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Optimum Methadone Compliance Testing

An Evidence-Based Analysis

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The Medical Advisory Secretariat is part of the Ontario Ministry of Health and Long-Term Care. The mandate of the Medical Advisory Secretariat is to provide evidence-based policy advice on the coordinated uptake of health services and new health technologies in Ontario to the Ministry of Health and Long-Term Care and to the healthcare system. The aim is to ensure that residents of Ontario have access to the best available new health technologies that will improve patient outcomes.

The Medical Advisory Secretariat also provides a secretariat function and evidence-based health technology policy analysis for review by the Ontario Health Technology Advisory Committee (OHTAC).

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Abbreviations

EDDP	2-ethylidene- 1,5-dimethyl-3,3-diphenylpyrrolidine
GC	Gas chromatography
GC/MS	gas chromatography/mass spectrometry
HPLC	High-performance liquid chromatography
LOD	Limit of Detection
MS	Mass spectrometry
MMT	Methadone Maintenance Treatment
OFT	Oral fluid testing
PCP	Phencyclidine
POC	Point of Care Testing
THC	tetrahydrocannabinol
THCCOOHC	11-nor-delta-9-tetrhydrocannabinol-9-carboxylic acid
UDT	urine drug testing

Executive Summary

Objective

The objective of this analysis was to determine the diagnostic utility of oral fluid testing collected with the Intercept oral fluid collection device.

Clinical Need: Target Population and Condition

Opioids (opiates or narcotics) are a class of drugs derived from the opium poppy plant that typically relieve pain and produce a euphoric feeling. Methadone is a long-acting synthetic opioid used to treat opioid dependence and chronic pain. It prevents symptoms of opioid withdrawal, reduces opioid cravings and blocks the euphoric effects of short-acting opioids such as heroin and morphine. Opioid dependence is associated with harms including an increased risk of exposure to Human Immunodeficiency Virus and Hepatitis C as well as other health, social and psychological crises. The goal of methadone treatment is harm reduction. Treatment with methadone for opioid dependence is often a long-term therapy. The Ontario College of Physicians and Surgeons estimates that there are currently 250 physicians qualified to prescribe methadone, and 15,500 people in methadone maintenance programs across Ontario.

Drug testing is a clinical tool whose purpose is to provide objective meaningful information, which will reinforce positive behavioral changes in patients and guide further treatment needs. Such information includes knowledge of whether the patient is taking their methadone as prescribed and reducing or abstaining from using opioid and other drugs of abuse use. The results of drug testing can be used with behavior modification techniques (contingency management techniques) where positive reinforcements such as increased methadone take-home privileges, sustained employment or parole are granted for drug screens negative for opioid use, and negative reinforcement including loss of these privileges for drug screens positive for opioid used.

Body fluids including blood, oral fluid, often referred to as saliva, and urine may contain metabolites and the parent drug of both methadone and drugs of abuse and provide a means for drug testing. Compared with blood which has a widow of detection of several hours, urine has a wider window of detection, approximately 1 to 3 days, and is therefore considered more useful than blood for drug testing. Because of this, and the fact that obtaining a urine specimen is relatively easy, urine drug screening is considered the criterion measure (gold standard) for methadone maintenance monitoring. However, 2 main concerns exist with urine specimens: the possibility of sample tampering by the patient and the necessity for observed urine collection. Urine specimens may be tampered with in 3 ways: dilution, adulteration (contamination) with chemicals, and substitution (patient submits another persons urine specimen). To circumvent sample tampering the supervised collection of urine specimens is a common and recommended practice. However, it has been suggested that this practice may have negative effects including humiliation experienced by patient and staff, and may discourage patients from staying in treatment. Supervised urine specimen collection may also present an operational problem as staff must be available to provide same-sex supervision. Oral fluid testing has been proposed as a replacement for urine because it can be collected easily under direct supervision without infringement of privacy and reduces the likelihood of sample tampering. Generally, the results of oral fluid drug testing are similar to urine drug testing but there are some differences, such as lower concentrations of substances in oral fluid than urine, and some drugs remain detectable for longer periods of time in urine than oral fluid.

The Technology Being Reviewed

The Intercept Oral Specimen Collection Device (Ora-Sure Technologies, Bethlehem, PA) consists of an absorbent pad mounted on a plastic stick. The pad is coated with common salts. The absorbent pad is inserted into the mouth and placed between the cheek and gums for 3 minutes on average. The pad absorbs the oral fluid. After 3 minutes (range 2min-5 min) the collection device is removed from the mouth and the absorbent pad is placed in a small vial which contains 0.8mL of pH-balanced preservative, for transportation to a laboratory for analysis. It is recommended that the person undergoing oral fluid drug testing have nothing to eat or drink for a 10- minute period before the oral fluid specimen is collected. This will remove opportunity for adulteration. Likewise, it is recommended that the person be observed for the duration of the collection period to prevent adulteration of the specimen. An average of 0.4 mL of saliva can be collected. The specimen may be stored at 4C to 37C and tested within 21 days of collection (or within 6 weeks if frozen).

The oral fluid specimen must be analyzed in a laboratory setting. There is no point-of-care (POC) oral fluid test kit for drugs of abuse (other than for alcohol). In the laboratory the oral fluid is extracted from the vial after centrifugation and a screening test is completed to eliminate negative specimens. Similar to urinalysis, oral fluid specimens are analyzed first by enzyme immunoassay with positive specimens sent for confirmatory testing. Comparable cut-off values to urinalysis by enzyme immunoassay have been developed for oral fluids

Review Strategy

Research Question

What is the diagnostic utility of the Intercept oral specimen device?

Inclusion criteria:

- Studies evaluating paired urine and oral fluid specimens from the same individual with the Intercept oral fluid collection device.
- The population studied includes drug users.

Exclusion criteria:

Studies testing for marijuana (THC) only.

Outcomes:

Sensitivity and Specificity of oral fluid testing compared to urinalysis for methadone (methadone metabolite), opiates, cocaine, benzodiazepines, and alcohol.

Quality of the Body of Evidence

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) system was used to evaluate the overall quality of the body of evidence (defined as 1 or more studies) supporting the research questions explored in this systematic review. A description of the GRADE system is reported in

Appendix 1.

Summary of Findings

A total of 854 potential citations were retrieved. After reviewing titles and abstracts, 2 met the inclusion and exclusion criteria. Two other relevant studies were found after corresponding with the author of the 2 studies retrieved from the literature search. Therefore a total of 4 published studies are included in this analysis. All 4 studies carried out by the same investigator meet the definition of Medical Advisory Secretariat level III (not a-randomized controlled trial with contemporaneous controls) study design. In each of the studies, paired urine and oral fluid specimens where obtained from drug users. Urine collection was not observed in the studies however, laboratory tests for pH and creatinine were used to determine the reliability of the specimen. Urine specimens thought to be diluted and unreliable were removed from the evaluation. Urinalysis was used as the criterion measurement for which to determine the sensitivity and specificity of oral fluid testing by the Intercept oral fluid device for opiates, benzodiazepines, cocaine and marijuana. Alcohol was not tested in any of the 4 studies. From these 4 studies, the following conclusions were drawn:

1. The evidence indicates that oral fluid testing with the Intercept oral fluid device has better specificity than sensitivity for opiates, benzodiazepines, cocaine and marijuana.
2. The sensitivity of oral fluids testing with the Intercept oral fluid device seems to be from best to worst: cocaine > benzodiazepines >opiates> marijuana.
3. The sensitivity and specificity for opiates of the Intercept oral fluid device ranges from 75 to 90% and 97- 100% respectively.
4. The consequences of opiate false-negatives by oral fluid testing with the Intercept oral fluid device need to be weighed against the disadvantages of urine testing, including invasion of privacy issues and adulteration and substitution of the urine specimen.
5. The window of detection is narrower for oral fluid drug testing than urinalysis and because of this oral fluid testing may best be applied in situations where there is suspected frequent drug use. When drug use is thought to be less frequent or remote, urinalysis may offer a wider (24-48 hours more than oral fluids) window of detection.
6. The narrow window of detection for oral fluid testing may mean more frequent testing is needed compared to urinalysis. This may increase the expense for drug testing in general.
7. POC oral fluid testing is not yet available and may limit the practical utility of this drug testing methodology. POC urinalysis by immunoassay is available.
8. The possible applications of oral fluid testing may include:
    a. Because of its narrow window of detection compared to urinalysis oral fluid testing may best be used during periods of suspected frequent or recent drug use (within 24 hours of drug testing). This is not to say that oral fluid testing is superior to urinalysis during these time periods.
    b. In situations where an observed urine specimen is difficult to obtain. This may include persons with “shy bladder syndrome” or with other urinary conditions limiting their ability to provide an observed urine specimen.
    c. When the health of the patient would make urine testing unreliable (e,g., renal disease)
    d. As an alternative drug testing method when urine specimen tampering practices are suspected to be affecting the reliability of the urinalysis test.

Possible limiting Factors to Diffusion of Oral Fluid Technology

- No oral fluid POC test equivalent to onsite urine dips or POC analyzer reducing immediacy of results for patient care.
- Currently, physicians get reimbursed directly for POC urinalysis. Oral fluid must be

analyzed in a lab setting removing physician reimbursement, which is a source of program funding for many methadone clinics.

- Small amount of oral fluid specimen obtained; repeat testing on same sample will be difficult.
- Reliability of positive oral fluid methadone (parent drug) results may decrease because of possible contamination of oral cavity after ingestion of dose. Therefore high methadone levels may not be indicative of compliance with treatment. Oral fluid does not as yet test for methadone metabolite.
- There currently is no licensed provincial laboratory that analyses oral fluid specimens.

Abbreviations

EDDP	2-ethylidene- 1,5-dimethyl-3,3-diphenylpyrrolidine
EIA	enzyme immunoassay
ELISA	Enzyme Linked Immunosorbent Assay (ELISA),
EMIT	Enzyme Multiplied Immunoassay Test (EMIT)
GC	Gas chromatography
GC/MS	gas chromatography/mass spectrometry
HPLC	High-performance liquid chromatography
LOD	Limit of Detection
MS	Mass spectrometry
MMT	Methadone Maintenance Treatment
OFT	Oral fluid testing
PCP	Phencyclidine
POC	Point of Care Testing
THC	tetrahydrocannabinol
THCCOOHC	11-nor-delta-9-tetrhydrocannabinol-9-carboxylic acid
UDT	urine drug testing

Objective

The objective of this analysis was to determine the diagnostic utility of oral fluid testing collected with the Intercept oral fluid collection device.

Background

Drug testing is a clinical tool whose purpose is to provide objective meaningful information to guide treatment. (1) Such information includes knowledge of the patients' adherence to methadone and or continual use of illicit or licit opioids.

Clinical Need: Target Population and Condition

Opioids (opiates or narcotics) are a class of drugs that are derived from the opium poppy plant. They can also be produced synthetically. Some specific opioids include morphine, heroin, and codeine. Most opioid drugs typically relieve pain and produce a euphoric feeling. Methadone is a long-acting synthetic opioid used to treat opioid dependence. It is also used to manage chronic pain. As a treatment for opioid dependence, methadone prevents symptoms of withdrawal, reduces opioid cravings and blocks the euphoric effects of short acting opioids such as heroin and morphine. (2). The goal of methadone treatment is essentially harm reduction. Persons with opioid dependence have an increased risk of exposure to Human Immunodeficiency Virus and Hepatitis C as well as experiencing other health, social and psychological crises. Removing or reducing a person's dependence on opioids will reduce these associated harms and foster a return to productive functioning. (3) Treatment with methadone for opioid dependence is often a long-term therapy. (2) The College of Physicians and Surgeons of Ontario (CPSO) estimates that there are currently 250 physicians qualified to prescribe methadone and 15,500 people in methadone maintenance programs across Ontario. (Personal communication, College of Physicians and Surgeons of Ontario, November 24, 2006)

Before treatment with methadone is initiated, clinicians need objective evidence to confirm opiate dependence. Once treatment is initiated clinicians then need to monitor the patient's progress to determine methadone dose adjustments and/or the need for other treatment interventions. Currently, laboratory analysis of urine (urinalysis) for drugs of abuse is the gold standard for objective patient monitoring. The results of a urine drug test may be used with behavior modification techniques (contingency management techniques) where positive reinforcements such as methadone take-home privileges or continued employment may be granted for negative drug screens (indicating no illicit or licit opiates use) and negative reinforcement such as decreased privileges for positive screens (indicating continued opiate use).(3) Determining the optimal method for monitoring requires consideration of the type of specimen used, the collection methods required to obtain the specimen, and the frequency of the specimen collection.

