Chronic Opioid Therapy Urine Drug Testing in Primary Care: Prevalence and Predictors of Aberrant Results

Judith A. Turner, PhD[1,2,3], Kathleen Saunders, PhD[4], Susan M. Shortreed, PhD[4], Linda LeResche, ScD[5], Kim Riddell, MD[6], Suzanne E. Rapp, MD[3], and Michael Von Korff, ScD[4]

[1]Department of Psychiatry and Behavioral Sciences, University of Washington, Seattle, WA, USA; [2]Department of Rehabilitation Medicine, University of Washington, Seattle, WA, USA; [3]Department of Anesthesiology and Pain Medicine, University of Washington, Seattle, WA, USA; [4]Group Health Research Institute, Seattle, WA, USA; [5]Department of Oral Medicine, University of Washington, Seattle, WA, USA; [6]Group Health, Seattle, WA, USA.

BACKGROUND: Urine drug tests (UDTs) are recommended for patients on chronic opioid therapy (COT). Knowledge of the risk factors for aberrant UDT results could help optimize their use.

OBJECTIVE: To identify primary care COT patient and opioid regimen characteristics associated with aberrant UDT results.

DESIGN: Population-based observational.

SAMPLE: 5,420 UDTs for Group Health integrated group practice COT patients.

MEASURES: Group Health database measures of patient demographics, medical history, COT characteristics, and UDT results.

RESULTS: Thirty percent of UDTs had aberrant results, including prescribed opioid non-detection (12.3 %), tetrahydrocannabinol (THC; 11.2 %), non-prescribed opioid (5.3 %), illicit drug (excluding THC; 0.6 %), non-prescribed benzodiazepine (1.7 %), and dilute (4.8 %). Adjusted odds ratios (95 % CI) of any aberrant result were higher for males than females (1.24 [1.07, 1.43]), patients with versus without prior substance use disorder diagnoses (1.42 [1.17, 1.72]), and current smokers versus non-smokers (1.50 [1.30, 1.73]). Odds ratios were lower for patients aged 45–64 (0.77 [0.65, 0.92]) and 65+ (0.40 [0.32, 0.50]) versus patients aged 20–44 and for patients on long-acting opioids only (0.72 [0.55, 0.95]) or long-acting plus short-acting (0.67 [0.54, 0.83]) versus short-acting only. Adjusted odds of prescribed opioid non-detection were lower for patients aged 45–64 (0.79 [0.63, 0.998]) and 65+ (0.44 [0.32, 0.59]) versus patients aged 20–44, for those on 40–<120 mg daily morphine-equivalent dose (0.52 [0.39, 0.70]) or 120+ mg (0.22 [0.11, 0.43]) versus <40 mg, and for patients on long-acting (0.35 [0.21, 0.57]) or long-acting plus short-acting (0.35 [0.24, 0.50]) opioids (versus short-acting only); and odds ratios were higher for patients with versus without prior diagnoses of substance use disorder (1.70 [1.31, 2.20]).

CONCLUSIONS: In this primary care setting, results were aberrant for 30 % of UDTs of COT patients, largely because of prescribed opioid non-detection and THC. Aberrant results of almost all types were more likely among patients under the age of 45. Other risk factors varied across aberrancies, but commonly included current smoking and prior substance use disorder diagnosis.

KEY WORDS: urine drug test; chronic opioid therapy; chronic pain; marijuana.
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INTRODUCTION

Epidemic levels of prescription opioid overdose, abuse, addiction, and diversion have followed dramatic increases in opioid prescribing for chronic non-cancer pain (CNCP) in the U.S.[1–6] Chronic opioid therapy (COT) guidelines recommend urine drug tests (UDTs) to improve patient safety and reduce diversion.[2,7–11] UDTs can help identify drug misuse/abuse (through detection of illicit drug, opioid, or benzodiazepine use unknown to the opioid prescriber) and diversion (a possibility when prescribed opioids are absent). However, little evidence exists regarding UDT use for various patient subgroups.[12] Guidelines vary in their recommendations, with two[9,13] recommending mandatory testing for all COT patients, one advising testing for patients at risk for substance use disorders (SUDs),[8] and two[8,14] commenting that screening low-risk populations increases false-positive results and is less cost-effective.[11] Knowledge regarding the risk factors for aberrant results could help inform evidence-based recommendations regarding UDTs for COT monitoring.

