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ALTERNATIVE TREATMENTS FOR PAIN MEDICINE (M JONES, SECTION EDITOR)

Review of the Current State of Urine Drug Testing in Chronic Pain: Still Effective as a Clinical Tool and Curbing Abuse, or an Arcane Test?

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Abstract

Purpose of Review Therapeutic use, misuse, abuse, and diversion of controlled substances in managing chronic non-cancer pain remain a major concern for physicians, the government, payers, and patients. The challenge remains finding effective diagnostic tools that can be clinically validated to eliminate or substantially reduce the abuse of controlled prescription drugs, while still assuring the proper treatment of those patients in pain. Urine drug testing still remains an important means of adherence monitoring, but questions arise as to its relevance and effectiveness. This review examines the role of UDT, determines its utility in current clinical practice, and investigates its relevance in current chronic pain management.

Recent Findings A review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. Literature was searched from year 2000 to present examining the relevance and role of UDT in monitoring chronic opioid therapy along with reliability and accuracy, appropriate use, overuse, misuse, and abuse. There are only a limited number of reviews and investigations on UDT, despite the fact that clinicians who prescribe controlled medications for chronic states commonly are expected to utilize UDT. Therefore, despite highly prevalent use, there is a limited publication base from which to draw in this present study.

Summary Regardless of experience or training background, physicians and healthcare providers can much more adequately assess opioid therapy with the aid of UDT, which often requires confirmatory testing by a laboratory for clinical and therapeutic prescribing decisions. It has become a strongly recommended aspect of pain care with controlled substances locally, regionally, and nationally. Incorporating UDT for all patients in whom chronic opioid therapy is undertaken is consistent with state and national guidelines and best practice strategies. Practice standards vary as to the frequency of UDT locally, regionally, and nationally, however.

Keywords Controlled substances · Opioids · Benzodiazepines · Illicit drugs · Abuse · Diversion · Substance use disorder · Prescription drug monitoring programs · Adherence monitoring · Compliance monitoring · Urine drug testing · Immunoassay · Chromatography · False positives · False negatives

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Introduction

The prescribing of opioid medication for chronic pain patients poses significant risks and challenges. These risks include but are not limited to unintentional opioid overdose, diversion of prescription medication to family members or others, and/or potential drug interactions with concurrent medications or abused substances. In 2010, approximately 5.1 million people used prescription pain medications for non-medical purposes [1•]. Based on data from the National Institute on Drug Abuse, it is estimated that 1 in 20 twelfth grade high school students abused controlled release oxycodone and 1 in 12 abused hydrocodone in the last 12 months [2]. Greater than 54% of those who abuse prescription pain relievers for non-medical reasons received their medications from family or friends, suggesting that a significant amount of drug diversion occurs.

Additionally, in 2008, the number of unintentional overdose deaths involving opioid medications was nearly double the number from cocaine and heroin combined [1•]. Recent evidence suggests that overdose deaths are not only related to supra-therapeutic levels of one medication, but rather are commonly related to polypharmacy including non-controlled substances [2, 3]. Common substances implicated in overdose deaths include benzodiazepines, muscle relaxants, and over the counter drugs such as antihistamines, alcohol, cocaine, and antidepressants which can have additive and/or synergistic respiratory depressant effects [2]. This suggests that patients who present for chronic pain management may consume other substances which could fatally interact with opioid pain medications.

Consequently, validated testing instruments that provide an effective and rational method of selecting patients for opioid therapy, predicting risk, and identifying aberrant behaviors once they arise substantially benefit practitioners in clinical practice. Such testing potentially curbs the risk of iatrogenic (e.g., doctor induced) addiction as well as opioid-related deaths. There is no single test which can reliably and accurately predict those patients not suitable for opioid therapy or identify those who need increased vigilance or monitoring during therapy. Instead, physicians must avail themselves of a number of tests available to help them identify which patients are at risk, or have already succumbed to opioid addiction or misuse. Nationally, screening for potential opioid abuse includes assessment of psychiatric illness, premorbid and comorbid substance abuse, assessment of aberrant drug-related behaviors, risk factor stratification, and utilization of opioid assessment screening tools.

One important and necessary tool in the physician's arsenal is urine drug testing (UDT), which is often an office-based procedure that attempts to improve the safety of patients who are prescribed opioid therapy [4]. UDT allows the clinician to monitor medication compliance and detect illicit substance use or unprescribed controlled substance use, all of which could avoid unintentional overdose and negative patient safety outcomes. A negative UDT for the patient's prescribed opioid could suggest possible diversion of medication to family/friends, or possible illicit sale of the medication [5]. Results of UDT could warrant discontinuation of further prescribing of opioid medication. Similarly, a positive UDT for illicit substances including cocaine, or another-prescribed opioid medication, could also warrant cessation of opioid prescribing related to the high risk of potential morbidity and/or mortality. Under these circumstances, the patient may need an evaluation by a substance abuse mental health practitioner, or benefit from substance abuse treatment. Because false-positive and false-negative results can occur, quantitative UDT becomes an essential component to successfully interpreting qualitative results in certain circumstances.

UDT is associated with multiple limitations secondary to potential pitfalls related to drug metabolism, reliability of the tests, and the knowledge of the pain physician. This comprehensive review provides an updated role of UDT for monitoring chronic opioid therapy along with reliability and accuracy, appropriate use, overuse, misuse, and abuse.

This review also addresses an important component of the physician perspective. Physicians face challenging daily ethical decisions pertaining to opioid management for controlling pain in their patients. There may not be physical examination, radiological, or other diagnostic testing evidence consistent with the degree of pain reported, and at present, there are no precisely accepted and reproducible measures of pain. Therefore, pain is largely subjective and often clinically linked with anxiety, mood disturbances, and abnormal sleep states. Furthermore, there is mounting regulatory and media scrutiny related to opioid prescribing for chronic non-cancer pain, in concert with data indicating a large number of opioid-related overdose deaths [6]. Physicians have become increasingly aware of and educated about opioid abuse. For example, they have developed a greater familiarity with community-based patterns of misuse, including the prevalence of illegal drugs and abusive practices for prescribed opioids. Nefarious reasons for obtaining an opioid prescription can occur in clinics and include diversion, addiction, and other complex behavioral patterns which are hard to measure in the abbreviated timeframe of a physician-patient clinic visit.