Type of Specimens

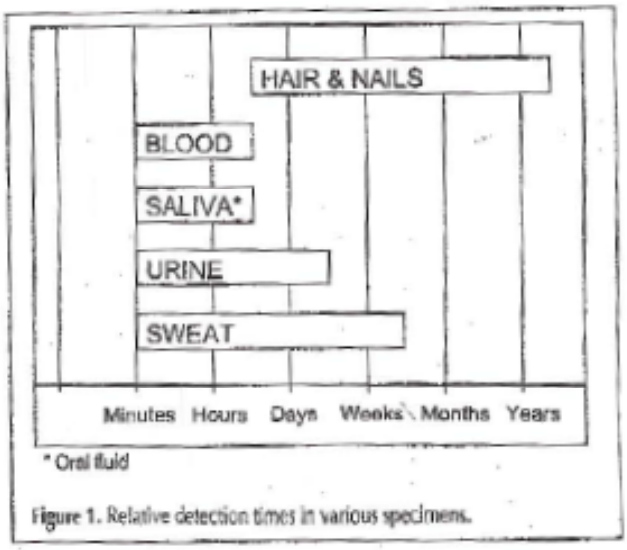
Body fluids including blood, oral fluid (saliva), and urine may contain metabolites and/or the parent drug of both methadone and drugs of abuse, and therefore provide a means for drug testing. Compared with blood which has a widow of detection of several hours, urine has a wider window of detection of approximately 1 to 3 days for most drugs and is therefore considered more useful than blood as a test medium. (1)[Figure 1] Because of this, and the fact that obtaining a urine specimen is relatively easy,

urine drug screening is considered the gold standard for methadone maintenance monitoring. (2) However, 2 main concerns exist with urine specimens: the possibility of specimen tampering by the patient and the necessity for observed urine collection.

Urine specimens may be tampered in 3 ways: dilution, contamination and substitution. Dilution of the urine specimen may occur directly by adding water to the specimen or indirectly by drinking an excessive amount of fluid before providing the urine specimen. Contaminating the urine specimen with chemicals such as bleach will disrupt the laboratory assay making metabolites undetectable. Finally, submitting another person's urine specimen, the same urine specimen on different days or using a urine substitute accounts for substitution. To circumvent specimen tampering, the supervised collection of urine specimens is a common and recommended practice. However, it has been suggested that this practice is humiliating for patients and staff and may discourage patients from staying in treatment. (3) Supervised urine specimen collection may also present an operational problem if same-sex supervision is required.

Saliva testing has been proposed as a replacement for urine because it can be collected easily under direct supervision reducing the likelihood of sample tampering. The collection process also does not constitute an infringement of privacy. Generally, the results of oral fluid drug testing are similar to urine drug testing but there are some differences such as lower concentrations of substances in oral fluid than urine, and some drugs remain detectable for longer periods of time in urine than oral fluid. (4) Because oral fluid approximates the blood level of a drug, its usefulness (like blood) is thought to be limited in adherence monitoring.

Figure 1: Detection Times for Various Specimens



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Pharmacology

Opiates may be administered by many different routes including but not limited to oral, rectal, intramuscular, intravenous, intranasal, and transdermal. They are metabolized by the liver and eliminated primarily by the kidneys. (5)

The duration of detection time for any drug depends on many factors: preparation and route of administration of the drug, dose, duration of use (chronic vs. acute), inter-individual variation in metabolic and renal clearance, type of specimen analyzed (urine, oral fluid, hair, sweat, blood), pH and concentration of the specimen, type of analyte assessed, and the concentration limits of quantification or cut-off values of the analytic technique.(6) The duration of detection for amphetamine, cannabis, cocaine, and heroin in blood, urine and oral fluid are reported in Table 1. (6) Verstreate (6) states that the detection times of drugs are extremely variable with the probability of detection increasing if the most sensitive analytical method is used (i.e., chromatography with mass spectrometry), if the metabolite that persists the longest is looked for, and if the specimen type that allows the longest possible window of detection is sampled. In general, hair offers the longest window of detection followed by urine, sweat, oral fluid and blood.

Duration of Detection for Opiates

Heroin is injected, smoked or administered intranasally. The dose used will increase as the person acquires tolerance to the drug. After a 12mg to 20mg intravenous dose of heroin, the detection time for morphine (a major metabolite of heroin) in blood, at a limit of detection (LOD) of 1ng/mL, is 20 hours. The detection time for morphine in blood ranges between 22 minutes to 2 hours after smoking 10.5mg of heroin. After an intranasal administration of 9mg of heroin, morphine is detectable in blood for 12 hours at a LOD of 1ng/mL. In chronic heroin users, morphine was detectable in blood for 29.2 hours on average and up to 5 days at a LOD of 25ng/mL. After an intravenous dose of 3, 6, and 12mg of heroin, 6-acetylmorphine also a metabolite of heroin, is detectable in urine at 2.3, 2.6 and 4.5 hours respectively, and total morphine at a LOD of 300ng/mL at 18.5, 24.8 and 35.3 hours respectively. In oral fluid, 6-acetylmorphine can be detected for 0.5 to 8 hours and morphine for 12 to 24 hours at a LOD of 1ng/mL. Codeine administered orally at a dose of 60 to 120mg was detectable in oral fluid by gas chromatography/mass spectrometry (GC/MS) for 21 hours at a LOD of 2.5ng/mL, and 7 hours at 40ng/mL.

Table 1: Duration of Detection

Drug (drug metabolite)	Half-life (hours) [minutes]	Blood		Urine		Oral	
		Cut-off Value (ng/mL)	Detection Time (hours)	Cut-off Value (ng/mL)	Detection Time (hours)	Cut-off Value (ng/mL)	Detection Time (hours)
Amphetamine	7-34	4	46	>1000	24-36	10	20-50
Tetrahydrocannabinol	0.5	10	5	10	10	1	31
						0.5	34
Cocaine	1	1	12			1	5-12
(benzolecognine)	6	10	48	1000	48-72	1	12-24
Heroin	[2-7]						
(6-acetyl-morphine)	[6-25]					1	0.5-8
(morphine)	2-3	1	20	300	11-54	1	12-24
Codeine						2.5	21
						40	7

The pharmacokinetics of methadone is highly variable with an elimination half-life (the time required for the blood levels to decline by 50%) ranging from 2 to 50 hours. After oral administration the onset of action is 30 minutes to 60 minutes, and the duration of action is 24 hours to 48 hours (48 hours with repeat dosing). (5) Unchanged methadone (parent drug) in urine represents 2 to 5% of the total dose.

Methadone is also pH dependent with less unchanged drug detected when the urine is alkaline than acidic. The major metabolite of methadone found in the urine is 2-ethylidene- 1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP).

Methadone Treatment

Methadone is usually administered once per day. The drug is diluted in Tang (an orange drink). Methadone treatment is divided into 3 phases, early stabilization, late stabilization and maintenance phase. [Table 2] (2) During the first 2 months of treatment, methadone must be consumed under direct supervision of a regulated health professional. After 2 months of treatment, methadone patients who are clinically stable can start to receive methadone for unsupervised administration. In this case, for every month the patient is stable they can receive one day's dose of methadone to take home for unsupervised administration. It will require 6 months of stable behavior to acquire 6 take home doses (carries) per week, which is the maximum number of carries allowed.(2)

Table 2: Phases of Methadone Treatment

Early Stabilization (0-2 weeks)	Late Stabilization (2-6 weeks)	Maintenance (6 weeks +)
Recommended initial daily dose is 10-30 mg For patients at a high risk of methadone toxicity prescribing a lower dose (10-20 mg) should be considered. Methadone must be consumed under direct supervision of a regulated health professional Restart the initial dose if the patient misses 2 doses in a row. Do not increase the dose for several days if the patient misses a dose.	Doses should be increased by no more than 5mg-15mg every 3-4 days and after the physician has assessed the patient for symptoms of withdrawal, ongoing opioid use or opioid craving. A dose between 50mg-120mg will be the optimal dose for most patients.	A clinically significant loss of tolerance to opioids may occur if 3 consecutive days of methadone are missed. If 4 or more days are missed the best course of action will be to restart methadone at 30mgs or less.
Urinalysis used to confirm opioid dependence and determine other drugs of use.	Urinalysis used to determine changes in drug use behavior to determine response to methadone treatment.	Urinalysis is used to confirm use of methadone (prevent diversion of methadone) and detect use of drugs of abuse other than methadone.

Existing Drug Tests Other Than Technology Being Reviewed

Urinalysis is the standard of practice in Ontario for methadone compliance testing. Analysis of sweat, hair, saliva and nail clippings for methadone compliance has also been reported in the literature. Currently there are no Health Canada approved test kits for sweat, hair or nail clipping specimens and because of this these specimen mediums will not be discussed further.

Urine Drug Test

The results of a urine drug test can be qualitative (yes/no) or quantitative depending on the analytic method used to analyze the specimen. For the results of any drug test to be meaningful, it is imperative that they are interpreted by the clinician caring for the patient. There is no standard urine drug test result that fits all clinical settings. The results must be interpreted within the clinical context of the patient in

order for the test results to have meaning and to impact on the clinical care of the patient.
To accurately interpret the result of a drug test, a detailed patient history of all medications used including any herbal preparations and the time of last substance use should be obtained. (1) Results of the drug testing process should be used along with the patient's self-reported history to determine the need for other treatment interventions. For example, if a person is supposed to be taking methadone, a negative test would be unexpected. In this case a negative test may alert the clinician to harmful behavior such as not taking methadone or bingeing and running out of the drug earlier than would be anticipated. Similarly, positive tests for benzodiazepines may be inappropriate unless the patient's history of anxiety disorder is appreciated. Common drugs tested for include, methadone and its metabolite, opiates, cocaine, and benzodiazpines. Routine testing for alcohol and marijuana is done by some but not all clinicians.

The College of Physician and Surgeons of Ontario recommends that during the initiation of methadone treatment, 1 urine drug test be done to confirm and determine the primary opioid of abuse. Thereafter, during the early and late stabilization phases of treatment (0-6 weeks) urine drug testing should be undertaken at least once per week and then weekly throughout the maintenance phase .(2) After 6 months of negative weekly urine drug screens, urine drug screening may be carried out biweekly (every 2 weeks) or monthly depending on the person's history of valid self-reported drug use, pattern of drug use and clinical stability. As mentioned, urine sample tampering can occur. Because of this the validity of the urinalysis increases if the sample is collected under supervision. (7) It is recommended by the CPSO that urine samples be obtained under direct supervision. (2)

The merits of drug testing have been debated in the literature. Proponents of the procedure advocate that it is necessary to confirm patient self-reporting. However, those opposed to it suggest drug testing may imply that patients cannot be trusted to tell the truth about their drug use and this may contribute to a negative patient-health care provider relationship.(8) In a metanalysis of 24 studies that examined the validity of self-reports in high-risk populations, Magura and Kang (9) found that 42% of drug users with positive urinalysis or hair analysis gave positive self-reports. These authors acknowledge that self-reports remain the best way of assessing the duration, frequency, intensity, routes of drug administration, social context of use and other patterns of drug use.(9) The CPSO have reported, based on Level III evidence (evidence from well-designed trials without randomization, pre-post, cohort, time series or matched case-control series), that urine drug testing combined with self-reports are more accurate than either method alone. (2)

Determining the Reliability of Urine Results

Specimen tampering can skew the reliability of the urinalysis results. Various practices have been used to obtain a reliable urine specimen including obtaining urine specimens under direct supervision and measuring the temperature of the urine. A urine temperature of 32.5ºC to 37.7ºC is a good indicator that the specimen was just provided from the identified donor. (10) Temperature can be measured by a heat sensitive strip (10) on the collection container or an infrared thermometer. However, it is still possible to circumvent temperature control methods by warming a substituted urine specimen in the axilla (armpit). Volume collection has also been used as an alternative to supervised collection because it can increase the validity of temperature readings and provides a second factor that of quantity, for ensuring the specimen came from the identified donor. (10)

Laboratory analyses of the urine specimen's pH and creatinine (a protein byproduct of muscle metabolism excreted in the urine (11)), offers important information about the reliability of the test results. (12) For example, negative results from a concentrated urine specimen are more reliable in terms of nonuse than negative results from a dilute sample. Likewise, because the pH of the urine specimen can affect the amount of methadone parent drug in the urine (less methadone parent drug is detected in alkaline urine) it

can help explain inappropriate negative results on a patient who is taking methadone as prescribed. (Personal communication, clinical expert, December 4, 2006) It is recommended that pH and creatinine be determined on all urine specimens. (Personal communication, clinical expert December 4, 2006) Other issues with drug testing and in particular, the validity of urine drug sampling include high false-negative rates with semi-synthetic and synthetic opioids. (2)

Kapur et al. (13) used a combination of sodium, chloride and creatinine values to develop a unique patient urine fingerprint to identify patients who submit the same urine specimen (bladder sharing). Using population relative frequency probabilities for urine creatinine, chloride, sodium and pH, the highest probability of occurrence of identical values in 2 specimens was 1 in 270. The author concluded that measuring the urine electrolytes as well as creatinine and pH can potentially identify duplicate specimens for further investigation. Kapur et al.(13) suggest that further investigation include a comparison of urine drug screening results (concentration of drug) followed by a chromatographic screen. Measuring the sodium chloride concentration in the urine can also determine if the specimen has been adulterated by table salt, which can disrupt the reliability of the urinalysis assay.