We reported a substantial increase in UDTs for COT patients at Group Health's (GH) integrated group practice after implementation of a multifaceted opioid risk reduction initiative.[15] Illicit drug detection was rare, raising the question of whether UDTs should be targeted to patient subgroups based on risk for aberrancies. Little research has examined predictors of UDT results in the primary care COT population. In pain clinic and other settings, some studies found illicit drugs (including tetrahydrocannabinol [THC]) to be more common among UDTs of males[16] and younger patients.[17,18] Among

veterans, UDT detection of illicit substances (including THC) was more common for those with SUD diagnoses.[19] Studies in diverse settings[18,20] found no significant association between opioid regimen characteristics and UDT detection of illicit drugs.

The purpose of this study was to identify primary care COT patient and opioid regimen characteristics associated with aberrant UDT results. In the state of Washington, the setting of this study, use of marijuana is legal for chronic pain. We examined THC separately from illicit drugs. We hypothesized that illicit drug and THC use would be more common among younger patients, males, and patients with SUD history, and that prescribed opioid non-detection would be more common among patients with a history of SUD , on low-dose opioid therapy, and with less-than-daily opioid supply. Other analyses were exploratory.

Text Box 1. GH Guideline (December 2011 update*) UDT Recommendations

Patient Risk Category	UDT Recommendation
Low: < 40 mg MED/day and low abuse risk (compliant with medication plan, no personal or family history of alcohol or drug abuse, no mental health issues)	Consider UDT
Medium: 40–120 mg MED/day or medium abuse risk (personal or family history of alcohol or drug abuse, personal or family history of mental health issues)	UDT at least once a year
High: on methadone, taking >120 mg MED/day of other opioid, or high abuse risk (current alcohol or drug abuse, age ≤ 25 years, significant psychiatric comorbidity, or repeated problems with opioid medication plan compliance)	UDT at least twice a year

**The original guideline (July 2010) defined low dose as < 20 mg MED, medium dose as 20–120 mg MED, and high dose as > 120 mg MED.*

METHODS

Study Setting and Sample

GH is a large nonprofit healthcare system in the state of Washington. GH patients are covered by individual, Medicare, Medicaid, state and federal employee, and employer-sponsored plans. The GH opioid risk reduction initiative, implemented in September 2010 in its integrated group practice, included COT patient care guidelines with UDT recommendations based on opioid dose and other risks (Text Box 1) as well as a pain management UDT.[15,21] We identified all pain management UDTs performed January 2011–December 2012 for patients aged ≥20 years. We obtained UDT, pharmacy, and patient data from GH databases. To limit the sample to UDTs for CNCP patients, we excluded those of patients who, in the one-year period prior to the UDT, had had hospice care, opioid prescriptions from oncologists, or more than one visit for cancer other than non-melanoma skin cancer. To ensure data availability, we excluded UDTs for patients not continuously enrolled at GH for the previous year. We calculated patients' days' supply of transdermal and oral opioids (except buprenorphine) covering the 90 days before each UDT. We included only UDTs for patients on COT, defined by GH as ≥70 days' opioid supply in the prior 90 days. We compared characteristics of patients with UDTs in our sample to those of the overall population of GH COT patients who met study eligibility criteria on 1/1/2012, the study midpoint. This study was approved by the GH Institutional Review Board.

Measures

UDT Results. The GH pain management UDT (Text Box 2) includes a screening immunoassay and liquid chromatography-tandem mass spectrometry (LC-MS/MS) confirmatory test. Text Box 3 lists the LC-MS/MS results examined in the study.

Predictors. We selected potential predictors based upon prior studies of predictors of UDT results (see Introduction) and prescription opioid misuse/abuse. The latter predictors include younger age,[18,22–29] male gender,[24,25,27,30] history of alcohol or other substance abuse,[22,23,25–29] history of mental health disorder,[4,22,25,27,29,31] current smoking,[32,33] high opioid dose,[28,29] and use of short-acting opioids.[28] From GH databases, we obtained patient gender and age at the time of the UDT (and for all GH COT patients at the study midpoint), and International Classification of Diseases, 9th revision, clinical modification (ICD-9-CM)[34] patient visit diagnoses within the previous two years. We classified these diagnoses into clinically meaningful categories using Clinical Classifications Software (CCS).[35] We identified CCS alcohol and SUD diagnoses, and defined mental health diagnoses as any in the CCS categories of adjustment disorders, anxiety disorders, mood disorders, personality disorders, psychotic disorders, intentional self-inflicted injury, and some miscellaneous disorders