Unfortunately, physicians have increasingly been blamed (and even prosecuted) for the rise in opioid drug abuse under the controversial "willful blindness" theory, which seemingly criminalizes doctors for trusting their patients' statements regarding drug use (or lack thereof) when making prescribing decisions. Those critical of the willful blindness theory argue that the physician's professional and moral obligations in forging a therapeutic alliance with a patient necessitate establishing trust, which can be destroyed when a physician appears to doubt his or her patient. Establishing a therapeutic alliance between opioid-prescribing physicians and their

patients warrants trust in the patient, but also verification by the physician. Verification has become a legal and ethical responsibility that has led to the emergence of urine drug testing as an integral part of physicians' prescribing practices. Agencies, policy makers, and prescribers of opioids regardless of specialty and years of service have concluded that urine drug testing is considered the best practice strategy, particularly due to the risk of opioid misuse, abuse, or addiction in the chronic pain population [7–9].

Urine drug tests are used not only to screen for the concomitant use of illicit drugs of abuse but also to monitor adherence to the prescribed medication regimen. Many practitioners are frequently faced with aberrant results of urine drug testing, triggering an in-depth discussion with the patient about the implications of continuing further care. Another important use of urine drug testing includes therapeutic monitoring. Just as a physician might follow hemoglobin A1C, or measure peak and trough antibiotic levels, quantitative (definitive) urine toxicology can provide clues to appropriate opioid choices, evidence of drug-drug interactions, and documentation of absorption and metabolism [10]. And it is in this context that prescribing physicians have established practice-based protocols reflecting the communities in which they provide care, such as custom profiles. These protocols may allow physicians to protect their patients from the abuses that may evolve from opioid regimens. Tools like custom profiles allow physicians to establish consistent ordering practices to advance and maintain a standard of care for patients, while still allowing physicians to make individual determinations of medical necessity for each test ordered—either by noting a standard array of tests that should be ordered or identifying reasons to deviate from the custom profile. Although custom profiles and similar administrative tools help establish a standard of care for a practice, they do not substitute for physicians' discretion and determination about which tests should be ordered for each individual patient.

Presumptive and Definitive Testing

Qualitative or presumptive urine drug testing is used to detect the presence or absence of drug classes or some specific drugs. Results may be positive, negative, or numeric, and methods of testing specimens may include TLC (thin-layer chromatography) or immunoassay [11]. Qualitative testing is used to verify compliance with treatment, identify potential illicit drug use or abuse, or evaluate aberrant behavior. Its value is greatest in detecting illicit substances, and also prescribed or unprescribed drugs, and over the counter medications. It is usually used as a screening or initial test for assessing compliance with chronic opioid therapy because it often lacks the capability to detect specific medications within a drug class. As a screening test, the initial qualitative immunoassay is less sensitive and specific and, therefore, must be interpreted in the context of confounding variables such as the substance being screened, testing method, and patient characteristics. If aberrant or indeterminate results are obtained from qualitative testing, then quantitative or definitive urine drug screening is ordered to clarify results/opioid use behavior. Moreover, presumptive UDT can cause false-positive or false-negative results which definitive testing can help to resolve [10]. Many office-based physicians use point of care (POC) immunoassay screening (presumptive) with a cup or dipstick because this technology offers immediate results whereas laboratory-based screening tests may require a day or two to report results. Positive results can be tested further by definitive testing in order to identify the specific drug present rather than a class of drug, help determine adherence to drug therapy, and identify abuse or diversion. Negative results are often used to exclude the use of illicit substances, or use of controlled substances (opioids, benzodiazepine, amphetamine) which are non-prescribed or not revealed to the physician at the time of testing.

Quantitative or definitive testing identifies specific medications within a class, illicit drugs, or metabolites which are present or absent as measured in nanograms per milliliter and incorporates gas chromatography-mass spectrometry (GC-MS) or liquid chromatography mass spectrometry (LC-MS/MS) assays [12]. Because presumptive testing (immunoassay) typically detects a medication class, a positive result does not provide information about which specific drug in the class has been detected. Therefore, definitive testing (quantitative) is important in identifying specific drugs in the urine which the practitioner can use to assess therapeutic compliance with a drug regimen, as well as diversion or abuse of other drugs within a class [13]. Furthermore, definitive testing provides much greater sensitivity and specificity compared to presumptive testing. Some experts feel that all presumptive urine samples (immunoassay tests) that are negative for prescribed, controlled substances (opioids, benzodiazepines); positive for non-prescribed controlled substances; and/or positive for illicit drugs should undergo definitive testing [14, 15]. This is a reasonable approach given that many opioids prescribed therapeutically cannot be detected with presumptive testing (qualitative) alone. Definitive testing is also capable of identifying variations in drug metabolism, and drug metabolism through minor pathways (e.g., codeine to hydrocodone). Clinicians are not able to determine drug dose or frequency by examining a drug or metabolite in a urine sample even with definitive testing.

Specimen Validity Testing

Another tool to assist in safe opioid prescribing includes specimen validity testing (SVT). SVT is used to ensure that the

provided urine sample has not been diluted, substituted, or adulterated. The measures used for SVT include pH, temperature, creatinine, and specific gravity, and [16] a test that measures the presence of oxidizing agents, which can adulterate the urine. According to the Substance Abuse and Mental Health Services Administration, a sample with a pH that is < 4 or > 11 is considered adulterated. Creatinine is excreted into the urine at a relatively constant rate, and is typically present in concentrations between 20 and 400 mg/dL [17]. Specific gravity (SG) measures the density of liquid compared to the density of water; SG values typically range from 1.0020 to 1.0200 in urine. SG, like creatinine, is a measure of urine concentration that determines the number of dissolved substances in solution. A sample with a creatinine between 2.0 and 20 mg/dL and an SG between 1.0010 and 1.0030 is considered dilute. Creatinine < 2.0 mg/dL and SG ≤ 1.0010 or ≥ 1.0200 are classified as substituted. In addition, a urine sample is classified as invalid when the creatinine and SG results are discrepant or when the pH is significantly outside of the typically expected range. Since there is no evidence that performing SVT on all samples is superior to targeted testing [13], practitioners could consider analyzing a patient's initial urine specimen, and then adding SVT randomly once a year. This will assist with accurate interpretation of results by maximizing the identification of a valid specimen. There are limitations of POC SVT, so clinicians should interpret results cautiously if they do not send the specimen for definitive testing.

