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Need and utility of a polyethylene glycol marker to ensure against urine falsification among heroin users

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ABSTRACT

Background: Deceptive methods of falsifying urine samples are of concern for anyone who relies on accurate urine toxicology results. A novel method to combat these efforts utilizes polyethylene glycol (PEG) markers administered orally prior to providing a urine sample. By using various PEG combinations to create a tracer capsule of unique composition, each urine sample can be matched to that individual. The goal of this study was to determine the effectiveness of using the PEG marker system among active heroin users screening for research studies.
Methods: Upon each screening visit, participants ($N = 55$) were randomized to provide an unobserved urine sample, or the PEG tracer procedure was used. LCMS analysis was used to distinguish the PEG combinations, and allowed us to provide a unique qualitative analysis of patterns of drug use ($N = 168$, total urine specimens).
Results: The unique composition of the tracer capsules was accurately detected in 83.5% of the urine specimens. Analyses of inconsistencies implicated a number of possible attempts at fraudulence (11.4%) and investigator/lab error (5.1%). Among this sample, the concurrent use of multiple classes of psychoactive drugs was more common than not, though concomitant drug use was often underreported.
Conclusion: Urine drug testing should be the minimum standard for obtaining information about drug use as self-report was unreliable even in a situation where there were no perceived adverse consequences for full disclosure. In cases where there are significant pressures for individuals to falsify these data, more protective collection methods such as the PEG marker system should be considered.

1. Introduction

Urine drug testing is a quick and easy method for clinicians and researchers to gain information about risk-related behaviors concerning substance abuse. Among opioid users in treatment, regular urine drug testing can identify aberrant drug-related behaviors and help to ensure treatment adherence and effectiveness (U.S. Food and Drug Administration, 2011). Among active opioid users, urine toxicology (Utox) results can inform us about drug use patterns, such as polysubstance abuse, that are thought to significantly increase risk of disease transmission and overdose (Roux et al., 2013; Gjersing et al., 2013). Accordingly, regular urine drug testing has been advocated by many state, policy, and organizational guidelines (Chou et al., 2009; Gudin et al., 2013; Manchikanti et al., 2012; Utah Dept. of Health, 2009). However, urine sample adulteration may be a problem in any clinical population that has an interest in false results (e.g., pre-employment and workplace screening; Owen et al., 2012).

There are several documented methods of tampering with urine samples: dilution by drinking excessive amounts of water or external dilution, and adulteration by mixing the urine with oxidants, soaps etc. (Honour, 1996; Mikkelsen and Ash, 1988). These methods can be detected with modern laboratory techniques (Federal Register, 2001). However, substitution of one's urine with a "clean" sample from another individual or synthetic urine remains a serious concern (Jaffee et al., 2007). The most common approach to prevent these methods of Utox falsification is supervision of the urination process. However, supervised urine collection can be burdensome to personnel and embarrassing to clients. Also, observed

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collection does not entirely ensure against fraudulence aided by clever devices, such as those containing life-like penises, synthetic urine, and heat packs (to keep the fake urine at body temperature; http://www.thewhizzinator.com/).

The current study tested a different method to detect sample manipulation, a labeling procedure that allows samples to be matched with a particular person (Gauchel et al., 2003; Huppertz et al., 2004). With this novel method, a tracer/marker substance is taken orally prior to the participant providing a urine sample. Urine samples can be matched to the particular patient by assessing for the specific marker substance previously ingested.

The marker substances are low molecular weight polyethylene glycols (PEGs) used for years as a galenic basis for drugs and considered "inactive ingredients" by the FDA. PEGs appear in urine 30 min after ingestion and are undetectable after 6–8 h (Christensen, 2014). By combining polyethylene glycols of different molecular weights, a large number of different polyethylene glycol chain mixtures can be obtained. Therefore, for a group of participants, unique tracer capsules can be offered that can be discriminated from each other, matching a participant to his or her sample.

The goal of this study was to determine the feasibility and effectiveness of using the PEG marker system among active heroin users screening for clinical studies within the Opioid Research Laboratory, part of the Division on Substance Abuse at the College of Physicians and Surgeons of Columbia University/New York State Psychiatric Institute (NYSPI). Throughout our normal screening procedure urine toxicology tests are performed numerous times in order to: verify experience with the drug under investigation, assess and diagnose abuse, and identify potential adverse drug interactions.

Falsification is a serious concern in cases where opioid users may lose money, privileges, or their freedom (Owen et al., 2012). However, in the present setting, specific inclusion/exclusion criteria related to drug use and toxicology results were not disclosed to potential study participants. As such, this study allowed us to examine the need for objective and protective methods of assessing drug use among a population with little perceived incentive to be deceptive. Finally, the analyses performed on the urine samples provided an objective way to assess drug use trends and concomitant drug use among a unique population of heroin users not currently in treatment or seeking treatment.