Text Box 2. GH Pain Management UDT

Test	Substances Detected
Screening immunoassay	Amphetamines Barbiturates Benzodiazepines Cocaine Opioids Tetrahydrocannabinol (THC)
Liquid chromatography-tandem mass spectrometry (LC-MS/MS) – performed to confirm all positive immunoassay results. A full opioid panel is performed regardless of the immunoassay result for opioids, except for methadone, which is confirmed only if present in the immunoassay.	Amphetamine Methamphetamine 3,4-methylenedioxymethamphetamine (MDMA; ecstasy) Opioids: codeine, morphine, 6-acetylmorphine (6-AM; heroin metabolite), hydrocodone, hydromorphone, methadone, oxycodone, and oxymorphone

Text Box 3. UDT LC-MS/MS Results Examined

LC-MS/MS Result	Definition
Prescribed opioid non-detection	No detectable (detection threshold = 20 ng/ml) amount of any opioid prescribed for the 90 days before the UDT. We excluded UDTs for patients for whom fentanyl, tramadol, or meperidine (not detected by LC-MS/MS) were the only opioids prescribed for the prior 90 days.
THC (marijuana)	
Non-prescribed opioid	Opioid for which patient had no prescription covering the 90 days prior to the UDT
Illicit drug	Non-prescribed amphetamine, methamphetamine, cocaine, PCP, MDMA (ecstasy), or 6-AM (heroin metabolite). We considered UDTs positive for illicit amphetamine only for patients with no prescriptions in the previous 90 days for stimulant medications detected as amphetamines.
Non-prescribed benzodiazepine	Benzodiazepine for which patient had no prescription covering the 90 days prior to the UDT
Dilute sample	

6-AM 6-acetylmorphine; LC-MS/MS liquid chromatography-tandem mass spectrometry; MDMA 3,4-methylenedioxymethamphetamine; PCP phencyclidine; THC tetrahydrocannabinol

Note: When examining opioid non-detection or substance presence, we excluded tests in which opioid or substance absence could not be confirmed due to dilute sample.

(e.g., eating disorders; we excluded sexual and gender identity, somatoform, and sleep disorders). We identified current smokers as patients with electronic health record (EHR) flags indicating current tobacco use or prior-year visits with tobacco use disorder diagnoses (ICD-9-CM code 305.1).[36] For descriptive purposes, we used ICD-9-CM codes[37] to identify pain diagnoses for past-year visits.

We calculated the mean daily morphine-equivalent dose (MED) and total days' supply for opioid prescriptions (except buprenorphine) covering the 90-day period before each UDT (or study midpoint).[38] For multiple same-date prescriptions, we counted only the highest value of days' supply. We categorized days' supply as less than daily (70–83), daily/near daily (84–96), or excessive (≥97). We characterized patients' opioids over the 90 days as short-acting only, long-acting (recommended usual dosing frequency ≤3 times daily – fentanyl, levorphanol, methadone, and sustained-release formulations of hydromorphone, morphine, oxycodone, oxymorphone, tramadol, and tapentadol[39]) only, or short-acting and long-acting.

Statistical Analysis

We conducted descriptive analyses, then logistic regression analyses predicting dilute samples and the following LC-MS/MS UDT results (excluding dilute samples): (1) any aberrancy; (2) prescribed opioid non-detection (defined as negative for all opioids prescribed for prior 90 days); (3) THC but no illicit drug; (4) non-prescribed opioid; (5) illicit drug; and (6) non-prescribed benzodiazepine. To better understand the contributions of individual predictors, we entered all predictors in a multivariable model for each outcome that had sufficient counts for reliable results. Regression models were estimated using generalized estimating equations.[40,41] We used an independence working correlation matrix and estimated standard errors using the robust sandwich estimator to account for dependence between some observations (multiple UDTs for some patients).[42]

RESULTS

Patient Characteristics

Among 10,405 pain management UDTs in 2011–2012 for patients aged ≥20 years, we excluded 3,183 because the patient had <70 days' opioid supply in the prior 90 days, 290 due to cancer exclusions, and 1,512 because the patient was not enrolled at GH for the prior year. The remaining 5,420 UDTs were performed for 3,809 patients. The study patient sample was similar to the overall GH COT patient population, albeit with more males and more patients under the age of 65, on long-acting opioids, and on moderate-high doses (Table 1).