Prescription Drug Monitoring Programs

Another initiative to improve the safety of opioid prescribing includes implementation of prescription drug monitoring programs (PDMPs) at the state level to track prescriptions of controlled substances [18••]. PDMPs are state-run databases that track prescribing and dispensing of controlled substances. These databases intend to reduce over-prescribing of pain medications by doctors in addition to identifying individuals at high risk for opioid use disorder, such as individuals with opioid prescriptions from multiple providers. The types of drugs that are tracked by the PDMPs vary by state [18••]. Typically, they include schedule II and III substances, which are those with a high abuse potential. The PDMPs are accessible to physicians, other health care providers, pharmacists, and law enforcement.

Recent research has shown that PDMPs are effective in reducing the number of prescriptions written for opioids [19]. Data have also shown that opioid-related mortality is lower in states with a PDMP than in states without a PDMP [20]. PDMP should ideally be reviewed at each office visit when opioids or other controlled substances are prescribed to ensure that patients have not obtained their prescriptions from another provider. PDMP can be an effective tool to minimize opioid abuse and diversion especially when combined with urine drug testing.

Opioid Prescribing in Chronic Non-cancer Pain

Opioids have been used for decades to treat pain and continue to be one of the most commonly prescribed medications for chronic pain. Although opioids have been controlled in the USA with regulations and restrictions, opioid utilization has been rising at an unprecedented pace. In an evaluation of opioid usage over a period of 10 years, Manchikanti et al. [21] showed an overall increase of 149% in retail sales of opioids from 1997 to 2007 in the USA, with an increase of 1293% for methadone, 866% for oxycodone, and 525% for fentanyl. Most concerning, the death rates from prescription opioid overdose nearly quadrupled from 1.5 to 5.9 deaths per 100,000 people from 2000 to 2014.

Although opioids can be a helpful method of treating chronic pain for selected patients, the mood-altering action of opioids, in addition to the physical dependence and rewarding properties of this class of drugs, can result in abuse (non-medical use) [22]. Opioid abuse and misuse occur for a variety of reasons, including self-medication for non-medical purposes, use for reward, compulsive use because of addiction, and diversion for profit. Individuals with chronic pain and co-occurring substance use disorders and/or mental health disorders such as depression and anxiety are at higher risk for misuse of prescribed opioids [23, 24]. Thus, the marked increase in opioid prescriptions has occurred simultaneously with a marked increase in the abuse of prescribed opioids and in accidental opioid overdoses.

A cultural shift in the prescribing habits of physicians over the last 20 years liberalized the use of opioids and has contributed to opioid over utilization [25]. Spurred by evidence of undertreatment of pain and aggressive marketing techniques by certain drug manufacturers, an exponential increase in the number of patients who were treated with opioids has occurred. The problem is further compounded by a lack of physician and healthcare provider training on key issues such as recognizing drug diversion, addiction, and signs of abuse; recent estimates suggest that only 20% of US physicians have received such training and these figures were much lower 5 to 7 years ago.

The association between a rising number of opioid prescriptions and increasing opioid-related morbidity and mortality has important public health implications [26–29]. In the last decade, federal and local lawmakers have implemented multiple policies and procedures to curb the rise of opioid prescribing and opioid-related morbidity [26, 30–36]. Specific policies include expanding the prescription drug

monitoring program (PDMP), strengthening Drug Enforcement Agency (DEA) efforts to apprehend inappropriate prescribers (i.e., "pill mills"), raising public awareness of the dangers of opioids, and improving abuse-deterrent technology [26, 30–36].

Preliminary studies indicate that these efforts may be helping to curb the rise of opioid prescribing [18••]. Incorporating data from the National Survey of Drug Use and Health, Ali et al. [18••] showed that the rate of opioids prescribed stabilized between 2010 and 2012. Certain medical specialties showed declines in the number of opioid prescriptions written during this period as well.

From 2012 to 2016, state and local authorities that aggressively combated opioid prescribing saw a decrease in the availability of opioids along with a slight decline in the associated overdose deaths [28–30]. Data from the Centers for Disease Control and Prevention reveal a decline of prescription opioid-related overdose deaths (excluding non-methadone synthetics) from 17,552 in 2011 to 16,652 and 16,443 in 2012 and 2013, respectively [6]. However, the 2015 report showed a significant increase to 17,536 deaths [6]. The number of opioid prescriptions and their non-medical use in the USA continue to pose significant concern to the well-being of chronic pain patients [37]. Nevertheless, opioid therapy for chronic pain remains a consideration when alternative therapies insufficiently control pain, and quality of life is impaired [7, 38].

Urine Drug Testing in Chronic Pain

Screening for opioid misuse in the outpatient setting provides an opportunity for early identification of a behavior outside the confines of the mutually agreed on plan of treatment (aberrant behavior) [24, 39]. This behavior may lead either directly or indirectly to morbidity and/or mortality. By identifying individuals who are high risk for behaviors such as drug diversion, drug abuse, polypharmacy, and consumption of illicit substances, the pain physician can take steps to reduce the risk of harm to these patients or society by implementing UDT. Urine drug testing is considered the gold standard in drug abuse testing given its good specificity, sensitivity, ease of administration, and cost. This is correlated to definitive testing (gas chromatography/mass spectrometry (GC/MS) technology). However, opponents of presumptive UDT testing with immunoassays debate its clinical value partly related to high false-positive readings from potentially non-illicit substances, given that UDT was adapted from forensic/occupational deterrent-based testing, and may not be optimal in the outpatient chronic pain setting [40]. However, the CDC in their recent guideline recommends UDT at the onset of opioid therapy and then at least yearly [9]. Furthermore, previous recommendations from experts in pain and addiction have outlined UDT as a "universal precaution" [8].