Immunoglobluin G (IgG) is used to determine if an oral fluid specimen has been diluted. The reliability of the test results are improved if the IgG is at least 0.1µg/mL. However, Crouch et al. (14) suggest that more research is needed to determine if this criterion is useful.

Urinalysis

Enzyme Immunoassay

There are 2 main types of urine drug tests: enzyme immunoassay (EIA) testing and chromatography (Table 3). An EIA test reports the presence or absence of a class of drugs (eg. opiates, benzodiazepine) according to a predetermined drug concentration cut-off. However, it does not report the specific drug used (eg. morphine, diazepam). Urinalysis by EIA testing can be done in a laboratory, in a clinic or doctor's office using a point-of-care (POC) test kit or a POC analyzer (e.g., Novx iMDx systems). EIA is a very sensitive screen for opioids and can detect opioids that have been in the body for 2 to 4 days. However, this test is not very specific and substances that have similar chemical structures will cross-react with the test detection processes and give false-positive results (15). A true-negative immunoassay test only indicates that at the time of specimen collection, the concentration of the drug metabolites were below the threshold limits required to report a positive. Other disadvantages of EIA analytic testing include variability in the range of drugs and metabolites detected. For example, tests for amphetamines/methamphetamine are highly cross-reactive and will test positive if such drugs as ephedrine and pseudoephedrine (common ingredients in over-the- counter cold remedies) are present. Quinolone-based antibiotics can potentially give false-positive results for opiates by EIA testing. Enzyme immunoassays also have a lower sensitivity for oxycodone, fentanyl, methadone and buprenorphine, which means a negative response cannot rule out the presence of these opioids. Additionally, false-positives for opioids may occur by EIA testing with the ingestion of poppy seeds. Specific types of EIA tests include Enzyme Linked Immunosorbent Assay (ELISA), Enzyme Multiplied Immunoassay Test (EMIT), Fluorescence polarization and radioimmunoassay. Immunoassy testing can be followed by a more specific technique such as GC/MS to identify the specific drug used.

Chromatography

Chromatography is done in a laboratory setting and provides information about the specific drug used (eg. morphine, diazepam) over and above the class of drug (opiate, benzodiazepine).(2;16) Chromatography will detect opioids that have been in the body for up to 1 to 2 days. GC/MS is considered the gold standard analytic technique. However, it is expensive and requires highly-trained technicians. (15) Other

types of chromatography methods include high-powered liquid chromatography alone or coupled with mass spectrometry, thin layer chromatography and liquid chromatography-mass spectrometry. Thin layer chromatography is the least expensive type of chromatography.

Table 3: Advantages and Disadvantages Drug Testing Analytic Procedures*

Type of test	Immunoassay	Chromatography
Advantages	*High sensitivity Detects class of drug Detects opioids for 2-4 days Depending on the test kit or analyzer used used EDDP can be measured as well as methadone. (eg. Novx analyzers http://www.novxsystems.com/)	*High Specificity Detects specific drug type Can distinguish methadone from EDDP
Disadvantages	*Poor specificity Cannot detect specific drug Often misses semi-synthetic and synthetic opioids such as Oxycodone or Fentanyl. False-positives with poppy seeds or quinolone antibiotics.	*Low sensitivity detects opioids for 1-2 days only

*EDDP refers to 2-ethylidene- 1,5-dimethyl-3,3-diphenylpyrrolidine
†Sensitivity is the test's ability to detect a class of drug while specificity is the ability to identify a particular drug

Point-of-Care Testing

POC testing can be done on-site at the clinic or doctor's office with either a single-use immunoassay test kit (often called a urine dipstick test) or an automated analyzer such as the Novx Class III iMDx system. In general, a dipstick (small chemically reactive slip of paper) is dipped into the urine specimen and a positive or negative result is visually indicated on the dipstick. The main purpose of POC testing is to exclude true-negatives (people not using drugs of abuse). Positive tests will require follow-up with a laboratory test if information about the specific drug of use is required. Advantages of POC testing include portability, ease of use, minimal training requirements and immediacy of results. Disadvantages are that they produce qualitative results (yes/no for drug use), have a lack of adequate quality assurance and quality control mechanisms, and lack documentation of results. For example, some POC tests produce a line and others no line on the urine dipstick for a positive results. Persons using these tests need to carefully review the product instructions before use. Currently other than for alcohol, there is no POC oral fluid test kit for methadone or other drugs of abuse.

Laboratory Based testing

Differences exist between and within laboratories doing EIA and chromatography analyses. Differences may include the analytes included in the test panel, the cross-reactivity patterns of the test, the cut-off concentrations and the drug interferences. The clinician interpreting these tests must be aware of these idiosyncrasies between tests and laboratories to accurately interpret the results of the urine drug tests. (1).

It is important to know the laboratory cut-off point or the drug concentration above which the test will report a positive result and below which the test will report a negative result. The LOD of a test is the lowest amount of analyte that a test can reliably identify in a specimen. The LOD will vary depending on the methodology used for the assay (i.e. GS/MS or high-performance liquid chromatography [HPLC]), the laboratory where it was performed and the specimen medium tested. It may be possible to specify "no threshold testing" at the LOD to increase the chance of detecting a substance in the specimen.

Types of Specimens for Drug Testing

Specimens used in drug testing other than urine include oral fluid, hair, and sweat. (17) Different biological specimens offer different information regarding the extent, frequency and impact o drug use. (11) An appreciation of the advantages and disadvantages of each specimen is required to fully understand their potential role in methadone compliance monitoring. Oral fluid is the mixture of saliva from 3 major and several minor salivary glands. Oral fluid contains plasma electrolytes such as potassium, sodium, chloride, and bicarbonate, and many other plasma constituents including enzymes, immunoglobulins, and DNA. (14;18) As a drug test medium, oral fluid has several advantages. Like urine it is easily collected but also has the added advantage of a reduced susceptibility to tampering due to direct observation during collection. The collection of oral fluids also removes invasion of privacy issues associated with supervised urine specimen collection. While urine allows for the testing of the drug metabolite (metabolized drug), oral fluid on the other hand mainly can detect the parent drug. This advantage removes ambiguities in test results associated with metabolic degradation. However, oral fluid has a narrower window of detection and lower analyte concentrations compared to urine. The concentration of analytes in oral fluid is generally proportional to blood. (19) Other disadvantages of oral fluids include the current lack of a POC test kit available for drugs of abuse, and potential contamination of the oral cavity by drugs that are smoked, insufflated or orally ingested, possibly increasing the drug concentration of oral fluid.

Hair provides a matrix for long-term retrospective profiling of drug use. However, hair colour and texture may affect the sensitivity of the test. As well, hair is not always available as a specimen. Sweat provides a prospective cumulative measure of drug use and can be collected via a sweat patch. It however, cannot detect prior exposure. Disadvantages include inter-person variability in sweat production, unknown minimum specimen volume, and contamination of specimen during application or removal of collection device. Table 4 provides the main characteristics (20) and Table 5 the advantages and disadvantages of different types of body fluid specimens for drug testing.

Table 4: Characteristics of Specimen Types for Drug Testing

	Blood	Saliva	Urine	Sweat	Hair
Collection Methods	Invasive	Non-invasive	Invasive	Noninvasive	Noninvasive
Principal Analyte	Parent drug or metabolites	Parent drug	Metabolites	Parent drug and Metabolites	Parent drug and metabolites
Window of Detection	up to 12 hours	*up to 24 hours	up to 3 days	Days	Months
Disadvantages	very narrow window of detection	narrow window of detection small sample amount limits repeat analysis	Specimen Adulteration Observed collection an invasion of privacy	Contamination of specimen during removal of collection device	Hair color and texture bias

* BZE can be measured in saliva up to 36 hours after use (21)

Reproduced with permission from Blackwell Publishing; Saliva Testing for Drugs of Abuse, Edward J. Cone, page 92 (20) In: Saliva as a Diagnostic Fluid. Editors Daniel Malamud and Lawrence Tabak, Published by the New York Academy of Sciences, Volume 694, 1993

Table 5: Advantages, Disadvantages of Specimens for Drug Testing

Type	Advantages	Disadvantages
Urine	• Intermediate window of detection (up to 3 days after drug use) • May detect marijuana up to 30 days inn chronic users. • Extensive scientific basis for testing methodology • Cutoffs established • Easily tested by commercial screening methods • Measures drug metabolites	• Must be supervised (intrusion of privacy) • Drug concentration influenced by hydration • Susceptible to tampering (adulteration) • Acidity (pH) of urine will affect the concentration of metabolites detected.
Oral Fluid	• Useful in the detection of recent drug use (up to 24 hours) • Easy access/non invasive • Resistant to tampering especially substitution because of observed collection. • Drug concentrations similar to blood • Measures parent drug	• Narrow window of detection (up to 24 hours after use) • Marijuana has a shorter window of detection than most drugs. • Oral contamination by drugs that are smoked or administered intra nasally. • Not available in Canada as point of care testing (other than saliva alcohol testing) • Limited sample amount obtained, repeat testing may not be possible
Hair	• Provides a longer window of detection (between 7 and 90 days after drug use • Resistant to tampering due to observed collection • Easy of collection	• Cannot detect recent drug use • Potential hair color and hair texture interference • Possible environmental contamination for some drug classes • Susceptible to adulteration by treating hair before collection
Sweat	• Provide cumulative measure of drug exposure • Can monitor drug intake for a period of days to weeks • Noninvasive specimen collection • Collection device is relatively tamper-proof • Yields higher proportions of parent drugs, such as cocaine, heroin or marijuana compared to urine	• Large variation in sweat production • Specimen volume unknown • Limited collection devices • High inter-subject variability • Risk of accidental removal of collection device • Risk of external contamination during application or removal • Cannot detect prior exposure • Uniform cut-off levels have not been established
Blood	Resistant to tampering	Narrow window of detection (12 hours) Invasive Risk of blood borne pathogen contamination to health care worker during specimen collection.

Urine versus Saliva

Two main differences regarding drug quantification should be noted between oral fluid and urine testing. First, the concentration of target drugs or metabolites found in oral fluid is lower than that found in urine. Second, the windows of detection in oral fluid will be shorter than that of urine (12). The detection period

in any specimen medium is dose-dependent with larger doses having a longer period of detection. (15) Cone et al. (12) suggests that by selecting appropriate cut-off concentrations, it should be possible to approximately match the performance of saliva testing to urine testing. Common ranges are reported in Table 6. (4) However, the clinician should consult the ranges used with the specific POC test kit or laboratory to accurately interpret the test results. Cut-off levels for oral testing are discussed under the section *New Technology Being Reviewed*.

Table 6: Recommended Cut-Off Values for a Positive Result for Urine Drug Testing

Drug	†Cut-off Concentrations (ng/mL)		Analytes Tested in Urine by Confirmation Testing	‡Urine Detection Time (days)
	Initial Testing	Confirmation		
Ampthetamine	1,000	500	Amphetamine	2-4
Barbiturates	200	200	Amobarbital, other barbiturates	2-4 for short acting; up to 30 for long acting
Benzodiazepines	200	200	Oxazepam, diazepam, others	Up to 30 for long acting
Cocaine	300	150	Benzoylecgonine	1-3 for sporadic use; up to 12 for chronic use
Codeine	300	300, 300	Codeine, morphine	1-3
Heroin	300	300, 10	Morphine, 6-acetylmorphine	1-3
Marijuana	100, 50, 20	15	Tetra-hydro-cannabinol (THC)	1-3 for casual use; up to 30 for chronic use
Methadone	300	300	Methadone	2-4
Methamphetamine	1,000	500, 200	Methamphetamine, Amphetamine	2-4
Phencyclidine	25	25	Phencylidine	2-7 for casual use; up to 30 for chronic use

†Values above cut-off values are interpreted as positive.
‡Duration of time on average that drug metabolite can be detected by test.