UDT Results

Aberrancies were observed in 30.6 % of the UDTs, including 12.3 % negative for all prescribed opioids, 11.2 % with THC, 5.3 % with non-prescribed opioids, 0.6 % with illicit drugs, 1.7 % with non-prescribed benzodiazepines, and 4.8 % dilute (Table 2). Examination of UDT results by patient and opioid characteristics indicates different patterns across different types of aberrancies (Table 3).

Predictors of UDT Results

In multivariable analyses (Table 4), adjusted odds ratios (AOR) and 95 % confidence intervals (CI) for any aberrant result were higher for males than females (1.24 [1.07–1.43]), patients with versus without prior SUD diagnoses (1.42 [1.17–1.72]), and current smokers versus non-smokers (1.50 [1.30–1.73]). They were lower for patients aged 45–64 (0.77 [0.65, 0.92]) and 65+ (0.40 [0.32, 0.50]) versus patients aged 20–44, those on 40–<120 mg daily MED (0.78 [0.65, 0.95]) versus <40 mg MED, and for patients on long-acting opioids only (0.72 [0.55, 0.95]) or long-acting plus short-acting opioids (0.67 [0.54, 0.83]) versus short-acting opioids only.

Prescribed opioid non-detection was more likely among patients with versus without prior SUD diagnoses (AOR = 1.70; 95 % CI = 1.31, 2.20). It was less likely among patients

Table 1. Characteristics of All Group Health COT Patients Who Met Study Inclusion Criteria on 1/1/2012 (Study Midpoint) and of Patients with UDTs in the Study Sample

Characteristic	All GH COT patients, 1/1/2012 *N*=5,380 % (n)	Study sample: COT patients with UDT 1/2011–12/2012* *N*=3,809 % (n)	Study sample: Number of UDTs 1/2011-12/2012 Mean (SD)
Male	36.6 (1,967)	39.4 (1,500)	1.5 (0.9)
Age (years)			
20–44	14.2 (763)	15.0 (573)	1.3 (0.7)
45–64	53.3 (2,866)	56.9 (2,168)	1.5 (0.8)
65+	32.6 (1,751)	28.0 (1,068)	1.4 (0.8)
Race			
White	84.1 (4,523)	84.5 (3,219)	1.4 (0.8)
African-American	4.3 (231)	4.2 (159)	1.4 (0.7)
Other	7.5 (402)	7.6 (291)	1.4 (0.7)
Missing data	4.2 (224)	3.7 (140)	1.5 (0.8)
Ethnicity			
Non-Hispanic	92.3 (4,966)	92.5 (3,522)	1.4 (0.8)
Hispanic	3.6 (192)	3.8 (143)	1.4 (0.7)
Missing data	4.1 (222)	3.8 (144)	1.5 (0.8)
Pain diagnosis, past year			
Back pain	61.4 (3,304)	59.8 (2,277)	1.4 (0.8)
Arthritis or joint pain	57.1 (3,072)	53.8 (2,050)	1.4 (0.8)
Limb extremity pain	42.3 (2,276)	41.0 (1,563)	1.4 (0.7)
General chronic pain	41.5 (2,232)	40.0 (1,522)	1.4 (0.9)
Neck pain	27.4 (1,473)	27.9 (1,064)	1.4 (0.7)
Abdominal pain	20.9 (1,123)	20.4 (778)	1.4 (0.8)
Fibromyalgia	13.4 (718)	12.8 (488)	1.4 (0.7)
Mental health diagnosis	55.2 (2,967)	55.5 (2,114)	1.4 (0.7)
Alcohol use disorder diagnosis	6.0 (325)	6.8 (261)	1.4 (0.9)
Substance use disorder diagnosis	11.1 (598)	12.4 (472)	1.5 (0.9)
Current smoker	26.2 (1,411)	28.9 (1,102)	1.4 (0.8)
Opioid daily dose (mean MED)			
<40 mg	67.4 (3,626)	63.7 (2,427)	1.3 (0.6)
40–<120 mg	24.3 (1,306)	26.6 (1,012)	1.5 (0.7)
≥120 mg	8.3 (448)	9.7 (370)	1.8 (1.4)
Days' supply, past 90 days			
Less than daily (70–83)	25.3 (1,362)	22.8 (869)	1.3 (0.5)
Daily/near-daily (84–96)	48.6 (2,616)	50.7 (1,930)	1.4 (0.8)
Excessive (≥97)	26.1 (1,402)	26.5 (1,010)	1.5 (0.9)
Opioid type			
Short-acting only	69.7 (3,750)	66.5 (2,532)	1.3 (0.6)
Long-acting only	7.8 (418)	8.9 (339)	1.6 (1.0)
Long-acting plus short-acting	22.5 (1,212)	24.6 (938)	1.3 (0.6)