Current data suggest that UDT is clinically valuable in the outpatient pain management setting if the trained practitioner is able to account for limits of UDT, including the potential for false-positive or false-negative qualitative (presumptive) screens. UDT allows the physician or provider to evaluate chronic pain patients' compliance with prescribed controlled substance therapy, monitor misuse or diversion of prescribed medications, or detect the use of illicit substances.

Updates in Urine Drug Testing

The role of UDT in the management of chronic pain patients on long-term opioid therapy has been further validated in recent studies. UDT allows the provider to better identify aberrant behavior including diversion or illicit substance use in addition to providing opportunities for intervention. For instance, Knezevic et al. [41••] performed a retrospective analysis of 500 patients on chronic opioid therapy who underwent regular UDT without prior notification. Eight percent of patients tested positive for a non-prescribed opioid, while 1% tested negative for their prescribed opioid and 12% tested positive for illicit substances. Repeated UDTs performed after patient education revealed 64% of these patients had improved compliance [41••]. In a retrospective study of 255,168 urine specimens, Yee et al. [42] also found improved compliance in patients whose frequency of UDT increased. Compliance for those on hydrocodone and oxycodone therapy increased 7 and 8% respectively after instituting more frequent UDT.

Similarly, Morasco et al. [43] studied a retrospective cohort of 83 Veterans Affairs (VA) chronic pain patients who tested positive for illicit or non-prescribed substances. Following positive UDT results, physicians changed treatment course most commonly by increasing frequency of future UDT. Clinicians documented plans to alter opioid prescribing (changing dose, terminating opioid therapy, or requiring more frequent fills) in 52% of cases, but only implemented them in 24% of cases [43]. This suggests that UDT provides important information to physicians regarding aberrant behavior, but physicians must be more adamant about implementing changes to medications based on the results. UDT can be viewed as an adjuvant tool to assist with clinical decision-making.

Algorithmic Approach for Urine Drug Testing

An algorithmic approach for UDT in patients who are prescribed opioids for chronic non-cancer pain, long-term cancer pain, or even chronic pain resulting from cancer treatments for patients in remission can help practitioners develop a

systematic and unbiased method to detect aberrant behavior. The first step is to determine the baseline measure of risk in these patients, and then to monitor for compliance. UDT must be performed utilizing appropriate principles and the results analyzed based on current evidence [44].

Baseline Urine Drug Testing

UDT is useful in establishing and confirming the reliability of patients' reported substance use. Baseline UDT should be implemented when the clinician is considering initiating opioid therapy [9]. This provides the prescriber with important information regarding potential existing illicit drug use, current opioid or benzodiazepine use, or use of other controlled substances before or shortly after implementing therapeutic opioids. UDT should be performed routinely to establish baseline information regardless of how much information is available from medical records, other physicians, prescription drug monitoring programs, and referral sources. Risk stratification tools such as the SOAPP-R [45] and COMM [46] can help guide the frequency of UDT. In fact, one study determined that the SOAPP-R was the most sensitive questionnaire for detecting the likelihood of aberrant behavior when compared to the Diagnosis, Intractability Risk, and Efficacy (DIRE) inventory, and the Opioid Risk Tool (ORT) [47]. This universal approach to baseline testing allows the clinician to avoid the stigma associated with drug testing, and treats UDT similar to other routine tests such as measurement of blood pressure [8]. It is also important to recognize that a large percentage of patients may test positive for opioids or other controlled substances prior to arriving at pain medicine settings, which could be due to legitimate prescriptions from prior providers. At the same time, patient report is often inconsistent with urine screening, PDMP, and the patient's medical record; therefore, clinicians should strongly consider combining UDT and PDMPs for substantially enhanced identification of these inconsistencies [48].

Although critics may argue that baseline presumptive UDT testing should be performed in select cases as opposed to routine testing, this approach may miss a significant portion of seemingly low-risk patients who would have otherwise tested positive for illicit substances. Studies have attempted to identify predictors of the likelihood of UDT in the chronic pain setting and have suggested the following: men, age 20–29, Medicaid as primary payer, African-American race, divorced/separated marital status, and a coexisting psychiatric/substance use diagnosis [49•, 50, 51]. These studies should not necessarily exclude opioid use in these specific populations, however. Although these predictors suggest an increased risk of illicit substance use or poor medication adherence, patients who do not fit these demographics still pose a risk, albeit lower of aberrant urine toxicology. For example, one study demonstrated the identification of illicit substances in older adults. There was a progressive decline in illicit substance detection from 18.3% for 20–29 years to 0.4% for 80–99 years in those who underwent UDT while being prescribed opioid therapy [49•]. Thus, it behooves the clinician to perform baseline UDT regardless of patient age or other demographics given the potential for detecting illicit substances in patients with chronic pain who may be considered for opioid therapy.

Monitoring for Compliance

During the titration or maintenance phase of opioid therapy, UDT can be useful in detecting non-compliance with the prescribed opioid, unauthorized illicit substance use, non-prescribed opioid use, doctor shopping, and/or drug diversion. Multiple investigators have researched the importance of UDT and adherence monitoring and have found supportive evidence that UDT reduces prescription and illicit drug abuse [52]. However, there is a paucity of evidence to guide clinicians in identifying patients with chronic pain who should have UDT and how often. Some recommendations include assessing patients' risks for opioid misuse, addiction, and aberrant drug-related behaviors, and then designing UDT based on the results.

