which the quantitation may not meet accuracy and precision requirements. It happens occasionally that a confirmation is less than the cutoff/LOQ, but equal to or higher than the LOD, i.e. the drug is present, but its concentration is below the cutoff. **If the**

pain management program receives a negative report when the patient claims to be taking the medication (for example, oxycodone), the program can call ARUP and ask that the data be reviewed to determine if the oxycodone is present, but below the cutoff. The cutoff for oxycodone is 5 ng/mL. If oxycodone is found to be present, an amended report will be generated, indicating: “Confirmed positive by mass spectrometry for oxycodone, concentration less than 5 ng/mL”.

- Additional drugs administered in chronic pain management.
ARUP can detect and quantitate additional drugs employed in pain management services. These are drugs for which a screen is not presently available, but a direct mass spectrometric analysis is available through ARUP. For a listing of these drugs, see the ARUP Laboratory Test Directory; common drugs requested to support pain management clinics are also listed at the end of this document.

C. INTERPRETATION AND APPLICATION

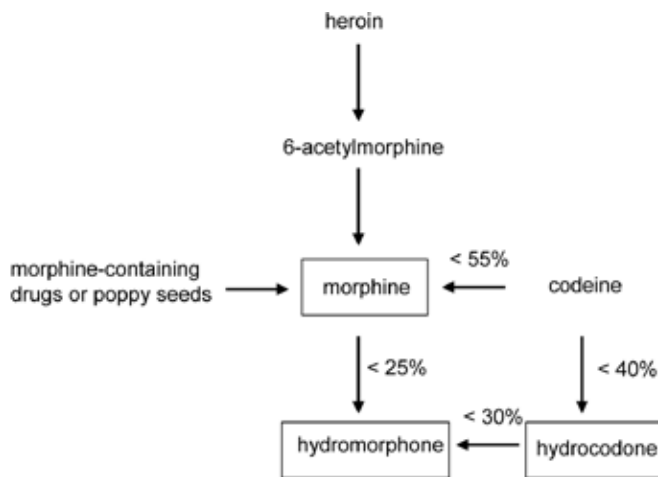
Issue of metabolism and presence of non-prescribed drugs:

- Most drugs are metabolized. Often, such as with cocaine and tetrahydrocannabinol (marijuana use), the metabolite is the only evidence of drug use that is detected by the laboratory. To appropriately interpret a drug testing result, it is important to be familiar with some major and minor metabolic routes, particularly those of the opiate and benzodiazepine classes.

Opiates

- The ARUP opiate confirmation method includes six opiates: morphine, hydrocodone, hydromorphone, codeine, oxycodone, and 6-acetylmorphine. The glucuronide conjugates are not hydrolyzed in the method. Therefore, those that form the glucuronide (all but hydrocodone) are reported as ‘free’ morphine, etc. This allows the inclusion of 6-acetylmorphine in the same procedure as the five prescription opiates. It is important to distinguish opiate drug abuse from legitimate use of opiate drugs.
- Many of the opiate and related medications available by prescription are extensively metabolized. For example, morphine comes from both heroin and codeine, hydrocodone comes from codeine, and hydromorphone comes from both hydrocodone and morphine – see diagram of common metabolic pathways for opiates, below. Differentiating between production from metabolism and direct use of an additional drug is sometimes difficult, and may lead to a conclusion of abuse that is not justified. If the patient has a prescription for the multiple opiates identified, abuse has not occurred. If the patient does not have a prescription for the drugs identified, other explanations, such as metabolism, should be considered. In some cases, a reliable decision about abuse can be made, but in others, it cannot be conclusively decided. In such a situation, the benefit of the doubt must go to the patient. In any case, we recommend ordering the complete opiate panel whenever patient compliance with drugs containing morphine, hydrocodone, hydromorphone, codeine, or oxycodone is questioned. The percentages in the following diagram and in statements added to the report represent estimates of the concentration of the possible metabolite divided by the concentration of the parent opiate, expressed as a percentage. The percentages were determined from a review of positive opiate results from approximately 2,000 positive urine opiate tests in the ARUP database.

Common metabolic pathways for opiates



NOTES: Those drugs appearing in boxes could be a parent drug or a metabolite of another drug. Percentages shown reflect proportion of free drug metabolized in urine based on an ARUP database study, 2006.