UDT urine drug test, COT chronic opioid therapy, MED morphine-equivalent dose

* *Patient characteristics are for the first UDT in the study period. The study sample of 5,420 UDTs reflected 3,809 unique patients. Among the first UDTs in the study period for these 3,809 patients, 60.6 % were for female patients. The median (interquartile range) =1 (1, 2) UDTs for each patient subgroup. Some percentages do not sum to 100 across variable categories due to rounding of decimals*

aged 45+ versus 20–44, on moderate (0.52 [0.39, 0.70]) or high (0.22 [0.11, 0.43]) doses versus low doses, with daily/near-daily opioid supply versus less-than-daily supply (0.78 [0.63, 0.96]), and on long-acting opioids (versus short-acting opioids only).

Adjusted odds of THC were higher for males than females (2.20 [1.76, 2.75]), patients with versus without prior SUD diagnoses (1.62 [1.22, 2.16]), and smokers versus non-smokers (1.97 [1.58, 2.46]). They were lower for patients aged 45–64 (0.71 [0.55, 0.94]) and 65+ (0.15 [0.09, 0.24]) versus 20–44, and for patients with daily/near-daily opioid supply (0.68 [0.54, 0.86]) versus less-than-daily. Non-prescribed opioids were more common among African-Americans than whites (2.07 [1.16, 3.69]) and among patients with excessive (versus less-than-daily) opioid supply (1.59 [1.03, 2.46]), and less common among patients aged 45+ versus 20–44.

The small number of UDTs positive for illicit drugs and non-prescribed benzodiazepines precluded multivariable analyses. In bivariate analyses (Table 4), illicit drugs were more likely among patients with versus without prior SUD diagnoses (OR [95 % CI] = 2.91 [1.36, 6.25]) and smokers versus non-smokers (2.22 [1.04, 4.71]), and less likely among patients aged 45+. Patients with versus without prior mental health disorder diagnoses (1.82 [1.10, 2.99]) and with opioid doses 120+ mg versus <40 mg daily MED (2.26 [1.22, 4.19]) were more likely to have non-prescribed benzodiazepines detected.

Males were less likely than females (AOR = 0.42, 95 % CI = 0.29, 0.59) and African-Americans were less likely than whites (0.18 [0.04–0.73]) to have dilute samples (Table 4). Smokers were more likely than non-smokers to have dilute samples (1.44 [1.07, 1.94]).

Table 2. Results of 5,420 UDTs for Patients on COT in 2011–2012

Result	Percent (n)
Any aberrant result*	30.6 % (1,647 of 5,387)
Non-detection of prescribed opioid†	12.3 % (656 of 5,334)
Positive for THC‡	11.2 % (576 of 5,162)
Also positive for illicit drug	0.2 % (11 of 5,162)
Also negative for prescribed opioids	1.9 % (98 of 5,120)
Positive for non-prescribed (in prior 90 days) opioid§	5.3 % (283 of 5,377)
Positive for illicit drug‡, ‖	0.6 % (29 of 5,162)
Also negative for prescribed opioid	0.2 % (8 of 5,120)
Positive for cocaine	0.3 % (13 of 5,162)
Positive for amphetamine	0.3 % (14 of 5,162)
Positive for methamphetamine	0.2 % (12 of 5,162)
Positive for MDMA	0
Positive for PCP	0
Positive for 6-AM	0
Positive for non-prescribed (in prior 90 days) benzodiazepine‡	1.7 % (90 of 5,162)
Dilute	4.8 % (258 of 5,420)

UDT urine drug test, COT chronic opioid therapy, MDMA 3,4-methylenedioxymethamphetamine (ecstasy), PCP phencyclidine, 6-AM 6-acetylmorphine (heroin metabolite), THC tetrahydrocannabinol (marijuana)

Note: 12.3 % (634 of 5,162 UDTs) were positive for a benzodiazepine, with or without a recent prescription.