A practical approach to UDT in patients who are potential candidates for opioid therapy includes performing baseline urine testing prior to their first prescription which is consistent with the Centers for Disease control recommendation in their guideline [9]. Then, compliance monitoring via another UDT can occur within 1 to 3 months after baseline testing, but should be based on level of risk as assessed by patient history of drug abuse and psychiatric disorders, family history of drug abuse, and screening questionnaires. Routine, random monitoring should occur approximately every 6–12 months with provisions to modify frequency of UDT or alter the therapy course for unexpected results, contested results by patients, or changes in behavioral patterns. Opioid risk stratification tools such as the SOAPP-R and COMM can help guide the frequency of testing by determining risk of misuse and abuse [45, 47]. If UDT reveals appropriate compliance and no aberrant behavior occurs during an initial test, then further testing would be required only once a year if no unexpected behavioral inconsistencies occur with the prescribed medication, illicit substances, or non-prescribed drugs during the course of opioid therapy. Patients with inconsistent results may require more frequent testing based on the philosophy of the prescribing physician and risk assessment. An example of an algorithmic approach is described in Fig. 1 [53]. Practitioners should be familiar with their states' specific UDT requirements and implement them accordingly.

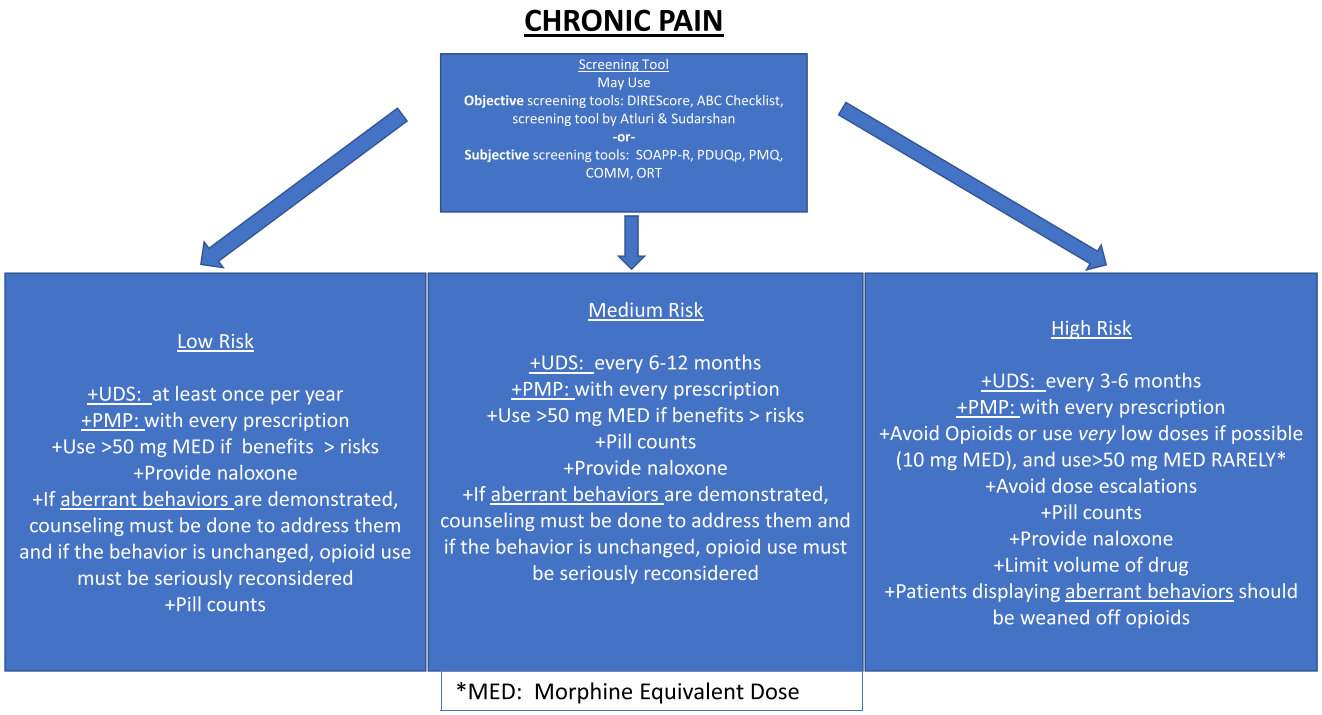

Fig. 1 Risk stratification and adherence monitoring

Interpretation of UDT Results

Appropriate interpretation of UDT results is critical to achieve fair and proper medical care for patients on opioid therapy. UDT can only assist in clinical decision-making and cannot be considered definitive. The ultimate clinical decision with respect to continuing, modifying, or discontinuing opioid therapy derives from a variety of sources such as an understanding of patient circumstances, the clinician-patient relationship, past medical history, data from PMPs, and the results of UDT. A thorough knowledge of UDT interpretation and full patient history are essential to interpretation, however, including an appropriately collected sample as well as identifying any tampering with the specimen. It is critical to understand the pharmacology of the drugs being tested (including their metabolites such as the production of oxymorphone from oxycodone, or the production of morphine from codeine for instance), appreciate the variations in collecting urine randomly, and be aware of the renal status of the patient. It is also important to be aware of inter-patient pharmacokinetic differences in absorption and distribution because similar doses do not lead to similar systemic drug exposures. For instance, there is a 2.5-fold variability in morphine absorption based on whether it is given via the oral, buccal, sublingual, or imtramuscular routes [44, 54]. Because physician knowledge of UDT interpretation is often inadequate, consulting with laboratory medicine or clinical pathology personnel when unexpected findings occur is recommended when clarification is needed [55].

