EXECUTIVE SUMMARY

Tufts Health Care Institute Program on Opioid Risk Management

Meeting on

THE ROLE OF URINE DRUG MONITORING AND OTHER BIOFLUID ASSAYS IN PAIN MANAGEMENT

June 2008

Pain is the most common presentation in a doctor's office and opioids are highly effective for alleviating persistent pain. Physicians face the complexities of treating chronic pain in face of co-morbid abuse and addiction. Practices treating chronic pain patients must confront the potential for prescription opioid abuse (POA): patient self-report and behavioral evaluations are unreliable indicators of POA, and urine drug monitoring (UDM) to screen for the presence of prescribed medication (reflecting treatment compliance) and of illicit or licit non-prescribed drugs, has grown as a component of pain management in primary and specialty settings. Yet, despite the potentially serious outcomes of UDM for patients (dismissal or major changes of the treatment program, negative outcomes for family/ workplace relationships), physicians are often uneducated about UDM. *This meeting was targeted at understanding the technical aspects of UDM and the challenges of interpreting screening results within the therapeutic context, reviewing the literature on UDM, developing preliminary guidelines for such monitoring in pain management, and discussing related payer issues.*

History: UDM was introduced in 1964 to monitor recovering heroin addicts in methadone treatment programs; its use was expanded in the 1970's, to contain pervasive use of heroin by members of the US armed forces in Vietnam. By the mid 1980's, the Reagan administration mandated that every federal agency be made drug free, and private companies also started to link drug use to absenteeism, loss of efficiency, personnel turnover, poor product quality, and injuries resulting from accidents; IBM initiated workplace testing, and many companies followed suit. Use of UDM in the clinical context was initiated in the 1990's, in the wake of widespread use of prescription opioids for the treatment of chronic pain and in response to the ensuing dramatic rise in POA.

Analytical Methods used in UDM: Early testing employed thin layer chromatography, spectrofluorimetry, or gas chromatography, but these techniques were unsuitable for large-scale applications. Legal challenges to results of UDM and a scathing report by the Defense Department's Einsel Commission (1983-1984) led to the establishment of a highly efficient military model that incorporated specific guidelines for sample collection and chain-of-custody, standardization of test procedures, requirements for strict quality control, and review of results by certified scientists.

Biological samples: Testing that reflects the unbound fraction of the drug in blood is most directly correlated with euphorigenic/pharmacological/toxic effects of the drug. *Blood* testing is most accurate, but is invasive. Most drugs are rapidly cleared from the blood, though some assays detect metabolites that have half-lives longer than the parent drug. *Urine* is the biological sample of choice for UDM: collection is non-invasive, and large volumes are readily obtained. Tests for cocaine, amphetamines, opiates, methadone, marijuana, and benzodiazepines in urine are now relatively inexpensive, and false positives are rare. For most drugs, detection time in urine averages 1-5 days, even when used in low doses. Some lipophilic drugs, such as cannabinoids, cannot be directly detected in urine (which is aqueous), but aqueous metabolites can be detected in urine, with lag times of 6-8 hours. Sample-tampering (substitution, dilution, etc.) must be considered when using urine. Collection of *saliva (oral fluid)* is non-invasive, and samples are less vulnerable to tampering; drug concentrations in saliva accurately reflect blood levels. However, on-site kits for benzodiazepines/marijuana in saliva are not reliable. *Hair* samples are appropriate when testing for chronic use; drugs typically appear in hair 6-8 days

after use; however, hair testing is costly/time-consuming, samples are susceptible to contamination and relationships between dosage, ingestion time and drug levels are not reliable.