Collection Methods

Because of the possibility of adulterated urine specimens, supervised urine specimen collection has been recommended. (2) Alternative methods include unsupervised collection with temperature testing of the urine, or mandatory volume collection with or without temperature testing. Other body fluid specimens including blood and saliva can be obtained under direct supervision without invasion of privacy. Moran et al.(10) conducted a clinic-based study to determine whether unsupervised urine collection with temperature testing was as reliable as supervised and unsupervised volume collection (50mL quantity and temperature tested). One hundred and twenty-five persons enrolled in an opiate treatment program in Alberta, Canada participated. Six samples were collected from each patient during 6 separate visits (1 sample every visit) according to the following schedule: (1) unsupervised (baseline); (2) supervised; (3) unsupervised; (4) supervised; (5) unsupervised with verbal instruction for 50mL quantity; and (6) unsupervised with temperature testing and mandatory 50mL quantity. Urine samples were tested for barbiturates, benzodiazpines, cannabis, cocaine, methadone, opiates and ethanol using EIA and results were confirmed by GC/MS. Eighty patients provided samples at all 6 time points. The study sample age ranged between 25 to 64 years of age (mean age of 40 years) and 66% were male. Persons had been enrolled in the opiate treatment program from 2 months to 18 years. Results indicated there was no significant difference in the number of positive urine samples between the 6 collection time periods or

across collection methods. The authors concluded that of the 3 collection methods evaluated (supervised, unsupervised and volume controlled) none was superior to the other in terms of detecting a positive test. The authors indicate that while laboratory costs are similar across collection methods, the resource costs may be lower with unsupervised collection methods. Limitations of this study include a high drop out rate as well as a lack of randomization to type of collection method.

Frequency of Drug Testing

Federal Regulations in the United States require 8 urine tests in the first year of MMT with quarterly tests done thereafter.(22) Wasserman et al. (22) determined the effectiveness of an intensive (twice per week) urine testing schedule compared to a less frequent testing schedule for identifying opioid and cocaine users. One hundred and sixty-six patients (67% male) enrolled in one of 4 MMT programs in the San Francisco Bay area for more than 3 months but less than 18 months participated in the study. The sampling frame included 528 patients of whom 243 were excluded for self-reported recent drug use, and 110 declined study participation. One hundred and seventy-five patients consented to treatment of which 9 had insufficient urine sample data (no sample collected or no sample results available). The mean age was 41.7 years (standard deviation [SD], 8.5) and the median duration of treatment was 6 months (interquartile range [IQR], 5). Patients in the intensive treatment group were asked to provide an unsupervised temperature monitored urine specimen twice a week over a 10-week period. Results of the urinalysis were not shared with the MMT program the patient was enrolled in, and therefore did not affect the treatment the patient was receiving. The patient also continued to provide urine specimens according to the standard frequency of the MMT program (once per week or once every 3-4 weeks) in which he/she was enrolled. All urine samples were tested for methadone, opioids, cocaine, marijuana, benzodiazepines, amphetamines, barbiturates, propoxyphene and phencyclidine initially using EIA technique first and then using either gas-liquid chromatography or thin-layer chromatography. Results of the patient's urinalysis from the intensive frequency urine testing schedule (treatment specimens) were compared with his/hers from the standard frequency urine testing schedule (control specimens). Urine results for the standard frequency testing schedule were obtained by chart review. Results indicated that in the intensive frequency treatment group, 117 (70.5%) patients were positive for opioids other than methadone and 102 (61.4%) were positive for cocaine whereas in the standard frequency schedule group only 77 (46.4%) patients were positive for opioids and 60 (36.1%) for cocaine. The intensive frequency schedule identified 51.9% (P <.001) more opioid users and 70.0% (P <.001) more cocaine users than the standard frequency program. Of the opioid drug users identified by the standard frequency schedule 93.5% (72/77) were correctly identified by the intensive program. However, half (45/89) of the patients identified as opioid negative (nondrug users) in the standard frequency schedule were identified as opioid positive (drug users) in the intensive frequency schedule. Results were similar for cocaine: of the 60 patients that were positive in the standard frequency schedule, 59 were found positive in the intensive frequency schedule and of the 106 patients that were negative on the standard frequency schedule, 43/106 (40.5%) were positive in the intensive frequency schedule. Limitations of the study included: standard frequency urine and intensive frequency urine were not collected at the same time point and the use of difference methodologies to analyze the urine specimen. It is therefore difficult to determine the accuracy of any false-positive and negative test results in either frequency testing program. As well, the results of the study may not be generalizable to persons enrolled in a MMT program longer than 18 months. Finally, the urine collection procedures of the 4 clinic sites participating in the standard frequency treatment were not uniform. Differences in the frequency of collection for the standard frequency schedule, how the specimen was collected (supervised vs. unsupervised), type of assay used, metabolites tested for, and administrative cut-off values used were noted between treatment groups. Of interest, in 14 intensive frequency schedule urine specimens, the patient was deemed negative but the standard frequency schedule urine specimen taken the same day was found to be positive. The different collection techniques,

assays and administrative cut-offs may have contributed to this systematic error.

Goldstein and Brown (23) suggest that there is no simple answer to how frequently a urine test should be done. Using methods for computing the probability of doing a urine test and detecting an event defined as absence of methadone and 2-ethylidene- 1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP), they determined that the probability of detecting an event that occurred randomly on average once every 7 days (1/7) with a testing interval of 1 urine test every 5 days (1/5) would be 3% (1/7 x 1/5). Thus, 97% of events would be missed. Increasing the interval to twice every 5 days would increase the probability of detection to 5.7% (1/7 x 2/5) or about once in every 17 urine tests. Infrequent testing primarily identifies persons who use substances frequently (daily for example). Early detection and treatment may require more frequent testing intervals. (4) Drug testing frequency should be sufficient to assist in making an informed decision about treatment. (4) Frequency of testing should be based on the patient's treatment progress and determined by clinical judgment. (1) In general, it is suggested that more testing should be performed earlier in treatment than later when the patient is stabilized. (4)

The CPSO (2) recommends that at least 1 urine drug test be collected and interpreted before methadone treatment begins. Urine testing can then be done on a fixed or random schedule. Weekly urine drug tests are recommended during the stabilization phase and should continue during the maintenance phase. Once 6 months of negative weekly urine drug tests are documented and/or the patient has acquired full carries privileges, urine collection may be reduced to biweekly or monthly depending on the patient's stability, pattern of drug use and validity of self-report. (2)

New Technology Being Reviewed

The Intercept oral fluid collection device consists of an absorbent pad mounted on a plastic stick. The pad is coated with common salts. The absorbent pad is inserted into the mouth and placed between the cheek and gums for 3 minutes. The pad absorbs the oral fluid. After 3 minutes (range 2min-5min) the collection device is removed from the mouth and the absorbent pad is placed in a small vial which contains 0.8mL of pH-balanced preservative for transportation to a laboratory for analysis. It is recommended that the person undergoing oral fluid drug testing have nothing to eat or drink for a 10-minute period before the oral fluid specimen is collected. Likewise, it is recommended that the person be observed for the duration of the collection period to prevent tampering with the specimen. An average of 0.4 mL of saliva can be collected. The specimen may be stored at 4C to 37C and tested within 21 days of collection (or within 6 weeks if frozen).

In the laboratory, the oral fluid is extracted from the vial after centrifugation and a screening test is completed to eliminate negative specimens. The specimen is analyzed first by EIA with positive specimens sent for chromatography to identify the specific drug.

The cut-off concentrations for saliva drug testing using the Intercept oral fluid collection device and the cross-reactivity profile for the device is reported in Tables 7 and 8 respectively.

Table 7: **Cut-Off Values for Positive Result for Saliva Drug Testing using Intercept Oral Fluid Collection Device**

Drug	†Immunoassay Cut-off Concentrations (ng/mL)	‡Saliva Detection Time (days)
Ampthetamine	100	1-2
Barbiturates	20	1-2
Benzodiazepines	1	1-3
Cocaine Metabolite	5	1-2

Opiates	10	1-2
Cannabinoids (TCH)	1	1-2
Methadone	5	1-3 (occasional use) 3-5 (chronic use)
Methamphetamine	40	1-2
Phencyclidine	1	1-2

*Information provided by Orasure Technologies Ltd. Bethlehem, PA
†Values above cut-off values are interpreted as positive.
‡Duration of time on average that drug metabolite can be detected by test.

Table 8: Cross-Reactivity Profiles for Intercept Oral Fluid Micro-Plate Assay *

Analyte	Cross Reactivity Analyte	% of Cross Reactive Analyte detected	Level of Detection (ng/mL)
Amphetamine Specific	D-amphetamine	100	100
	MDA	49	204
	PMA	32	1553
	Mephentermine	15	685
Barbiturates	Secobarbital	100	20
	Amobarbital	43	46
	Aprobarbital	29	69
	Butabarbital	185	11
	Butalbital	109	18
	Pentobarbital	68	29
	Phenobarbitla	50	40
	Talbutal	170	12
Benzodiazepines	Nordiazepam	100	1
	Alprozolam (Xanax)	151	0.66
	Chlorazepate	70	1.44
	Lonezepam	0.5	66.66
	Desalkylflurazepam	17	5.81
	Diazepam	135	0.7
	Estzolam	130	0.8
	Flurazepam	49	2.0
	alph-Hydrozyalprazolam	10	10.1
	Medazepam	17	5.7
	Midazolam	49	2.0
	Nitrazepam	39	2.5
	Prazepam	107	0.9
	Temazepam	55	1.8
	Triazolam	26	3.8
Cannabinoids	Δ^9-THC	100	1
	Δ^8-THC	105	0.94
	11-nor9-CarboxyΔ^9-THC	279	0.36
	11-Hydroxy-Δ^9-THC	174	0.57
	Cannabinol	15	6.62
Cocaine Metabolite	Benzoylecgonine	100	5
	Cocaine	64	7.8
	Cocaethylene	200	2.5
Methadone	LAAM	18	28
	Methadone	100	5
Methamphetamine	D-Methamphetamine	100	40
	Fenfluramine	26	154
	MDMA	288	14
	MDEA	69	58
	PMMA	645	6
Opiates	Morphine	100	1.0
	6-Acetylmorphine	65	1.56
	Codeine	>100	0.25
	Diacetylmorphine	43	2.27
	Dihydrocodeine	185	0.54
	Hydrocodone	76	1.32

Analyte	Cross Reactivity Analyte	% of Cross Reactive Analyte detected	Level of Detection (ng/mL)
	Hydromorphine	20	5.05
	Oxycodone	1	100
	Dexromethrophan	0.05	2000
Phencyclidine	Phencyclidine	100	1
	Dextromethorphan	0.004	24,331
	Doxylamine	0.002	61,350
	Ketamine	0.004	26,316
	Diphenhydramine	0.024	4,082

* Data provided by Orasure Technologies Inc., Bethlehem, PA

Regulatory Status

The Intercept oral fluid collection device and Micro-plate EIA is the only oral fluid test kit licensed by Health Canada for substance abuse testing. Both devices are rated as class 2 devices by Health Canada. (Table 9).

Table 9: Regulatory Status*

Company Name	Device Class	Licence	Licence Name	Trade Name	Purpose/Intended Use
Orasure Technologies, Inc.	2	64485	Intercept oral specimen collection device	Intercept oral specimen collection kit	Intended for use in the collection, preservation and transport of oral specimens. For testing for any of the following drugs using the Orasure technologies intercept micro-plate assays- Amphetamines, Barbiturates, Benzodiazepines, Cocaine, Marijuana, Methadone, opiates, phencyclidine.
	2	30027	Methadone Intercept Micro-Plate EIA (saliva)	Methadone Intercept Micro-plate EIA (saliva)	Is intended for use by clinical laboratories in the qualitative determination of methadone in oral fluid.
	2	19230	Opiates Intercept Micro-Plate EIA	Opiates Micro-Plate EIA	Intended for use in the qualitative determination of opiates in oral fluid collected with the Intercept drugs of abuse (DOA) Oral Specimen collection device.
	2	23498	Methamphetamine Intercept Micro-Plate EIA	Methamphetamine Intercept Micro-Plate EIA	Intended for use by clinical laboratories in the qualitative determination of methamphetamine in oral fluids.
	2	23500	Cocaine Metabolite Intercept Micro-Plate EIA	Cocaine Metabolite Intercept Micro-Plate EIA	Intended for use by clinical laboratories in the qualitative determination of cocaine and cocaine metabolites in oral fluid.