- Major pathways for opiate metabolism.
 - Morphine from codeine
 - > When the free morphine concentration, as a percent of free codeine in a urine specimen, is less than 55 percent, the presence of morphine may be the result of metabolism. ARUP adds the following comment to the report:
 - > **Free morphine, as a percent of free codeine in this specimen, is less than 55 percent. Free morphine may have come from metabolism of codeine and not from direct use of morphine. Interpretation of drug abuse due to the presence of morphine in this specimen may not be justified.** (ARUP database study, 2006)
 - > Note: the conversion of codeine to morphine is mediated by cytochrome P450 2D6 (CYP2D6), an enzyme that is known to exhibit genetic variability. Genetic testing for CYP2D6 variants is available separately at ARUP. Call Client Services for details.
 - Hydromorphone from hydrocodone
 - > When the free hydromorphone concentration, as a percent of hydrocodone in a urine specimen, is less than 30 percent, the presence of hydromorphone may be the result of metabolism. ARUP adds the following comment to the report:
 - > **Free hydromorphone, as a percent of hydrocodone in this specimen, is less than 30 percent. Hydromorphone may have come from metabolism of hydrocodone, and not from direct use of hydromorphone. Interpretation of drug abuse due to the presence of hydromorphone in this specimen may not be justified.** (ARUP database study, 2006)
 - Morphine and 6-acetylmorphine from heroin
 - > Detection of 6-acetylmorphine, along with morphine, is definitive evidence for the use of heroin. However, failure to detect 6-acetylmorphine (short half-life) when morphine is present does not rule out use of heroin. Morphine can also be derived from poppy seeds and morphine-containing medications such as MS Contin®.
- Minor pathways for opiate metabolism.
 - Hydrocodone from codeine
 - > Oyler, et al found that hydrocodone may derive from codeine metabolism in some patients. When the hydrocodone concentration, as a percent of free codeine in a urine specimen, is less than 40 percent, the presence of hydrocodone may be the result of metabolism. ARUP adds the following comment to the report:
 - > **Hydrocodone, as a percent of free codeine in this specimen, is less than 40 percent. Hydrocodone may have come from metabolism of codeine and not from direct use of hydrocodone. Interpretation of drug abuse due to the presence of hydrocodone in this specimen may not be justified.** (J. Analy Toxicol. 24:530-535, 2000; ARUP database study, 2006)
 - Hydromorphone from morphine
 - > Cone, et al recently reported evidence of morphine metabolism to hydromorphone as a minor metabolic pathway. When the free hydromorphone concentration, as a percent of free morphine in a urine specimen, is less than 25 percent, the presence of hydromorphone may be the result of metabolism. ARUP adds the following comment to the report:
 - > **Free hydromorphone, as a percent of free morphine in this specimen, is less than 25 percent. Hydromorphone may have come from metabolism of morphine and not from direct use of hydromorphone. Interpretation of drug abuse due to the presence of hydromorphone in this specimen may not be justified.** (J. Analy Toxicol. 30:1-5, 2006; ARUP database study, 2006)
- Oxycodone is not a metabolite of any opiate. If oxycodone is identified and not expected, the patient is taking oxycodone apart from the pain management program.

Amphetamines

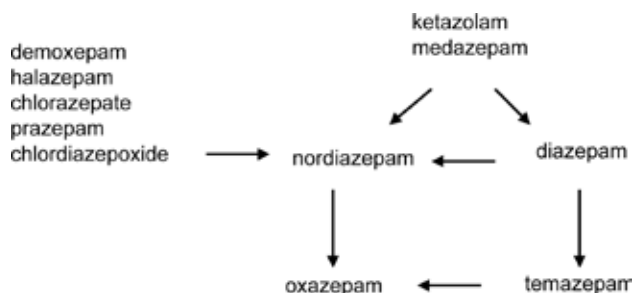
- Amphetamine arises from metabolism of methamphetamine.
- Methylenedioxymphetamine (MDA) arises from methylenedioxymethamphetamine (MDMA, also known as Ecstasy).
- For pain management patients that are prescribed seligilene (Eldepryl®), it is expected that the l-isomer of methamphetamine and amphetamine will be detected in the urine. The ARUP test does not distinguish between the d- (abused form) and the l-form produced by metabolism of seligilene. A note to this effect is added to the report. The d- and l-forms can be differentiated by further testing at the request of the client and at an additional charge.
- Positive results are expected when patients are prescribed methamphetamine-containing drugs such as Desoxyn® and amphetamine-containing drugs such as Adderall®.

Benzodiazepines

- Benzodiazepines are extensively metabolized (see diagram below), often resulting in a pattern that prevents the laboratory from determining which benzodiazepine was taken, since many of them have common metabolites, while the parent drugs are

not detected. For example, demoxepam, halazepam, chlorazepate, prazepam, chlordiazepoxide, and diazepam produce the common metabolite nordiazepam. Use of diazepam (Valium®) may generate positive results in urine for diazepam, nordiazepam, oxazepam, and temazepam. However, some metabolites are unique to a particular benzodiazepine, e.g. alpha-hydroxyalprazolam arises only from alprazolam (Xanax®), hydroxyethylflurazepam and desalkylflurazepam from flurazepam (Dalmane®), and alpha-hydroxytriazolam from triazolam (Halcion®).