2. Methods

2.1. Overview

Data were collected between 2013 and 2014 at the NYSPI Substance Use Research Center located in upper Manhattan. Urine samples used in the current analysis were obtained from volunteers screening for six experimental studies with the Opioid Research Laboratory (IRB#s 6255, 6107, 5879, 6021, 6883R, 6400). Our clinical studies investigate the subjective and reinforcing effects of various opioids, and novel treatment medications among various populations of opioid users who are not seeking treatment for drug abuse (at time of their study participation). See Jones et al. (2011, 2014) for examples of this research.

Potential participants were recruited locally with newspaper advertisements and word-of-mouth referrals. Although the exact wording of the advertisements differed from study to study, the verbiage typically sought "intravenous and intranasal heroin users," or "healthy heroin users." After completing an initial telephone screening interview, eligible participants were scheduled for in-person screening at NYSPI that included: detailed medical history and drug use questionnaires, medical evaluation, psychiatric evaluation, a naloxone challenge to assess opioid dependence, and an interview with a research psychologist to discuss patterns of drug use in detail. Screening typically required 4–5 visits, and was conducted over the course of 3–4 weeks to determine eligibility (with urine collected at each visit). As an addendum to the screening process for the six inpatient studies mentioned above, participants were offered the opportunity to participant in the current study (IRB# 6817). Those who agreed signed separate study consent and completed the procedures described below. Participants were paid between $20 and $45 for each visit ($20 for the inpatient study screening procedures, plus a possible $25 for days they received a PEG tracer). All study procedures were approved by the NYSPI IRB.

2.2. Procedures

Prior to providing each individual urine sample, participants were randomized to one of the two conditions: Testing as Usual (TAU) and Marker group (i.e., participants could have provided urine samples using both procedures). Participants were randomized to a specimen collection procedure upon each visit using a Latin Square randomization scheme (Bailey, 2008). Urine specimens from participants assigned to the TAU sample were collected using our current practice, without direct observation. Participants were provided with a urine cup and given access to a private bathroom. When participants were assigned to provide a urine sample with Marker, they were given a gel capsule containing 100 mg of PEG marker material, which they consumed with 100 mL of a flavored beverage (e.g., soda, fruit juice, Gatorade), under the supervision of a study nurse (Fig. 1). Participants waited 30 min–1 h and then provided a urine sample in a standard urine cup (without supervision). All participants, when assigned to the Marker condition, received an active PEG tablet (i.e., there was no placebo tablet).

Participants met with a research nurse to assess for any immediate adverse effects following consumption of the Marker capsule. At their next visit (or via phone), they were asked if they experienced any adverse drug effects after leaving the research center.

All urine samples were initially tested using an 11-Panel DrugCheck® Dip Drug Tests with the following positive result cut-offs: Amphetamine: 1000 ng/mL, Barbiturate: 300 ng/mL, Benzodiazepine: 300 ng/mL, Buprenorphine: 10 ng/mL, Cocaine: 150 ng/mL, Methamphetamine: 500 ng/mL, Methadone: 200 ng/mL, Opiates (morphine, codeine, heroin): 300 ng/mL, Oxycodone: 100 ng/mL, PCP: 25 ng/mL, THC: 50 ng/mL. The results of this test were entered into the participants' study chart and on the sample reporting form that accompanied the urine sample for confirmatory Liquid Chromatography-Mass Spectrometry (LCMS) assessment for drugs of abuse and detection of the PEG tracers (when applicable).

The marker substances are low molecular weight polyethylene glycols. The chemical structure of polyethylene glycols is HO-(CH_2-CH_2-O)$_n$-H with "n" varying between 8 and 1000 or more. Polyethylene molecules of chain lengths between 8 and 17 repeating units resulting in molecular weights ranging from 370 to 766. For the purposes of the current study, PEGs of four different molecular weights were used: PEG370 (PEG-8), PEG414 (PEG-9), PEG458 (PEG-10), and PEG503.3 (PEG-11). An individual marker capsule could contain a single PEG or any combination of the 4. The barcode on each gel capsule identified the PEG or PEG combination used (Fig. 1). The unique PEG identifier was only known to Avee laboratory staff.

2.3. Aims

This study was designed to determine the safety and efficacy of the PEG marker system by assessing adverse events related to PEG capsule consumption, reliable identification of the PEG combination administered in the urine sample, and a comparison of attempts at fraudulence/substitution between TAU and Marker conditions. In addition, patterns of drug use among heroin users not currently seeking treatment were assessed using self-report, urine dip tests, and LCMS.

2.4. Statistical analyses

Continuous and categorical participant variables were summarized descriptively (Table 1). Independent-samples T-test was planned to compare fake urine falsification attempts between the Marker and TAU groups, though this analysis

Table 1
Demographic characteristics of study participants (N = 55).

	Mean (SD) or participants (%)
Demographics	
Age	46.78 (7.45)
Sex	
Male	51 (93)
Female	4 (7)
Ethnic/racial category	
African American	28 (51)
Caucasian	7 (13)
Hispanic	15 (27)
Multiracial	5 (9)
Opioid use	
Heroin bags per day	5.17 (2.48)
Years of use	18.12 (11.62)
Route of administration preference	
Intranasal	35 (63.6)
Intravenous	20 (36.4)