Company Name	Device Class	Licence	Licence Name	Trade Name	Purpose/Intended Use
	2	23502	Amphetamine Specific Intercept Micro-Plate EIA	Amphetamine Specific Intercept Micro-Plate EIA	Intended for use by clinical laboratories in the qualitative determination of amphetamine in oral fluid.
	2	23503	PCP Intercept Micro-Plate EIA	PCP Intercept Micro-Plate EIA	Intended for use by clinical laboratories in the qualitative determination of phencyclidine in oral fluid.
	2	30029	Cannabinoids Intercept Micro-Plate EIA (saliva)	Cannabinoids Intercept Micro-Plate EIA (saliva)	Intended for use by clinical laboratories in the qualitative determination of cannabinoids in oral fluid.
	2	30031	Barbiturates Intercept Micro=Plate EIA (Saliva)	Barbiturates Intercept Micro=Plate EIA (Saliva)	Intended for use by clinical laboratories in the qualitative determination of barbiturates in oral fluid.
	2	60684	Benzodiazepines Intercept Micro-Plate EIA	Benzodiazepines Intercept Micro-Plate EIA	Intended for use in the qualitative determination of benzodiazepines in oral fluid collected with the Intercept oral specimen collection device.
	3	912	Q.E.D. Saliva Alcohol Test†	Q.E.D Ethanol Control For A150	Saliva alcohol test is used for quantitative alcohol detection.

*EIA refers to enzyme immunoassay; PCP refers to Phencyclidine.
†Point-of- care testing kit

Literature Review on Effectiveness

Research Question

What is the diagnostic utility of oral fluid testing collected with the Intercept oral fluid collection device?

Methods

Inclusion criteria

- Studies evaluating paired urine and oral fluid specimens from the same individual
- Oral fluid is collected using the Intercept oral fluid collection device.
- Population studied is drug users.

Exclusion criteria

- Studies testing for marijuana (THC) only.

Outcomes:

- Sensitivity and specificity of oral fluid testing compared to urinalysis for methadone (methadone metabolite), opiates, cocaine, benzodiazepines, and alcohol.

Study Eligibility

One reviewer who was not blinded to author, institution, and journal of publication evaluated the eligibility of the citations retrieved from the literature search. Articles were excluded based on information reported in the title and abstract, and the full document of potentially relevant articles was retrieved for further assessment.

Data Extraction

One reviewer extracted data from the included studies. Information on the study population, study methods, study interventions, and study outcomes, were recorded. Where possible, the primary author of the study was contacted for missing data.

Quality of the Body of Evidence

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) system (24) was used to evaluate the overall quality of the body of evidence (defined as 1 or more studies) supporting the research questions explored in this systematic review. A description of the GRADE system is reported in Appendix 1.

Results of Literature Review

Summary of Medical Advisory Secretariat Review

The Medical Advisory Secretariat conducted a computerized search of the literature in the following databases:

- OVID MEDLINE
- Ovid In Process and Not-Yet-Indexed Citations
- EMBASE
- Cochrane Library

The literature search was limited to English-language articles with human subjects published between 1996 and September 2006. Letters, editorial, comments, case reports, and non-systematic reviews were excluded. The literature search strategy is available in Appendix 2.[1]

Other relevant databases searched included, PsychInfo, the Center for Substance Abuse Research (CESAR) and the International Health Technology Assessment Agency database. The World Wide Web was searched for published guidelines, assessments, and policy decisions. Bibliographies of references of relevant papers were searched for additional references that may have been missed in the computerized database search.

A total of 854 potential citations were retrieved. After reviewing titles and abstracts, 2 met the inclusion and exclusion criteria. Two other relevant studies were found after corresponding with the author of the 2 studies retrieved from the literature search. Therefore a total of 4 published studies are included in this analysis (Table 10).

Table 10: Quality of Evidence of Included Studies*

Study Design	Level of Evidence	Number of Eligible Studies
Large RCT, systematic reviews of RCT	1	0
Large RCT unpublished but reported to an international scientific meeting	1(g)	0
Small RCT	2	0
Small RCT unpublished but reported to an international scientific meeting	2(g)	0
Non-RCT with contemporaneous controls	3a	4
Non-RCT with historical controls	3b	0
Non-RCT presented at international conference	3(g)	0
Surveillance (database or register)	4a	0
Case series (multisite)	4b	0
Case series (single site)	4c	0
Retrospective review, modeling	4d	0
Case series presented at international conference	4(g)	0

* RCT refers to randomized controlled trial, g, grey literature.

[1] The search strategy was very broad, and considered various methods of drug detection and issues around patient compliance. After the search was run, the decision was made to focus only on articles evaluating the Intercept Oral Specimen Collection Device.

Description of Included Studies

Study 1

A Comparison Between the Intercept Oral Fluid Collection Device and Urinalysis Among Baltimore City Probationers, 2006 (25)

Yacoubian and Cone (25) compared the results of urinalysis by EIA and GC/MS to oral fluid testing by EIA and GC/MS among Baltimore city probationers. **METHODS:** Paired oral fluid and urine specimens were obtained from 288 adults. Unsupervised urine specimens were collected on the same day as the oral fluid specimens but after the study subjects completed an interview administered survey. Urine specimens were screened in the laboratory using Syva Enzyme Multiplied Immunoassay Test II Plus (an EMIT test) using the following cut-offs: cocaine and opiates, 300ng/mL; benzodiazepines, 200ng/mL; marijuana, 50ng/mL; and Phencyclidine [PCP] 25ng/mL. All positive urine tests were confirmed with GC/MS for opiates including morphine, codeine, hydrocodone, hydromorphone, and oxycodone; benzodiazepines including hydroxy alprazolam, nordiazepam, oxazepam, lorazepam, diazepam, temazepam, hydroxy ethyl flurazepam, hydroxy midazolam, and hydroxy triazolam, as well as for cocaine metabolite, PCP and marijuana. Oral fluid samples were collected using the Intercept collection device under direct supervision. An Intercept collection swab was rubbed between the lower cheeks and gums on each side (1 swab each side) of the mouth simultaneously for 3 minutes. Saliva stimulation was not needed. The swabs were inserted into a vial and the sample was stored for 1 week before being shipped to the laboratory for analysis. The oral fluid samples were analysed using the Micro-plate Enzyme Immunoassay (an EIA test) at the following cut-offs: benzodiazepines 1ng/mL; cocaine metabolite (benzoylecgonine), 5ng/mL; opiates, 10ng/mL; and marijuana (delta-9-tetrahydrocannabionol [THC]) and PCP, 1ng/mL. All positive samples were confirmed with GC/MS laboratory analysis for the following drugs: hydrocodone, hydromorphone, oxycodone, morphine, codeine, 6-aceytl morphine, cocaine metabolite, alprazolam, estazolam, diazepam, mordiazepam, prazepam, PCP and THC. A unique identification number linked the pairs of oral fluid and urine samples per patient. Urine specimens were analyzed in a different laboratory than the oral fluid specimens. Study investigators also surveyed both the probationer and the probation officers to determine their views on the usefulness of the oral fluid collection method. The GC/MS urine results were used as the reference standard. **RESULTS:** The sampling frame included 343 probationers. Of these, 288 (84%) provided oral fluid and urine specimens. A lab error reduced the number of paired oral fluid and urine specimens to 223 probationers. Survey data was obtained from 279 probationers and 50 probation staff. The mean age of the probationers was 34.4 years of age (range, 18-67). Eighty percent of subjects were on probation for a drug-related offense. The sensitivity and specificity for the following comparisons were performed:

1. Oral fluid EIA compared with the oral fluid GC/MS
2. Urinalysis EMIT compared with the urinalysis by GC/MS
3. Oral fluid EIA compared to the urinalysis by GC/MS
4. Oral fluid EIA compared to the urinalysis by EMIT

Results of these comparisons are reported in Tables 11 through 14.

Table 11: Sensitivity and Specificity of Oral Fluid EIA Compared With Oral Fluid by GC/MS

Drug	Sensitivity	Specificity
Opiates	89	100
Benzodiazepines	100	99
Cocaine	96	98
Marijuana	84	100
Phencyclidine	100	99

Table 12: Sensitivity and Specificity of Urinalysis by EMIT Compared With Urinalysis by GC/MS.

Drug	Sensitivity	Specificity
Opiates	100	98
Benzodiazepines	100	100
Cocaine	95	100
Marijuana	97	98
Phencyclidine	n/a	100

Table 13: Sensitivity and Specificity of Oral Fluid EIA Compared With Urinalysis by GC/MS.

Drug	Sensitivity	Specificity
Opiates	77	96
Benzodiazepines	100	99
Cocaine	92	96
Marijuana	39	98
Phencyclidine	n/a	99

Table 14: Sensitivity and Specificity of Oral Fluid EIA Compared With Urinalysis by EMIT

Drug	Sensitivity	Specificity
Opiates	75	97
Benzodiazepines	80	99
Cocaine	94	94
Marijuana	35	97
Phencyclidine	n/a	99

Survey Results

Results of the survey administered to probationers and staff are reported in Table 15 and 16 respectively.

Table 15: Results of Survey With Probationers

Questions	Response
Compared to the urine specimens, did you feel more comfortable providing the oral fluid compared with urine specimen?	Yes=74%
Do you feel that oral fluid specimens are less invasive than urine specimens?	Yes=74%
Did it take longer to provide a urine specimen compared to an oral specimen?	Yes=53%
Have you ever tried to adulterate your urine specimen?	Yes=97%
Do you think that oral fluid specimens could be adulterated?	Yes =13%
How would you rate the overall oral fluid collection experience compared to the urine collection experience?	Very much better=52% Somewhat better=20% The same=23% Worse=5%

Table 16: Results of Survey with Probation Staff

Questions	Response
Would you feel more comfortable collecting an oral fluid specimen?	Yes=76%
Do you feel that the collection of oral fluid specimens would be less invasive than urine specimens?	Yes=76%
Do you think it would take longer to collect the urine specimen compared with the oral fluid specimen?	Yes=88%
Have you ever had clients try to adulterate their urine specimen?	Yes=86%
Do you think oral fluid specimens could be adulterated?	Yes = 24%
Compared to the urine specimens how would you rate the overall oral fluid collection experience compared to the urine collection experience	Very much better= 56% Somewhat better= 32% The same= 10% Worse= 2%

CONCLUSION: The sensitivity of the oral fluid test for opiates and marijuana is lower than that for benzodiazepines and cocaine. The sensitivity of oral fluid testing for opiates remained at 77% when oral fluid by GC/MS was compared with urinalysis by GC/MS. (Personal communication, G.S.Yacoubian, November 21, 2006) Of note, the sensitivity for opiates was 89% when oral fluid EIA was compared with oral fluid GC/MS, whereas it was 100% when urinalysis EIA was compared with urinalysis GC/MS. This may support the necessity to use GC/MS analysis with oral fluid specimens to reduce the number of false-negatives. Probationers and probation staff preferred the oral fluid collection compared to urine collection. The authors conclude that the usefulness of oral fluid testing should be determined after considering issues of personal invasiveness, ease of collection, cost, accuracy and consequences of false-positives or negative results. LIMITATIONS: Results of this study will be generalizable to those tests that have similar cut-offs to the urinalysis EMIT and oral fluid EIA test used in this study. Because of the narrow window of detection of oral fluids (up to 24 hours) compared to urine (1-3 days) the sensitivity for opiates and marijuana may be lower compared to urinalysis if probationers abstained from recent drug use within 24 hours before their testing date but not 2 to 3 days before the test date. The study did not measure the sensitivity and specificity for methadone. It is unknown if random or consecutive enrollment was undertaken. Finally, urine collection was unsupervised.

Study 2

A Comparison of the Intercept Oral Specimen Collection Device (IOSCD) to Laboratory Urinalysis Among Baltimore City Treatment Clients, 2004 (26)

Yacoubian and Wish (26) determined the sensitivity and specificity of oral fluid testing to urinalysis in 169 adults from 2 intensive outpatient clinics and 1 MMT clinic in Baltimore City, Maryland, United States. **METHODS:** Patients were enrolled in the study consecutively as they presented to the facility for treatment. Paired urine and oral fluid specimens were collected from each study participant. Urine collection was not supervised. Urine specimens were sent directly to the laboratory and analyzed by the EMIT for amphetamines (cut-off 300ng/mL), marijuana (cut-off 100ng/mL), benzodiazepines, metabolite (crack and powder), cocaine, methadone, and opiates (cut-off 300ng/mL). Oral fluid specimens were sent to a different laboratory to that of the urine specimens and were analyzed using ELISA for the same drugs

at comparable cut-off values to the urinalysis EMIT. No GC/MS analyses were performed on either the urine or oral fluid specimens. A unique identifier number linked the paired urine and oral fluid samples. Urinalysis by EMIT was used as the reference standard. **RESULTS:** Of the 169 paired urine specimens, 163 were analyzed. Three oral specimens were of insufficient quantity to analyze and 3 urinalysis results were lost. The mean age of the participants was 43 years. Sixty percent were from an outpatient drug treatment facility and 40% were attending a methadone maintenance clinic. There was 1 amphetamine-positive urinalysis detected and therefore no further analysis was completed on this drug group. The sensitivity and specificity of oral fluids compared to urinalysis for 4 drug classes are reported in Table 17.