** Aberrant result = illicit drug, non-prescribed benzodiazepine, non-prescribed opioid, THC, prescribed opioid non-detection, or dilute sample. The denominator is 5,387 because UDTs for 33 patients prescribed only fentanyl, meperidine, or tramadol (not detected by the UDT) in the prior 90 days were excluded (it is unknown whether the result would have been aberrant due to no opioid in the urine). Another 14 UDTs for patients prescribed only tramadol, meperidine, or fentanyl were classified as aberrant for another reason, so their UDTs were not excluded.*

† Excluding 43 UDTs because of inability to definitively confirm absence of opioids due to dilute sample and 43 UDTs for patients prescribed only fentanyl (n=8; another patient prescribed fentanyl had a dilute urine sample so was already excluded), tramadol (n=32; three others prescribed only tramadol were already excluded due to dilute samples), or meperidine (n=3)

‡ Excluding 258 UDTs because of inability to exclude presence of illicit drug, THC, or benzodiazepine due to dilute urine sample

§ Non-prescribed opioids: excluded 43 of the 5,420 UDTs because of dilute sample.

‖ Illicit drug = amphetamine (in a patient with no prescription filled in the prior 90 days for a stimulant medication that is detected as amphetamine in the UDT), cocaine, methamphetamine, 6-AM (heroin metabolite), MDMA (ecstasy), PCP

DISCUSSION

Among UDTs performed in 2011–2012 for COT management of primary care patients in the integrated group practice of a large nonprofit healthcare system in the state of Washington, aberrant results were common (30.6 %), largely due to non-detection of prescribed opioids (12.3 % of UDTs) and detection of THC (11.2 %). Males, smokers, patients under the age of 45, and patients with prior SUD diagnoses had higher odds of aberrant results. Patients prescribed only short-acting opioids also had higher odds of aberrant results, apparently due to the greater likelihood of prescribed opioid non-detection. Patients on low opioid doses had higher odds of any aberrancy than those on moderate, but not high, doses. This may be explained by the findings that both moderate and high doses were negatively associated with one aberrancy (opioid non-detection), whereas only high dose was associated with another aberrancy, and this association was in the opposite direction (positive association with non-prescribed benzodiazepine).

Cocaine, amphetamine, and methamphetamine were each detected in <0.5 % of the UDTs and consistent with general population estimates of their use.[43] No UDT detected ecstasy, PCP, or heroin. The last finding is unsurprising, given heroin's rapid metabolism and its estimated use by only 0.1 % of the general population.[43]

This study extends prior knowledge regarding risk factors for aberrant UDTs. Most prior studies focused only on predictors of illicit drug detection and included THC with other illicit drugs.[16–19] Our findings confirm the importance of younger age, SUD history, and smoking as risks for aberrancies, and reveal that risk factors vary across aberrancy types. In this setting, male gender predicted only THC detection; furthermore, history of mental health and alcohol use disorders (at least in the past two years) generally did not predict aberrancies.

As hypothesized, younger patients and patients with a history of SUD had greater odds of illicit drug detection. Low frequency of UDT illicit drug detection has also been reported for older patients in pain clinics.[17,18] Patients with prior SUD diagnoses had almost three times greater odds of an illicit drug finding. Among Veterans Affairs healthcare network COT patients, the percentage of UDTs positive for illicit substances (including THC) was about three times higher for those with prior-year SUD diagnoses.[19] We found that smokers had over twice the odds of an illicit drug result. Little previous research has examined associations between smoking and chronic pain patient UDT results, although smoking is associated with opioid misuse/abuse among chronic pain patients[32,33] and with illicit drug abuse in the general population.[44] Our hypothesis that males would have more illicit drug results was not confirmed; findings in previous studies were mixed.[16,18] Consistent with prior studies,[18,20] we found no significant association between opioid regimen characteristics and illicit drugs.

By far, the most common non-opioid substance detected was THC (11.2 % of UDTs), replicating findings in a study of veterans on COT.[20] Marijuana is the most commonly used recreational drug.[43] An estimated 7.3 % of the U.S. population uses marijuana, with approximately 7.6 million Americans using marijuana daily or almost daily.[43] Currently, 20 states (including Washington) plus the District of Columbia allow marijuana for medical use, and two states (including Washington) have legalized its recreational use. Associations have been reported between marijuana use and physical and mental health problems,[45] and between UDT detection of THC and opioid misuse,[23] but little is known concerning marijuana's effects on COT patient safety and outcomes. This is an important priority for future research.