Common metabolic pathways for benzodiazepines



Cocaine

- Cocaine is metabolized to benzoylecgonine, m-hydroxybenzoylecgonine, and when donor has been drinking large amounts of alcoholic beverages while using cocaine, cocaethylene is produced *in vivo*. Sometimes the concentration of parent cocaine is so low as to not be detected, while one or more of the remaining three metabolites is detected by ARUP in urine or serum/plasma. All of the metabolites are unique to cocaine use, and do not arise from any other source.

Cannabinoids

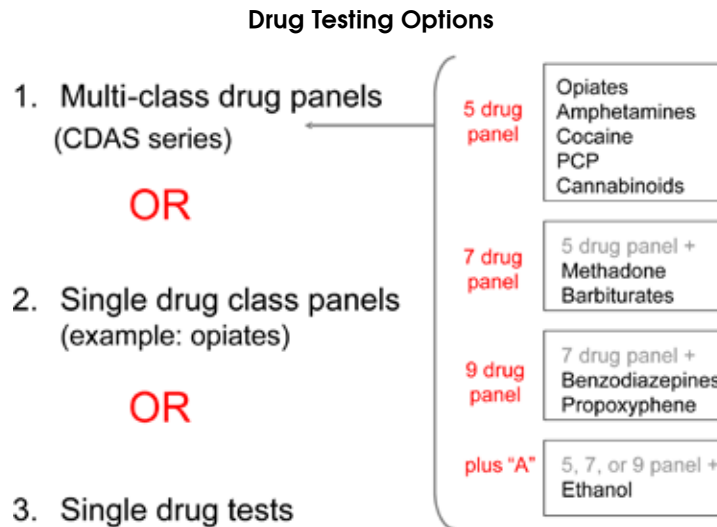
- Tetrahydrocannabinol (THC) from marijuana use is metabolized primarily to 11-nor- Δ^9 -tetrahydrocannabinol (9-THCA). Parent THC is generally not detected in urine. ARUP identifies and quantitates 9-THCA in urine and serum/plasma. This metabolite is specific to marijuana use, and does not derive from any other source. The prescription drug dronabinol (Marinol®) contains parent THC, which is metabolized to 9-THCA. This testing cannot distinguish between use of Marinol and marijuana.

Additional scenarios for drug testing results and possible explanations:

- Drug prescribed but not detected (diversion or non-compliance with dosing regimen).
 - Dilute urine (see discussion on cutoff concentrations above).
 - NOTE: Overhydration, via consuming large amounts of water prior to submitting a urine specimen for drug testing, is the most common strategy for "beating the drug test." Dilute urine can be detected through measurement of creatinine concentration and/or specific gravity.
 - Non-compliance: patient not taking drug at all, or less frequently than prescribed (concentration below LOD).
 - Poor drug absorption. Variable bioavailability is noted with oral or transmucosal administration of methadone, fentanyl, codeine, hydromorphone, and morphine. Patients with malabsorptive conditions such as celiac disease may not absorb drugs well due to reduced intestinal surface area available for absorption. Transdermal absorption will vary based on the condition of the skin onto which drug is applied.
 - Accelerated metabolism due to drug-drug interactions or genetic variation in drug metabolism.
- Drug not prescribed, but detected.
 - Drug metabolism (see discussion above).
 - Incorrect prescription was filled.
 - Patient has not disclosed prescription(s) from other health-care providers.
 - Patient is voluntarily taking a drug that was not prescribed by pain management program.
- Drug prescribed detected, but concentration appears inappropriate.
 - Dilute or concentrated specimen (detected in urine by specific gravity and/or creatinine).
 - Dosing less or more frequent than prescribed.
 - Time lapse between last dose and last voiding (urine) or phlebotomy (serum/plasma).
 - Clinical status, particularly changes in metabolism or elimination such as renal insufficiency or hepatic impairment.
 - Genetic variability in drug metabolism.

Test options

- There are many testing options available through ARUP. The most comprehensive testing option is a multi-drug panel that spans several drug classes and includes creatinine concentration (in urine). These tests include both an initial test (screen) and a confirmatory test for any drug that is identified in the screen. Specific drug classes or specific drugs may also be ordered separately. See the schematic below for a summary, and the lists of tests that follow for test codes that can be used to order testing or get more information about testing.