Practitioners should know which agents can interfere with UDT results (presumptive–IA testing), leading to false positives [56–58]. False positives can occur from cross-reactivity with other substances. For example, seroquil can cross-react with methadone leading to a false-positive presumptive IA test result for methadone. Dextromethorphan and chlorpromazine can cross-react with opioids leading to a false-positive presumptive IA test result for opioids [40]. Consequently, definitive testing would be needed to confirm positive results. Interference can occur due to the efforts of patients to avoid the current urine screening/testing system. For example, they can alter their intake of a prescribed or non-prescribed medication in anticipation of upcoming testing. There are several methods of subverting UDT that include urinary dilution (high water intake or diuretic use to lower the concentration of the drug in the urine below the cutoff level for a positive result), urine substitution (freeze-dried "clean" urine that a patient reconstitutes before providing a urine sample), and in vitro adulterants ("urinaid" containing glutaraldehyde which interferes with presumptive IA testing) [59]. Other modalities for defeating UDT exist, but it is helpful to have a general understanding of some of them when confronted with unexpected results, especially if repeated discrepancies occur. Abnormal or unexpected results should be interpreted with caution. In general, five scenarios can occur when interpreting UDT results. Bear in mind that lab error can occur if UDT is negative for a prescribed opioid, UDT is positive for a non-prescribed opioid or benzodiazepine, or UDT is positive for illicit substances.

1. UDT positive for prescribed drugs and negative for any other drugs—illicit or licit (an expected result);
2. UDT negative for prescribed opioid;
3. UDT positive for non-prescribed opioid or benzodiazepines;
4. UDT positive for illicit drugs;
5. UDT specimen tampering(e.g., low urine creatinine or cold urine sample).

Expected UDT Result

UDT positive for prescribed drug and negative for illicit substances indicate an expected UDT result. In this situation, the patient may be tested yearly. Based on ongoing risk assessment yielding suspicious behavior, however, UDT may need to occur periodically with a frequency of three times within the first 15 months and yearly thereafter. If the presumptive test can detect the specific drug of interest and reliably rule out any suspected illicit drugs or non-prescribed controlled substances, then additional definitive testing need not occur.

UDT Negative for Prescribed Opioid

Possible explanations for a negative UDT include drug diversion, hoarding, irregular intake of the opioid (binge use, self-escalation), or false-negative results related to infrequent dosing schedules (undetectable "trough" levels). It is important for a physician to determine the truth regarding false negative versus possible drug diversion since this will severely impact prescribing decisions. When faced with this situation, the clinician should seek definitive (quantitative) testing for the specific drug. The physician should always be careful when making any accusation of diversion, since the point-of-care urine drug screen (presumptive testing by IA) may be unreliable and the pharmacokinetics of the drugs may interfere with detection. As a point of illustration, a patient prescribed oxycodone every 4 to 6 h as needed for pain may not be taking the medication as frequently as prescribed if the painful episodes subside. A urine drug test ordered 4–5 days after the last dose might be negative for the prescribed opioid due to infrequent dosing (false negative). Moreover, the urine retention time of the opioid may fall outside the window of detection. Conversely, a negative urine drug test on a patient with fewer pills than expected based on the dosing schedule may indicate diversion.

If drug diversion is suspected, more stringent monitoring could be implemented that includes increasing the frequency of office visits, scheduling UDT more often, prescribing fewer pills with each visit, involving a substance abuse specialist for management, and possible discontinuation of opioid therapy depending on physician judgment [23]. Practitioners will often escalate the frequency of UDT or even begin reducing the dose at this point until a rational explanation for the unexpected result is determined.

UDT Positive for Non-prescribed Opioid or Benzodiazepine

Potential explanations for such a result include false-positive testing, abuse or addiction, metabolites of a prescribed drug, or the patient obtained the medications from alternate sources including other physicians ("doctor shopping" or following ER visits, dental procedures, or surgical procedures). In this situation, the clinician may repeat the presumptive UDT with immunoassay and perform definitive testing via GC/MS to confirm the results. Patients have also been known to scrape their pills into the sample cup, leading to positive point of service testing (presumptive testing). The clinician must also be aware that immunoassay techniques (presumptive testing) are subject to cross-reactivity as mentioned earlier. Drugs that may cause a false-positive result on presumptive testing are listed in Table 1 [31].

In these cases, urine samples should be further analyzed with definitive testing (quantitative) through a laboratory, which can confirm specific opioids (distinguishing, for instance, between hydrocodone, hydromorphone, and morphine), identify possible poor conversion of prodrugs (e.g., drugs that are rapidly converted into active metabolites such as hydrocodone) to an active drug (e.g., hydromorphone), and confirm metabolites (confirms that the medications were actually ingested and not just placed into the cup).

The state's prescription drug monitoring program should be accessed and documented in the medical record to determine if the patient has obtained opioids/benzodiazepines from different providers. In general, the prescription drug monitoring program should be accessed with the provision of every opioid irrespective of UDT. In the event that another provider has prescribed controlled substances to the patient, the clinician should educate the patient about appropriate use of opioids and review/reiterate conditions of their existing opioid agreement. The clinician should also consider that the patient may have received opioid or benzodiazepine therapy for a recent surgical/dental procedure which may have led to a positive urine drug test. Thus, a thorough history should be obtained in cases of unexpected UDT to determine possible etiologies.

UDT Positive for Illicit Substances

Patients who test positive for illicit substances may be occasional or frequent users or possibly have a substance use disorder. Patients who use illicit substances are at increased risk for opioid misuse, abuse, diversion, and overdose death. Thus, such patients should be advised that continued use of the illicit substance is incompatible with opioid therapy, jeopardizes

Table 1 Drugs that may cause a false-positive result on presumptive testing

Test or drug category	Drugs that may cause a false-positive result
Amphetamines	Amantadine (Symmetrel), bupropion (Wellbutrin), chlorpromazine, desipramine (Norpramin), fluoxetine (Prozac), L-methamphetamine (in nasal decongestants*), labetalol (Normodyne), methylphenidate (Ritalin), phentermine, phenylephrine, phenylpropanolamine, promethazine (Phenergan), pseudoephedrine, ranitidine (Zantac), thioridazine, trazodone (Desyrel)
Benzodiazepines	Oxaprozin (Daypro), sertraline (Zoloft)
Cocaine	Topical anesthetics containing cocaine
Opiates	Dextromethorphan, diphenhydramine (Benadryl), Fluoroquinolones (*ciprofloxacin*, *levofloxacin*, and *ofloxacin*), poppy seeds, quinine, rifampin, verapamil(in methadone assay)
Phencyclidine	Dextromethorphan, diphenhydramine, ibuprofen, imipramine (Tofranil), ketamine (Ketalar), meperidine (Demerol), thioridazine, tramadol (Ultram), venlafaxine (Effexor)
Tetrahydrocannabinol	Dronabinol (Marinol), non-steroidal anti-inflammatory drugs (*ibuprofen*, *naproxen* (*Naprosyn*), and *sulindac* (*Clinoril*)), proton pump inhibitors (pantoprazole[Protonix])

their safety, and violates their opioid agreement. Realistically, most clinicians will not feel comfortable continuing current treatment with opioids and will discontinue therapy, but it is of value to discuss the situation with the patient in order elicit an explanation for the result. It is also important to direct the patient to substance abuse treatment, or at least to a mental health practitioner for continued risk assessment.