Table 17: Sensitivity and Specificity of Oral Fluid ELISA Compared With Urinalysis EMIT

Drug	Sensitivity	Specificity
Methadone	100	92
Opiates	83	99
Benzodiazepines	100	100
Cocaine	82	96
Marijuana	39	93

CONCLUSION: The sensitivity of the oral fluid test is 100% for methadone, 83% for opiates, 100% for benzodiazepines, 82% for cocaine and 39% for marijuana. Specificity is at least 92%. **STUDY LIMITATIONS:** GC/MS testing was not done on the oral or urine specimens. Urine collection was unsupervised.

Study 3

A Comparison of the Intercept Oral Specimen Collection Device to Laboratory Urinalysis Among Baltimore City Arrestees, 2002 (27).

Wish et al.(27) compared oral fluid testing with urinalysis in a sample of 284 urban arrestees in Baltimore City, Maryland, United States known to be recent users of cocaine and heroin. **METHODS:** Arrestees were selected at random from a sampling frame of persons in custody for less than 48 hours. After consent was obtained, the participant was interviewed and then asked to provide a urine specimen. Urine collection was not supervised. Urine samples were sent to a single laboratory that used the EMIT to screen for amphetamines, marijuana, metabolite (crack and powder), cocaine, opiates, and PCP. Amphetamine-positive urine specimens only were further analyzed with gas chromatography (GC). Cut-off levels were 300 ng/mL for amphetamines, 100ng/mL for marijuana, 300ng/mL for cocaine and opiates, and 25ng/mL for PCP. Participants were also asked to supply an oral specimen obtained under direct supervision using the Intercept oral specimen collection device. The Intercept swab was rubbed between the lower cheek and gums for 2 minutes and the swab was then inserted into a vial for transportation to the lab. No saliva stimulation was used by the participant. Oral specimens were screened for the same 5 substances as were the urine specimens but they were sent to a different laboratory than the urine specimens. Cut-off levels for oral fluids were 40ng/mLl for amphetamines, 5 ng/mL for cocaine, 10ng/mL for opiates, and 1ng/mL for marijuana and PCP. Neither urine nor oral fluid specimens were analyzed by GC/MS **RESULTS:** Urine and saliva specimens were obtained from 284 arrestees (85% of sampling frame). There were 2 amphetamine-positive but 0 PCP-positive urinalyses and because of this, the sensitivity and specificity of these substances were not determined. The sensitivity and specificity was determined for cocaine, opiates and marijuana only (Table 18). Urinalysis by EMIT was used as the reference standard.

Table 18: Sensitivity and Specificity of Oral Fluid EIA Compared With Urinalysis EMIT

DRUG	Saliva Sensitivity (%)	Saliva Specificity (%)
Opiates	90	99
Cocaine	95	98
Marijuana	56	99

CONCLUSION: The authors conclude that oral fluid analysis is as effective as laboratory urinalysis for the detection of recent cocaine and opiate use, but is less useful for recent marijuana use. **STUDY LIMITATIONS:** Urine and oral fluid samples were analyzed by GC/MS. The urine collection was not supervised.

Study 4

A Comparison of Saliva Testing to Urinalysis in an Arrestee Population, 2001 (19).
Yacoubian, Wish and Perez (19) compared oral fluid drug testing using the Intercept oral collection system to urinalysis for accuracy in drug detection among adult arrestees chosen at random in 3 counties within the state of Maryland, United States. **METHODS:** One hundred and fourteen arrestees were interviewed regarding their history of drug use. An unsupervised urine sample was obtained and sent to a single laboratory that analyzed the specimen using the EMIT. Urine specimens were screened for amphetamines, barbiturates, benzodiazepines, marijuana, metabolite (crack and powder) cocaine, methadone, methaqualone, opiates, PCP and propoxyphene. All amphetamine-positive urine specimens were also analyzed by GC. EMIT cut-off levels were: amphetamines, 1000ng/mL (300ng/mL for GC); marijuana, 100ng/mL; PCP, 25ng/mL; cocaine and opiates, 300ng/mL. Oral fluid specimens were collected after the urine specimens. A swab was rubbed between the lower cheek and gums for 2 minutes. Saliva specimens were sent to a different laboratory to that used for the urinalysis but which also used EMIT testing to screen for amphetamines, metabolite (crack and powder) cocaine, marijuana, opiates, and PCPs. EMIT cut-off levels were: amphetamine, 40ng/mL; cocaine, 5ng/mL; opiates, 10ng/mLL and marijuana and PCP, 1ng/mL. **RESULTS:** Sensitivity and specificity were determined for cocaine, opiates and marijuana but not amphetamine or PCP as these substances were not detected. The sensitivity and specificity of oral fluid testing compared with urinalysis is reported in Table 19. Results of urinalysis indicated that 19% of arrestees used cocaine, 7% used opiates and 18% used marijuana. Saliva testing indicated that 20% used cocaine, 6% opiates but only 1% marijuana.

Table 19: Sensitivity and Specificity of oral fluid EMIT compared with urinalysis EMIT

DRUG	Saliva Sensitivity (%)	Saliva Specificity (%)
Opiates (n=8)	88	100
Cocaine (n=22)	100	99
Marijuana (n=21)	5	100

CONLUSION: The authors state that oral fluid testing may be useful for detecting recent cocaine and heroin use among chronic drug users, such as those who are likely to use the drug within 12 to 24 hours of the drug test. Oral fluid testing may not be useful to measure recent marijuana use.
STUDY LIMITATIONS: Of the 114 arrestees, 8 were opiate-positive and 22 were cocaine-positive by urinalysis. Therefore only 8 opiate-positive and 22-cocaine positive urine specimens were compared to their paired oral fluid specimen to determine the accuracy of oral fluid testing for opiate and cocaine detection. Urine collection was unsupervised.

Summary of Findings of Literature Review

A summary of the characteristics of the included studies is reported in Table 20.

Table 20: Characteristics of Included Studies*

Study	Population	N	Participants with Positive Drug Use as per Urinalysis % (n)		Comparison
Yacoubian 2006	Baltimore City, USA Probationers	223	Opiate Benzodiazepines Cocaine Marijuana PCP	14 (31) 1 (22) 17 (38) 15 (33) 0 (0)	OF EIA and urinalysis GC-MS OF EIA and urinalysis EMIT
Yacoubian 2004	60% outpatient clinic patients 40% MMT clinic patients	163	Methadone Opiates Benzodiazepines Cocaine Marijuana	44 (71) 18 (29) 4 (7) 24 (39) 8 (13)	OF ELISA and urinalysis EMIT
Wish 2002	Adult arrestees in Baltimore City, Maryland, USA	284	Opiates Cocaine Marijuana	46 (131) 42 (119) 26 (74)	OF EIA and urinalysis EMIT
Yacoubian 2001	Adult Arrestees in Anne Arundel, Charles and Prince George's counties within Maryland, USA	114	Opiates Cocaine Marijuana	7 (8) 19 (22) 18 (21)	OF EMIT and urinalysis EMIT

*EIA refers to enzyme immunoassay; EMIT, Enzyme Multiplied Immunoassay Test OF, oral fluid; PCP, Phencyclidine.

Grade Level

The body of evidence is limited to 4 clinical research studies. The GRADE assessment profile is reported in Tables 21 through to 24. The GRADE Level of the body of evidence for the outcomes of sensitivity and specificity for opiates is moderate, and for methadone is low.

TABLE 21: Grade Assessment Profile Sensitivity of Oral Fluid Testing for Opiates

Quality Assessment						Summary of Findings				
						No. of Subjects		Effect		
No. of studies	Design	Quality	Consistency	Directness	Other modifying factors	Intercept Oral Fluid	Urinalysis	Sensitivity %	Quality of body of evidence	Outcome
Outcome: Sensitivity of oral fluid testing for opiates (oral fluids collected with the Intercept Oral fluid collection device)										
4	Non-randomized Controlled MAS Level 3	Moderate	No inconsistency	Direct	none	784	784	75-90	Moderate	Critical

TABLE 22: Grade Assessment Profile Specificity of Oral Fluid Testing for Opiates

Quality Assessment						Summary of Findings				
						No. of Subjects		Effect		
No. of studies	Design	Quality	Consistency	Directness	Other modifying factors	Intercept Oral Fluid	Urinalysis	Specificity%	Quality of body of evidence	Outcome
Outcome: Specificity of oral fluid testing for opiates (oral fluids collected with the Intercept oral fluid collection device)										
4	Non-randomized Controlled MAS Level 3	Moderate	No inconsistency	Direct	none	784	784	96-100	Moderate	Critical

TABLE 23: Grade Assessment Profile Sensitivity of Oral Fluid Testing for Methadone

Quality Assessment						Summary of Findings				
						No. of Subjects		Effect		
No. of studies	Design	Quality	Consistency	Directness	Other modifying factors	Intercept Oral Fluid	Urinalysis	Sensitivity%	Quality of body of evidence	Outcome
Outcome: Sensitivity of oral fluid testing for methadone (oral fluids collected with the Intercept Oral Fluid Collection Device)										
1	Non-randomized Controlled MAS Level 3	Moderate	1 Study only	Direct	Sparse data, only one study	163	163	100	Low	Critical

TABLE 24: Grade Assessment Profile Specificity of Oral Fluid Testing for Methadone

Quality Assessment						Summary of Findings				
						No. of Subjects		Effect		
No. of studies	Design	Quality	Consistency	Directness	Other modifying factors	Intercept Oral Fluid	Urinalysis	Specificity%	Quality of body of evidence	Outcome
Outcome: Specificity of oral fluid testing for methadone (oral fluids collected with the Intercept oral fluid collection device)										
1	Non-randomized Controlled MAS Level 3	Moderate	1 Study only	Direct	Sparse data, only one study	163	163	92	Low	Critical

In the body of evidence, either urinalysis EIA or GC/MS were used as the criterion measure (gold standard) against which oral fluid testing was evaluated. Two issues require discussion: whether urinalysis is indeed an appropriate criterion measure and whether urinalysis EIA or GC/MS is the most appropriate criterion.

A criterion measure is by definition reliable and valid. Reliability reflects the amount of random and systematic error inherent in any measurement. (28) Validity determines if a test is measuring what it is intended to measure. A valid test is one in which there is a high degree of confidence in the inferences based on the results of the test. For a scale to be valid it must be reliable. Therefore reliability is a necessary but not sufficient condition for validity.

Other Health Technology Policy Assessments have evaluated the diagnostic utility of a new test as a replacement for a criterion measure. (29;30) Streiner and Norman (31) suggest that some reasons for developing a new test when a criterion measure already exists may include: that the existing test is expensive, is invasive, is dangerous, is time-consuming or that results may not be known until it is too late. Another reason may include that the newer test may have increased reliability compared to the criterion measure. New tests must be subjected to validation tests, either concurrent validation or predictive validity depending on the purpose of the test. The most commonly used design for concurrent validity is to administer the new test and the criterion measure at the same time /id}.(31) Results of the comparison may be analyzed with indices of sensitivity and specificity (31)or with a measure of correlation. If claims of a tests status as a criterion measure are thought to be false, then the new test must be validated by construct validity methodologies. A test often holds the status as a criterion measure because it is the best test that exists at the time but should also be supported by a theoretical construct.

Urinalysis is an accepted criterion measure for establishing exposure to drugs which are excreted primarily by the kidneys. The presence of the appropriate metabolite in the urine is a valid and reliable indication of exposure to the parent drug. However, reliability of this test may be skewed for those people who metabolize the parent drug more slowly than average, who ingest a drug outside the window of detection for urinalysis, and for non-drug substances with metabolites similar to those for drugs (e.g., poppy seeds). Similarly, reliability of oral fluid testing is hampered by fast metabolism of the parent drug, as well as ingestion of the drug outside the window of detection as well as false-positives from substances such as poppy seeds. Urinalysis is also the standard of practice in Ontario, nationally and internationally for drug testing in MMT programs. Thus, a comparison of a proposed new method of drug testing to urinalysis would be scientifically and clinically meaningful.

In the body of evidence evaluated in this report, urinalysis either by EIA or GC/MS, has been used as the criterion measure. Concurrent validity of oral fluid testing has been undertaken by comparing results of oral fluid testing to those of urinalysis, expressed as indices of sensitivity and specificity. This comparison is sufficient for the purpose of test validation.