D. ARUP ORDERABLE DRUGS OF ABUSE TESTS FOR PAIN MANAGEMENT PURPOSES

Multi-Class Drug Panels in Urine and Serum/Plasma

- 0092182 Drugs of Abuse 5 Panel, Urine - Screen with Reflex to Confirmation/Quantitation
Marijuana, cocaine, opiates, phencyclidine, amphetamines
- 0092183 Drugs of Abuse 5A Panel, Urine - Screen with Reflex to Confirmation/Quantitation
Same as 5 panel above, plus alcohol
- 0092184 Drugs of Abuse 7 Panel, Urine - Screen with Reflex to Confirmation/Quantitation
Same as 5 panel above, plus barbiturates and benzodiazepines
- 0092185 Drugs of Abuse 7A Panel, Urine - Screen with Reflex to Confirmation/Quantitation
Same as 7 panel, plus alcohol
- 0092186 Drugs of Abuse 9 Panel, Urine - Screen with Reflex to Confirmation/Quantitation
Same as 7 panel, plus methadone and propoxyphene
- 0092187 Drugs of Abuse 9A Panel, Urine - Screen with Reflex to Confirmation/Quantitation
Same as 7 panel above, plus alcohol
- 0092420 Drugs of Abuse 9 Panel, Serum or Plasma – Screen with Reflex to Confirmation/Quantitation
Same as 9 panel, urine

Single Drug Class Panels by Mass Spectrometric Confirmation/Quantitation without Screen

- 0090369 Cannabinoids – Urine
- 0090676 Cannabinoids – Serum/Plasma
- 0090359 Cocaine Metabolite (Benzoylecgonine) – Urine
- 0090684 Cocaine & Metabolites – Serum/Plasma
- 0090364 Opiates – Urine
- 0092354 Opiates – Serum/Plasma
- 0090366 Phencyclidine – Urine
- 0091571 Phencyclidine – Serum/Plasma
- 0090439 Amphetamines – Urine
- 0091372 Amphetamines – Serum/Plasma

- 0090357 Barbiturates – Urine
- 0090358 Benzodiazepines – Urine

Additional Drugs of Interest in Pain Management

- 0090362 Methadone & Metabolite – Urine
- 0090699 Methadone & Metabolite – Serum/Plasma
- 0090368 Propoxyphene & Metabolite – Urine
- 0091363 Propoxyphene & Metabolite – Serum/Plasma
- 0092570 Fentanyl & Metabolite – Urine
- 0092569 Fentanyl & Metabolite – Serum/Plasma
- Buprenorphine (by referral)
- Oxymorphone (by referral)
- Tramadol (by referral)

Call ARUP Client Services (800-522-2787) or see the ARUP Laboratory Test Directory (www.aruplab.com) for ordering information related to single therapeutic drugs and drugs of abuse not listed here.

Contact the medical director of Clinical Drug Abuse Testing at ARUP to further discuss testing options and with questions regarding test results.

Table. ARUP drug detection-urine: drugs covered, screen and confirmation cutoffs, and detection time.

Drug or Drug Class	Screen Cutoff Immunoassay ng/mL	Analyte Confirmed GC-MS or LC-MS/MS	Conf Cutoff Mass Spec ng/mL	Detection time in days (unless otherwise noted)
Amphetamines	300	Amphet, methamp, MDMA, MDA	200	1-3 1-3
Barbiturates	200	Amobarbital Butalbital Pentobarbital Phenobarbital Secobarbital	50	Intermediate acting 2-4 Short/inter acting 1-4 Short acting 1-3 Long acting 7-21 Short acting 1-3
Benzodiazepines	200	Nordiazepam Oxazepam Temazepam Diazepam Lorazepam Alprazolam Hydroxyalprazolam Hydroxytriazolam Hydroxyethylflurazepam Desalkylflurazepam Midazolam	20	3-10 3-10 1-4 2-6 1-5 1-3 3-6
Cocaine	150	Benzoylcegonine (BE)	50	2-5
Ethyl Alcohol	40 mg/dL	Ethanol	40 mg/dL	0.5-1
Heroin		Morphine, 6-acetylmorphine	25	6-18 hr
Methadone	150	Methadone, EDDP	25	2-3
Opiates	300	Codeine (free) Morphine (free) 6-AM (heroin metab, free) Hydrocodone Hydromorphone (free) Oxycodone (free) (Oxycontin – SR)	5 2	1-3 1-3 1-3 1-3 2-4 1-3 2-4
PCP	25	Phencyclidine	10	3-8
Propoxyphene	300	Propoxyphene Norpropoxyphene	25	0.25-2
THC metabolite (marijuana)	20	9- THCA	4	2-21



*An enterprise of the University of Utah
and its Department of Pathology*

ARUP LABORATORIES
500 Chipeta Way
Salt Lake City, UT 84108-1221
Phone: (800) 522-2787
Fax: (801) 584-5209
www.aruplab.com

Reorder Number 1718.07
©Copyright 2007.