The use of cannabis requires special consideration given that it is illegal at the federal level, but approved for medical use in several states (Marijuana Policy Project: *State Policy*. http://www.mpp.org/states). Similar to opioids, marijuana can lead to misuse due to its rewarding properties. In fact, both THC and opioids trigger the release of dopamine in the nucleus accumbens through common mu opioid receptors in the ventral tegmental area [60, 61]. The risk factors for misuse of opioids in pain may predict a similar risk for patients using medicinal cannabis for pain control; therefore, the same or modified screening tools used for opioid therapy could identify cannabis misuse. Concurrently, clinicians can consider similar assessment and stratification methods for structuring care and monitoring of medicinal cannabis therapy such as informed consent, establishment of goals, and UDT [62]. Presumptive (IA) UDT for cannabis makes sense for patients using it therapeutically because clinicians will want to know whether a patient is consuming the drug rather than diverting it. However, the urine retention time of cannabis, a lipid-soluble drug could extend to almost a month in chronic smokers [63]. This can make the interpretation of positive urine results challenging if a patient's urine is tested less than a month before discontinuing the substance. If clinicians are concerned about a patient consuming synthetic cannabinoids such as spice, K2, and Joker, then definitive testing should be performed.

If opioid therapy continues in the context of a positive result for an illicit substance, the clinician should reiterate the salient features of the opioid agreement, advise the patient to stop illicit substance use, and repeat UDT with definitive testing on a regular basis. Failure to comply with these measures would result in termination of opioid therapy. However, practitioners may have varying thresholds for termination of opioids, i.e., "three strikes" or "zero tolerance" for example.

Additionally, the window of detection for opioids in the urine is variable for both screening and definitive testing. Most opioids will appear in the urine screen for 1–3 days after intake, but this may vary according to the substance. For example, methadone triggers a positive result for 5–10 days, cocaine is positive for 1–3 days, amphetamines for 2–4 days, benzodiazepines for up to 30 days, and marijuana for 1–3 days for sporadic use and up to 11 weeks for chronic use (Table 2).

Table 2 Window of detection for opioids in the urine

Drug	Window for detection
Hydrocodone	1–2 days
Oxycodone	1–3 days
Morphine	3–4 days
Methadone	5–10 days
Hydromorphone	1–2 days
Meperidine	1–2 days
Codeine	1–3 days
Heroin	1–3 days
Benzodiazepines	Up to 30 days
Barbiturates	2–10 days
Marijuana	1–3 days for casual use, 11 weeks for chronic use
Cocaine	1–3 days
Amphetamine	2–4 days
Methamphetamine	2–4 days
Heroin	1–3 days
Phencyclidine	2–8 days

This variability in detection makes the interpretation of results challenging for practitioners, whereas laboratories have sophisticated equipment for definitive testing that can provide specific testing and analysis of the results.

Point of Care Urine Testing

Point of care testing (POCT) refers to diagnostic testing performed at or near the site where clinical care is delivered (e.g., at the patient-provider interface). The appeal of POCT stems from convenience and availability; the immediate administration of a test during an office visit allows the treating physician, patient, and other members of the care team to obtain results before the patient leaves the clinical encounter. This allows for the formulation of real-time treatment decisions and helps to improve clinical and economical outcomes [64]. POCT eliminates the need to wait for hours or days while laboratory results arrive. The development of handheld and transportable instruments has allowed for the utilization of POCT for blood glucose testing, cholesterol screening, rapid cardiac marker diagnostics, pregnancy testing, fecal occult blood analysis, infectious disease screening, urine strip testing, and drugs of abuse screening among others.

In recent decades, various methods of POCT have become broadly adapted into all fields of clinical practice, and POCT continues to grow at a rate of almost 10% annually, totaling approximately seven billion dollars in sales worldwide each year [65]. Among pain physicians, use of the point of care (POC) urine (dipstick) immunoassay has become commonplace. Amid growing concerns over the overuse, abuse, and diversion of opioids among patients living with chronic noncancer pain, POC urine drug testing remains a helpful tool for identifying illicit substances and curtailing the abuse of controlled substances, especially when used in conjunction with other monitoring methods and prescription monitoring programs [64, 66].

The POCT urine (dipstick) immunoassay test utilizes antibodies to qualitatively detect the presence of drugs or drug metabolites [66]. In the clinical setting, the goals of POC urine testing are to (1) monitor compliance with the prescribed medication regimen and (2) monitor abuse of other drugs [64–66]. Marijuana, cocaine, opiates, amphetamines, and phencyclidine are the most commonly tested substances, and these comprise the "Federal Five" drugs included on most automated immunoassay tests [66]. Other drugs that may be detected via immunoassay include benzodiazepines, barbiturates, lysergic acid diethylamide (LSD), methadone, fentanyl, oxycodone, tramadol, and buprenorphine [65].