The optimal reliability is achieved using GC/MS analytical methods. Therefore comparison of the new test (oral fluid testing) by GC/MS to urinalysis by GC/MS would be optimal to assess validity. However, urinalysis is often done as a POC testing. Therefore comparison of the new test to urinalysis by EIA has practical utility. There is no oral fluid POC testing procedure for drugs of abuse other than alcohol. This may reduce the practical utility of oral fluid testing.

The GRADE assessment assigns a GRADE level of low to bodies of evidence comprised of studies that are not randomized controlled trial (RCT) designs. There are opportunities within the GRADING system for such bodies of evidence to improve their designation. However, the authors of the GRADING system acknowledge that it may not be applicable for bodies of evidence that evaluate diagnostic technologies. This is because the RCT study design is not always a useful design for evaluating the diagnostic utility of new tests. The Grade Working Group is developing a document that will aid in evaluating the quality of evidence for diagnostic studies.(32) Until this becomes available, where evidence of diagnostic utility is concerned the Medical Advisory Secretariat has modified the current GRADE system such that the MAS Level III evidence (non-RCT with contemporaneous controls) is given a GRADE level of moderate.

Cut-Off Value

A summary of the immunoassay test cut-off values used in each study is presented in Table 25. Similar cut-off values were used for the oral fluid screening assay across the 4 studies. The authors did not report

the screening cut-off value for methadone in the oral fluid studies. Similar cut-off values were used between studies on all drug classes except for marijuana. A cut-off of 50ng/mL was used in Yacoubian 2006, and 100ng/mL was used in the other 3 studies. Cone (11) states that a change in the cutoff concentration of an assay can substantially change its ability to detect a drug or drug metabolite. Researchers must select drug assays with equivalent performance characteristics if comparisons within and between studies are to be made.(11)

Table 25: Cut-Off Values for Oral Fluid and Urinalysis Screening Immunoassays.

Drug	Oral Fluid Cutoffs (ng/mL)				Urinalysis Cutoffs (ng/mL)			
	Yacoubian 2001	Wish 2002	Yacoubian 2004	Yacoubian 2006	Yacoubian 2001	Wish 2002	Yacoubian 2004	Yacoubian 2006
Methadone	n/a	n/a	not reported	n/a	n/a	n/a	300	n/a
Opiates	10	10	not reported	10	300	300	300	300
Benzodiazepines	n/a	n/a	not reported	1	n/a	n/a	300	200
Cocaine (Benzoylecgonine)	5	5	not reported	5	300	300	300	300
Marijuana	1	1	not reported	1	100	100	100	50
PCP	1	1	not reported	1	25	25		25

A summary of the GC/MS cut-off values used in the Yacoubian 2006 study is presented in Table 26.

Table 26: Cut-Off Values for Oral Fluid and Urinalysis Confirmatory Assays

Drug	Oral Fluid Screening Cutoffs(ng/mL)	Urinalysis Screening Cutoffs (ng/mL)
Hydrocodone	10	300
Hydromorphone	10	300
Oxycodone	10	300
Morphine	5	300
Codeine	5	300
6-acetylmorphine	1	
Benzoylecgonine	2.5	150
hydroxyl alprazolam		200
lorazepam		200
temazepam		200
diazepam	0.5	200
hydroxyl ethyl flurazepam		200
hydroxy midazolam		200
hydroxy triazolam		200
nordiazepam	0.5	200
oxazepam		200
estazolam	0.5	
alprazolam	0.5	
prazepam	0.5	
PCP	0.5	15
THC	0.5	15

Summary of Sensitivity Results

The range of sensitivity results for oral fluid collected with the Intercept oral fluid device is reported in

Table 27. A summary for each drug class follows.

Table 27: Sensitivity (%) of Oral Fluid Testing

	STUDY			
SUBSTANCE	**Yacoubian 2006**	**Yacoubian 2004**	**Wish 2002**	**Yacoubian 2001**
Methadone	n/a	‡100	n/a	n/a
Opiates	*77 †75	‡83	§90	‖88
Benzodiazepines	*100 †80	‡100	not reported	not reported
Cocaine	*92 †94	‡82	§95	‖100
Marijuana	*39 †35	‡39	§56	‖5
Phencyclidine	*n/a †n/a	not reported	not reported	not reported

*OF (EIA) compared with Urinalysis (GC/MS)
†OF (EIA) compared with urinalysis (EMIT)
‡OF (ELISA) compared with urinalysis (EMIT)
§OF (EIA) compared with urinalysis (EMIT)
‖OF (EMIT) compared with urinalysis (EMIT)

Opiates

There was 1 study that compared oral fluid immunoassay to urinalysis GC/MS and 4 that compared oral fluid immunoassay to urinalysis immunoassay. Sensitivity for oral fluid immunoassay was 77% when compared with urinalysis GC/MS and ranged from 75 to 90% when oral fluid immunoassay was compared with urine immunoassay. The sensitivity for opiates did not change when oral fluid GC/MS was compared with urinalysis GC/MS. (Personal communication, G. Yacoubian, November 24, 2006)

Benzodiazepines

There was 1 comparison of oral fluid immunoassay to urinalysis GC/MS and 2 comparisons of oral fluid immunoassay with urinalysis immunoassay. Sensitivity for oral fluid screen by immunoassay was 100% when compared with urinalysis GC/MS, and 80 to 100% when oral fluid immunoassay was compared with urinalysis immunoassay.

Cocaine

There was 1 comparison of oral fluid immunoassay to urinalysis GC/MS and 4 that compared oral fluid immunoassay to urinalysis immunoassay. Sensitivity of oral fluid immunoassay was 92% when compared with urinalysis GC/MS, and ranged from 82 to 100% when oral fluid immunoassay was compared with urinalysis immunoassay.

Marijuana

There was 1 comparison of oral fluid immunoassay to urinalysis GC/MS and 4 that compared oral fluid immunoassay to urinalysis immunoassay. Sensitivity of oral fluid immunoassay was 39% when compared with urinalysis GC-MS and ranged from 5 to 56% when oral fluid immunoassay was compared with urinalysis immunoassay.

Phencyclidine

Sensitivity of PCP could not be determined because of a low rate of use.

Summary of Specificity Results

The range of specificity results for oral fluid collected with the Intercept oral fluid device is reported in Table 28. A summary for each drug class follows.

Table 28: Specificity (%) of Oral Fluid Testing

	STUDY			
SUBSTANCE	**Yacoubian 2006**	**Yacoubian 2004**	**Wish 2002**	**Yacoubian 2001**
Methadone	n/a	‡92	n/a	n/a
Opiates	*96 †97	‡99	§99	‖100
Benzodiazepines	*99 †99	‡100	not reported	not reported
Cocaine	*96 †94	‡96	§98	‖99
Marijuana	*98 †97	‡93	§99	‖100
Phencyclidine	*99 †99	not reported	not reported	not reported

*OF (EIA) compared with Urinalysis (GC/MS)
†OF (EIA) compared with urinalysis (EMIT)
‡OF (ELISA) compared with urinalysis (EMIT)
§OF (EIA) compared with urinalysis (EMIT)
‖OF (EMIT) compared with urinalysis (EMIT)

Opiates

There was 1 comparison of oral fluid immunoassay to urinalysis GC/MS and 4 comparisons of oral fluid immunoassay to urinalysis immunoassay. Specificity for oral fluid immunoassay was 96% when compared with urinalysis GC/MS and ranged from 97 to 100% when oral fluid immunoassay was compared with urinalysis immunoassay.

Benzodiazepines

There was 1 comparison of oral fluid immunoassay to urinalysis GC/MS and 4 comparisons of oral fluid immunoassay to urinalysis immunoassay. The specificity for oral fluid immunoassay was 99% when compared with urinalysis MS/GC and was at least 99% when oral fluid immunoassay was compared with urinalysis immunoassay.

Cocaine

There was 1 comparison of oral fluid immunoassay to urinalysis GC/MS and 4 comparisons of oral fluid immunoassay to urinalysis immunoassay. The specificity for oral fluid immunoassay was 96% when compared with urinalysis GC/MS and was at least 94% when oral fluid immunoassay was compared with urinalysis immunoassay.

Marijuana

There was 1 comparison of oral fluid immunoassay to urinalysis GC/MS and 4 comparisons of oral fluid screen by immunoassay to urinalysis immunoassay. The specificity of oral fluid immunoassay was 98% when compared with urinalysis GC/MS and was at least 93% when oral fluid immunoassay was compared urinalysis immunoassay.

PCP

There was 1 comparison of oral fluid immunoassay to urinalysis GC/MS and 1 comparison of oral fluid immunoassay to urinalysis immunoassay. The specificity for oral fluids was 99% for both comparisons.

Overall Conclusions

Several conclusions have been drawn from the body of evidence evaluating the testing of oral fluids collected with the Intercept oral fluid collection device.

1. The evidence suggests that oral fluid testing has better specificity than sensitivity for opiates, benzodiazepines, cocaine and marijuana.
2. The sensitivity of oral fluid testing seems to be from best to worst: methadone> cocaine > benzodiazepines >opiates> marijuana.
3. Oral fluid testing has better sensitivity than specificity for methadone. The sensitivity is 100% and the specificity is 92%. Methadone sensitivity and specificity was determined in 1 clinical study only.
4. The sensitivity and specificity for opiates of the Intercept oral fluid device ranges from 75 to 90% and 97 to 100% respectively.
5. The consequences of opiate false-negatives by oral fluid testing need to be weighed against the disadvantages of urine testing, including invasion of privacy issues and adulteration or substitution of the urine specimen.
6. The window of detection is narrower for oral fluids than urine and because of this oral fluid testing may best be used in situations where there is more frequent drug use. When drug use is thought to be less frequent or remote, urinalysis may offer a wider (24-48 hours more than oral fluids) window of detection.
7. The narrow window of detection for oral fluid testing may mean more frequent testing is needed compared to urinalysis. This may increase the expense for drug testing in general.
8. POC oral fluid testing is not yet available and may limit the practical utility of this drug testing methodology. POC testing by immunoassay for urinalysis is available.
9. The possible applications of oral fluid testing may include:
    a) Because of its narrow window of detection compared to urinalysis oral fluid testing may best be used during periods of suspected frequent or recent drug use (within 24 hours of drug testing). This is not to say that oral fluid testing is superior to urinalysis during these time periods.
    b) In situations where an observed urine specimen is difficult to obtain. This may include persons unable to void under observation (e.g. shy bladder syndrome) or with other urinary conditions limiting their ability to provide an observed urine specimen.
    c) When the health of the patient would make urine testing unreliable (e.g., renal disease).
    d) As an alternative drug testing method when urine specimen tampering practices are suspected to be affecting the reliability of the urinalysis test.

Existing Guidelines for Use of Technology

The standards of practice for drug monitoring in an MMT program across Canadian provinces are reported in Table 29. Guidelines for methadone treatment in Canada, and the United States are described below.

Canada

Table 29: Provincial Standards of Practice for Drug Monitoring in MMT Programs across Canada

Province	Is urine testing the Standard of Practice for MMT programs?	Is oral fluid testing used within an MMT program?
British Columbia	Yes	No
Alberta	Yes	No
Saskatchewan		
Manitoba	Yes	No
Ontario	Yes	No
Quebec	No data	No data
New Brunswick	Yes	No
Nova Scotia	Yes	No
Prince Edward Island	Yes	No
Newfoundland	Yes	No
Nunavut	Methadone treatment not provided in Nunavut	N/A
Yukon	No data	No data
North West Territories	No data	No data

Health Canada

Therapeutic Products Directorate Guidelines: The use of Opioids in The Management of Opioid Dependence. 1992: Section 5.5 (33)

1. The urine collection process should be done at least twice per week during the first 3 months of treatment. In some instances, it may be advisable to supervise the urine collection
2. A minimum of 1 urine drug screen is advised prior to initiation of methadone maintenance.
3. Urine drug screening must be carried out no less than once per week at random for the first 3 months of treatment and at least twice per month at random thereafter.

NOTE: Collecting urine samples on a more frequent basis than they are tested has economic advantages and can be a deterrent to illicit drug use. Not knowing which urine sample will be tested may serve as a deterrent.

4. Urine specimens should be screened for methadone and its metabolites, commonly abused drugs, and any other drugs known to be abused in the community.
5. It is expected that illicit drugs will not be used during treatment. Positive drug screening results (the presence of an unacceptable drug and/or the unexplained absence of methadone or its metabolites) should lead to the adjustment of the treatment plan. Repeated positive urine tests require mandatory review of treatment and/or consideration of withdrawal of methadone.
6. In cases where urine drug testing results indicate treatment noncompliance, it is advisable to confirm the initial screening procedure by a second method based on a different chemical principle.