Test methods and interpreting results. *Immunoassays* are relatively inexpensive, and least labor-intensive, and are used for initial screening tests, and to distinguish negative from presumptive positive samples. *Gas chromatography/mass spectroscopy (single stage or tandem)* are used for confirmatory testing and identification of specific drugs/metabolites, and are highly specific and reliable; but they are expensive and labor-intensive. Some expertise is required to draw clinical inferences from test results, especially for certain classes of drugs (e.g., metabolic conversion of codeine into morphine may be interpreted as self-administering of a non-prescribed opiate in a patient on high doses of codeine). Antibodies used for immunoassays may not be specific (e.g., some antibodies against amphetamines also cross-react with some over-the-counter drugs such as ephedrine/pseudoephedrine). Considerable individual genetic variation exists in the body's ability to metabolize specific drugs (e.g., 10% of the population cannot metabolize codeine into morphine, and inter-individual rates of methadone metabolism differ up to 50-fold). Sample concentrations of specific drugs may also be affected by interactions with concurrent medication, the rate at which the patient's body distributes the drug, specific enzyme deficiencies in individual patients, or inhibition/induction of cytochrome 450 system. Illicit drug users may be skilled in how to beat test results. Commonly used strategies are: 1) not showing up or not cooperating; 2) substituting clean or artificial urine samples for their own, or *in vivo* hydration to effectively lower drug concentration in urine to below cut-off values; 3) interfering with detection by adulterating the sample with a chemical that oxidizes the drug or its metabolite. These strategies can be combated by direct observation of specimen collection, use of lower detection thresholds, using adulteration dip sticks, testing of oral fluid samples, and other approaches.

UDM in a clinical pain practice: UDM should be used as a consensual diagnostic test, targeted at documenting compliance with a treatment plan, and as part of a "universal precautions" approach for assessing and treating chronic pain patients; to preserve trust and mutual respect between doctor and patient, forensic testing has no place in a clinical practice. Physicians should use results of compliance testing to communicate more openly and effectively with patients, to discover and address drug problems that the patient may not disclose spontaneously, and to build a relationship based on mutual trust. Inappropriate negative results can be used to discover whether patients are diverting their medication (a crime), or overusing it to treat unresolved pain and then running out of their pills (potentially pseudoaddiction). Testing in a pain practice should be done across the board for all new patients that are being considered for treatment with a controlled substance. UDM practices vary, with some practitioners advocating testing of all patients at all visits (akin to addiction treatment), and others advocating 2-3 "random" tests through the year. Importantly, the presence of an illicit or non-prescribed licit drug in a patient's urine may indicate inappropriate use of those drugs, but the patient may be perfectly compliant with their analgesic therapy (albeit at high risk for non-compliance). The management of such patients is not well defined, but begins with an open, non-judgmental dialog, and tailoring of treatment boundaries as needed to help patients comply with the requirements of therapy. An inappropriately negative finding for opiates that are prescribed for frequent ongoing use may mean either that the patient has overused the medication (possibly indicating an unresolved pain problem), or that the patient is diverting medication: the first is a

medical issue, while the second is a criminal one. One must always explore the motive behind the behavior when results are not as expected. This is the "Art of Medicine".

Outcome studies, clinical research gaps: Decisions about administering UDM in the therapeutic setting are motivated by a variety of factors, including the need to monitor compliance, or identify and mitigate abuse/diversion by patients, but are based on few systematic outcome studies. Charts for chronic pain patients from 12 US family practices indicate that 8% of primary care physicians ordered urine tests; responses to a written questionnaire reveal that 7% of family practitioners and internal medicine physicians ordered tests for new pain patients and 15% for established ones. UDM can be effective as a tool in identifying opioid misuse beyond self-report or behavioral monitoring: 6% of patients in a pain management center were inappropriately positive for an opioid relative to patient self-report; in a separate study, 7.5% were inappropriately negative for prescribed opioids. And 21% of patients receiving opioids, showing no drug-related behaviors, had inappropriate positive screens for illicit drugs or non-prescribed medication. The scarcity of such studies points to an urgent need for investigations in three key areas: *understanding current UDM practices in management of non-cancer chronic pain, investigating clinical outcomes of UDM, and evaluating strategies for implementing UDM in chronic pain management*.

Payer issues: Random drug testing in schools, the military, or the workplace is paid for by the department of education/local schools, military, or workplace, respectively. However, payment policies of third party payers for UDM in medical practice vary according to a number of factors, including if physicians are addiction-certified, or if they work at a pain clinic, substance abuse treatment center, a hospital-based clinic, or a hospital emergency room. Policies on the need for prior authorization vary. Reimbursement for Medicaid patients also varies by the sate, whereas payment under Medicare remains a challenge. Clearly, incorporating UDM in clinical practice, which can be considered an emerging standard of care in the safe prescribing of opioids, will not be accomplished without reimbursement.