There are several limitations to POC urine drug testing. First, while the POC urine drug test is relatively quick, inexpensive, and sensitive, its lack of specificity limits its utility to screening purposes only; thus, any result that is inconsistent with a patient's prescribed medication merits confirmation via definitive testing such as mass spectrometry before confronting the patient, altering treatment plans, or taking any further action [64, 66]. False positives are common, and physicians must consider the use of over the counter medications and supplements that may interfere with testing results [66]. Second, POCT urine immunoassay provides only qualitative, not quantitative results, meaning that it is not useful for the determination of sub- or supra-therapeutic dosages. Third, the POC urine drug test is unable to differentiate between a parent drug and its metabolites. Fourth, although the POC urine test screens for the presence of certain drugs (e.g., morphine and codeine), several other opioids (e.g., fentanyl, tramadol, buprenorphine, hydromorphone, hydrocodone, oxymorphone) may or may not be included in the assay [64, 66, 67]. Thus, a negative opiate screening test may not necessarily mean that a patient is not using an opioid as directed. Finally, the urine can easily be altered in several ways, such as the addition of commercially available adulterants or by the acquisition of urine of another individual [64].

Ultimately, the POCT urine immunoassay is not without its limitations but remains a useful tool for basic monitoring of certain prescription regimens and primarily for detecting the use of illicit drugs. It can inform about potential substance misuse, especially in conjunction with a thorough patient history and other risk mitigation methods. Physicians should be mindful of its weaknesses and seek conclusive results via confirmatory testing before making clinical decisions that alter patient care.

Oral Fluid (Salivary) Testing

As a result of advances in drug testing capabilities during recent years, the use of alternative specimens to blood or urine has emerged as an interesting and promising method of drug testing [68, 69]. Such alternatives include oral fluid, hair, and sweat, and each of these specimens has associated benefits and drawbacks [69]. Oral fluid testing has emerged as a relatively quick and convenient matrix for the detection of certain drugs in the saliva. Compared to urine testing, oral samples are more difficult to tamper with because the collection of oral fluid specimens can be observed by practitioners without substantial invasion of patient privacy, thereby minimizing the risk of adulteration or substitution of the specimen [70, 71]. The use of commercially available adulterants such as Clear Choice®, Fizzy Flush™, Spit and Clean®/™ mouth wash, and Listerine® has not been shown to affect drug concentrations in oral fluid if the sample is collected 30 min after using these adulterants [68].

Oral fluid testing is most commonly used for drugs of abuse testing in employees working in certain workplaces where the strict avoidance of drugs is important for personal safety and the safety of others [68]. Oral fluid may be tested for various drugs including opiates, amphetamines, cocaine,

benzodiazepines, and cannabinoids [68, 69, 72]. The parent drug or its metabolites may remain in the saliva for up to 48 h after the last use [69, 72]. This window of detection is typically shorter than that of UDT. Additional capabilities of oral fluid testing include the detection of ethanol and the detection of HIV antibodies [68].

Among the limitations of oral fluid testing include the potential for contamination of oral samples by ingested food and beverages. Another potential disadvantage is the fact that certain drugs (such as amphetamines, cannabis, antihistamines, antipsychotic drugs, anticholinergic drugs, and certain antidepressant drugs) affect the secretion of oral fluid, which may lead to inadequate sample volume during specimen collection [68, 69]. Additionally, oral fluid drug concentrations may not always accurately reflect drug concentrations in the blood, particularly when the drug is smoked or inhaled [69, 73]. Despite these limitations, oral fluid testing is an exciting alternative to other matrices of drug testing or monitoring, and its future looks promising. Further studies are needed to evaluate, among other parameters, the optimal drug cutoff concentrations for oral fluid drug testing.

Pharmacogenetic Testing

Continual therapeutic failure with opioids or their adverse effects may merit genetic testing. The value of such testing resides in customizing a specific medication or dose of a medication based on the extent of a patient's drug metabolism. For instance, does the analgesic response of an opioid or its adverse effects correlate with certain drug-metabolizing enzymes: normal metabolizer, intermediate metabolizer, poor metabolizer, or ultrarapid metabolizer. If so, then eliminating the drug or modifying the dose may lead to a better patient response. One cross-sectional study found that the number of genetic variants among patients in an outpatient pain clinic was similar to the average population [74]. Moreover, the authors reported just modest associations with opioid dose requirements and these genetic variants. However, there are pharmacogenetic guidelines that describe methods of using genetic tests for optimizing drug therapy in patients, and it includes several medications used for chronic pain such as opioids, tricyclic antidepressants, NSAIDS, and triptans (www.cpicpgx.org. Accessed 6/21/2019). The result of variant metabolic phenotypes (e.g., poor or ultrarapid) on a patient's response to a drug may be interpreted through metabolic ratios obtained with quantitative urine results. Certain patterns of metabolism can help clarify drug testing results or drug-drug interactions. For example, a patient who is a poor metabolizer may not produce an expected urine metabolite and the practitioner might misinterpret this absence as non-compliance with prescribed opioid therapy. Monitoring metabolic ratios of opioids in the urine with quantitative testing (e.g., ratio of hydromorphone to hydrocodone) may help identify a variation in a patient's genotype that leads to a given metabolic phenotype [75]. The clinician could then change a drug's dose to produce a better analgesic response, reduce or eliminate an adverse effect, or explain unexpected UDT results. The evidence to date does not support routine genetic testing of pain patients, but physicians might consider genotyping to clarify repeatedly inadequate or unexpected responses to opioids.

Conclusion

Urine drug testing remains a valuable method of assisting the clinician in medical decision-making for patients on opioid therapy. Current evidence highlights the added benefit of implementing this strategy for risk mitigation by providing information about a patient's use of a prescribed opioid regimen, use of illicit substances, and use of non-prescribed controlled substances. More clinicians are implementing POCT into their practices to rule out the presence of illicit substances before prescribing an opioid, but the limitations of this test often require definitive testing. Oral fluid testing offers some advantages to UDT, but the window of detection is often shorter and there are specific limitations to test interpretation. Pharmacogenetic testing can clarify complex responses to opioids and has not yet been adopted as a standard in clinical practice. Clinicians can incorporate information from this review into an algorithm for diagnostic testing in their current practice.

Data Availability Available upon request from the corresponding author.

Compliance with Ethical Standards

Conflict of Interest The authors declare no conflict of interest as relates to this body of work.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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