United States

Substance Abuse and Mental Health Services Administration (SAMSHA) Center for Substance Abuse Treatment (CSAT), within the U.S. Department of Health and Human Services (DHHS) Rockville, MD, United States. (4)

BEST PRACTICE GUIDELINES: Oral fluid drug testing is an alternative to urine drug testing approved by SAMSHA for the use in opioid treatment programs but only when a qualified offsite laboratory performs the assay. SAMSHA states that there is sufficient information to confirm the adequacy of oral fluid testing in the opiate treatment program setting, but that the choice of drug-testing methodology is an informed medical judgment decision (4). The guidelines recommend oral fluid testing when drug testing must be observed because it is more respectful and less invasive and observation does not require watching patients void.

Policy Development

Considerations

Possible limiting factors to diffusion of oral fluid technology include:

- No oral fluid POC test equivalent to onsite urine dips or POC analyzer, reducing immediacy of results for patient care.
- Currently physicians get reimbursed directly for POC urinalysis. Oral fluid must be analyzed in a lab setting removing physician reimbursement, which is a source of program funding for many methadone clinics.
- Small amount of oral fluid specimen obtained; repeat testing on same sample will be difficult.
- Reliability of positive oral fluid methadone (parent drug) results may decrease because of possible contamination of oral cavity after ingestion of dose. Therefore high methadone levels may not be indicative of compliance with treatment. Oral fluid does not as yet test for methadone metabolite.
- There currently is no licensed provincial laboratory that analyses oral fluid specimens.

Diffusion – International, National, Provincial

Urine drug testing is the standard of practice among the provinces and territories of Canada. The 2005 United States SAHMSA guidelines endorsed oral fluid drug testing in opiate treatment programs as an alternate to urine drug testing when drug testing must be observed.

Target Population

The target population includes persons enrolled in a MMT program in Ontario. The CPSO estimates that currently 15,500 persons in Ontario are being treated for opiate addiction through MMT. There are 3 approaches to methadone treatment:

1. Fully funded multidisciplinary methadone clinics where a physician, nurse, social worker are on site (i.e. Breakaway Clinic in Toronto) and can be located within a multi-service organization (e.g., community health centre).

2. Physicians in solo or group practices who bill the Ontario Health Insurance Plan (OHIP) for the services they provide (i.e., Ontario Addiction Treatment Centres)
3. Community based health organizations who offer methadone programs through existing funding (i.e., needle exchanges), and the physicians bill OHIP for their services.

There are about 150 provincially funded substance abuse programs across the province. There were 158,000 admissions to substance abuse services in 2005-06 and of those an estimated 3,000 clients are receiving MMT.

In 2005/06, the ministry provided $730,000 Cdn (8 new Full Time Equivalents [FTE]) in annual base funding to 14 community agencies across the province to support existing unfunded community case management for people on MMT. It is the ministry's expectation that for every FTE, a minimum of 25 clients would be served. Case management services include:; addiction counseling, coordinating access and referrals to appropriate community services, coordinating/networking with other methadone providers, and to identify and respond to emerging client needs.

Patient Outcomes

The purpose of methadone treatment is harm reduction. The purpose of drug testing for persons enrolled in an MMT program is to determine those harmful behaviors that could benefit from intervention with respect to substance abuse. Such behaviors may include diverting methadone and continual use of illicit substances.

Ethics and/or Legal Considerations

Methadone is a schedule I, controlled substance in Canada. The Office of Controlled Substances, Health Canada permits physicians to prescribe methadone. In Ontario, the College of Physicians and Surgeons provides guidelines and training for practitioners interested in providing MMT. (8)

System Pressures

Currently there is no provincially licensed laboratory in Ontario with the ability to analyze the Intercept oral fluid specimen.

OHIP schedule of laboratory LMS (Labour, Material and Supervision) fee codes for drugs of abuse are available for urinalysis only. Each code is granted a specific number of units. The price per unit is 51.7 cents. The fee for the laboratory test is determined by multiplying the number of units by the per unit value (51.7 cents). The following LMS codes are used:
L073: Target drug testing, urine, qualitative or quantitative, 17 units ($8.79)
L078: Drugs of Abuse Screen, urine, 68 units ($35.16)
L079: Broad spectrum toxicology screen, urine, includes confirmatory testing (GC/MS), 72 units ($37.22)
A maximum of 144 units / patient within a 7 day period of LMS fee codes L073, L078, L079 combined is allowed.

Stakeholder Analysis

Currently, physicians get reimbursed directly for POC urinalysis. Oral fluid must be analyzed in a lab setting removing physician reimbursement which is a source of program funding for many methadone clinics. Reducing this source of funding may risk closure of physician run methadone clinics.

The CPSO estimates that there are 250 physicians in Ontario licensed to prescribe methadone.
For oral fluid testing to become available to clinicians the Provider Services Branch of the Ministry of Health and Long-Term Care will need to develop LMS fee codes for oral fluid testing as well as protocols for when oral fluid testing should be used. Awareness of the potential to use both urine and oral fluid testing at the same time on the same patient must be addressed in the fee codes to maintain costs.
The CPSO would need to be involved in disseminating information about oral fluid testing, its relative pros and cons, and diagnostic utility

Appendices

Appendix 1

The Grade Evaluation (24) system has 4 levels: very low, low, moderate, and high. The criteria for assigning the GRADE level are outlined below.

Type of evidence

- RCT: given a high GRADE level to start
- Observational study: given a low GRADE level to start
- Any other evidence: given a very low GRADE level to start

Decrease grade if:

- Serious limitation to study quality (-1, reduce GRADE level by 1 so a high GRADE level will become a moderate grade) or very serious limitation to study quality (-2, reduce GRADE level by 2 so a high GRADE level will become low grade)
- Important inconsistency (-1, reduce GRADE level by 1)
- Some (-1) or major (-2) uncertainty about directness
- Imprecise or sparse data (-1)
- High probability of reporting bias (-1)

Increase GRADE level if:

- Strong evidence of association-significant relative risk of >2 (< 0.5) based on consistent evidence from 2 or more observation studies, with no plausible confounders (+1, increase GRADE level by 1, so a moderate grade will become high. However a high grade will remain high)
- Very strong evidence of association-significant relative risk of > 5 (< 0.2) based on direct evidence with no major threats to validity (+2, increase GRADE level by 2, so a low grade will become a high grade)
- Evidence of a dose response gradient (+1)
- All plausible confounders would have reduced the effect (+1).

Overall GRADE Level definitions

High:	Further research is very unlikely to change our confidence in the estimate of effect.
Moderate:	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low:	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low:	Any estimate of effect is very uncertain.

Appendix 2

Search date: September 6, 2006
OVID MEDLINE, In-Process and Other Non-Indexed Citations, EMBASE, INAHTA, Cochrane Library

Database: Ovid MEDLINE(R) <1996 to August Week 4 2006>
Search Strategy:

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1 exp Nails/ (1254)
2 exp Urinalysis/ (1835)
3 exp Breath Tests/ (4000)
4 exp Saliva/ (6957)
5 exp Mouth Mucosa/ (5694)
6 exp Sweat/ (504)
7 exp Hematologic Tests/ (49432)
8 exp Hair/ (6623)
9 exp Substance Abuse Detection/ (2387)
10 exp Drug Monitoring/ (5706)
11 exp Patient Compliance/ (15457)
12 or/1-11 (97083)
13 exp methadone/ (2463)
14 12 and 13 (296)
15 (monitect or fastect or quicktox or cedia or verdict or accusign or cobas or multigent or syva or vitros or intercept or bio-rad or synchron or advia or surestep or orasure or acon or axsym or aeroset or x-stsrems or profile).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (81433)
16 13 and 15 and (9 or 10 or 11) (11)
17 14 or 16 (296)
18 limit 17 to (humans and english language) (267)
19 (systematic$ review$ or random$ or metaanalysis or meta-analysis).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (296345)
20 18 and 19 (71)
21 18 (267)
22 limit 21 to (case reports or comment or editorial or letter or "review") (43)
23 21 not 22 (224)
24 20 or 23 (225)

Database: EMBASE <1980 to 2006 Week 35>
Search Strategy:
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1 exp methadone treatment/ (1775)
2 exp Hair Analysis/ or exp Drug Hair Level/ (2190)
3 exp drug blood level/ (110610)
4 exp drug urine level/ (18421)
5 exp urinalysis/ (28073)
6 exp nail/ (2732)
7 exp Sweat/ (779)
8 exp Cheek Mucosa/ (1765)
9 exp Breath Analysis/ (6340)
10 exp drug saliva level/ or exp drug sputum level/ (1961)
11 exp Drug Monitoring/ (24799)
12 exp Patient Compliance/ (34321)
13 exp Patient Monitoring/ (57970)
14 or/2-13 (259743)
15 1 and 14 (424)
16 *METHADONE/ (6111)
17 16 and 12 (158)
18 15 or 17 (506)
19 (monitect or fastect or quicktox or cedia or verdict or accusign or cobas or multigent or syva or vitros or intercept or bio-rad or synchron or advia or surestep or orasure or acon or axsym or aeroset or x-stsrems or profile).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (122282)
20 (1 or 16) and (11 or 12 or 13) and 19 (12)
21 18 or 20 (509)
22 limit 21 to (human and english language) (460)
23 limit 22 to yr="1996 - 2006" (338)
24 (systematic$ review$ or meta-analysis or metaanalysis or random$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (373557)
25 23 and 24 (78)
26 23 (338)
27 limit 26 to (editorial or letter or note or "review") (51)
28 Case Report/ (901734)
29 26 not (27 or 28) (273)
30 25 or 29 (279)

Search date: November 3, 2006
OVID MEDLINE, Medline In-Process & Other Non-Indexed Citations, EMBASE, INAHTA, Cochrane Library

Database: Ovid MEDLINE(R) <1996 to October Week 4 2006>
Search Strategy:
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1 exp Urinalysis/ (1869)
2 exp Narcotics/ur [Urine] (396)
3 exp Substance-Related Disorders/ur [Urine] (595)
4 or/1-3 (2742)
5 exp Saliva/ or saliva.mp. (10220)
6 exp Mouth Mucosa/ (5794)
7 5 or 6 (15712)
8 4 and 7 (35)
9 exp self-disclosure/ (2419)
10 self-report$.mp. (24334)
11 9 or 10 (25747)
12 exp Substance Abuse Detection/ (2447)
13 exp Street Drugs/ (2761)
14 exp Substance Abuse Treatment Centers/ (1733)
15 exp Narcotics/ (21256)
16 exp Opioid-Related Disorders/ (5064)
17 exp Patient Compliance/ (15864)
18 exp Treatment Refusal/ (4608)
19 exp Street Drugs/ (2761)
20 exp Drug Monitoring/ (5853)
21 exp Substance Abuse Treatment Centers/ or exp Substance-Related Disorders/ (55529)
22 or/12-21 (97914)
23 8 and 22 (26)
24 11 and 12 (129)
25 23 or 24 (155)
26 limit 25 to (humans and english language) (151)

Database: EMBASE <1980 to 2006 Week 43>
Search Strategy:
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1 exp Urinalysis/ (28580)
2 exp Drug Urine Level/ (18506)
3 1 or 2 (46032)
4 exp Saliva Analysis/ (2176)
5 exp Drug Saliva Level/ (1634)
6 4 or 5 (3760)
7 3 and 6 (490)
8 self-report$.mp. or exp Self Report/ (36788)
9 8 and (3 or 6) (561)
10 7 or 9 (1042)
11 exp Substance Abuse/ or exp Drug Abuse/ (51483)
12 (substance abuse adj1 (detect$ or test$)).mp. [mp=title, abstract, subject headings, heading word,

drug trade name, original title, device manufacturer, drug manufacturer name] (68)
13 exp Drug Determination/ (54354)
14 exp METHADONE TREATMENT/ (1796)
15 exp Drug Dependence Treatment/ (5761)
16 exp Street Drug/ (240)
17 exp Patient Compliance/ (35053)
18 exp Drug Monitoring/ or exp Drug Screening/ (77076)
19 or/11-18 (210790)
20 10 and 19 (423)
21 limit 20 to (human and english language and yr="1996 - 2006") (233)
22 limit 21 to (editorial or letter or note) (11)
23 Case Report/ (910304)
24 21 not (22 or 23) (218)

Glossary

Analyte	A substance to be isolated during chromatography
Chromatography	The collective term for a family of laboratory techniques for the separation of mixtures.
Enzyme Immunoassay (EIA)	The general term for an expanding technical arsenal of testing which allows a full range of quantitative analyses for both antigen and antibodies. These tests use color-changed products of enzyme-substrate interaction or inhibition to measure the anigen-anibody reaction. Examples if EIA procedures are EMIT, ELISA, MAC and MEIA

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