As hypothesized, younger patients, males, and patients with a history of SUD had greater odds of THC detection. Adjusting for other characteristics, males and smokers had

Table 3. UDT Results for Patient and Opioid Subgroups

Variable	All UDTs *N*=5,420 UDTs %*	Any aberrant result *n*=1,647/ 5,387 UDTs %†	Prescribed opioid non-detection *n*=656/ 5,334 UDTs %†	THC, no illicit drug *n*=565/ 5,162 UDTs %†	Non-prescribed opioid *n*=283/ 5,377 UDTs %†	Illicit drug *n*=29/ 5,162 UDTs %†	Non-prescribed benzodiazepine *n*=90/5,162 UDTs %†	Dilute *n*=258/ 5,420 UDTs %†
Gender								
Female	59.7	29.0	12.1	7.9	5.2	0.6	1.7	6.2
Male	40.3	32.9	12.7	15.3	5.4	0.5	1.8	2.7
Age, years								
20–44	13.8	41.8	18.4	18.0	9.3	1.4	1.7	4.9
45–64	58.6	33.4	13.1	13.2	5.0	0.4	2.1	4.8
65+	27.5	18.9	7.4	2.6	3.9	0.4	1.1	4.7
Race								
White	84.6	29.5	11.4	10.3	4.8	0.5	1.8	5.1
African-American	4.0	34.4	15.0	16.0	9.4	0.9	0.5	0.9
Other	7.7	37.3	19.1	11.6	6.6	1.5	1.3	4.6
Missing	3.8	37.9	15.6	17.3	8.7	0	2.5	1.9
Ethnicity								
Non-Hispanic	92.3	30.2	12.1	10.5	5.2	0.6	1.7	4.9
Hispanic	3.7	33.2	12.2	13.2	5.0	0	2.5	2.5
Missing	3.9	38.0	17.1	18.8	7.1	0	2.4	2.8
Mental health diagnosis								
No	44.7	29.2	11.5	10.7	5.1	0.6	1.2	4.5
Yes	55.3	31.7	12.9	11.1	5.4	0.5	2.2	5.0
Alcohol use disorder diagnosis								
No	93.3	30.5	12.1	10.9	5.4	0.5	1.7	4.9
Yes	6.7	31.1	14.5	12.2	3.9	0.9	2.3	3.3
Substance use disorder diagnosis								
No	86.6	29.6	11.9	10.1	5.1	0.5	1.6	4.8
Yes	13.5	37.0	14.8	16.7	6.6	1.3	2.4	4.5
Current smoker								
No	69.9	27.0	11.4	8.2	5.1	0.4	1.5	4.3
Yes	30.1	38.8	14.4	17.5	5.6	0.9	2.2	6.0
Opioid daily MED								
<40 mg	59.9	33.5	17.0	11.0	4.9	0.7	1.4	4.5
40–<120 mg	28.6	26.1	6.6	11.0	5.3	0.5	2.0	4.6
120+ mg	11.5	26.7	2.3	10.3	7.1	0.3	3.1	6.4
Days' supply								
Less than daily	20.4	32.1	16.0	12.3	3.7	0.4	1.6	3.4
Daily/near-daily	52.3	30.4	12.3	10.3	5.4	0.6	1.7	5.0
Excessive	27.3	29.8	9.6	11.2	6.1	0.6	1.9	5.2
Opioid type								
Short-acting only	63.3	34.1	17.2	11.2	5.2	0.6	1.5	4.7
Long-acting only	9.9	24.9	4.2	10.2	5.6	0.4	2.2	5.0
Long-acting plus short-acting	26.9	24.5	4.1	10.7	5.3	0.5	2.1	4.7

UDT urine drug test, THC tetrahydrocannabinol, MED morphine-equivalent dose
* *Percentage of all 5,420 UDTs. For example, among the 5,420 UDTs, 59.7 % were for females.*
† *Percentages are based on UDTs for each subgroup. For example, among UDTs for females, 29 % had an aberrant result.*

approximately twice the odds and patients with prior SUD diagnoses had 1.6 times the odds of THC detection. It is unclear why patients with less-than-daily opioid supply also had higher odds; this may reflect patient preference for marijuana as a primary method for managing pain and/or physician reluctance to prescribe opioids daily for marijuana users.

Non-prescribed opioids (detected in 5 % of UDTs) were more common among patients under the age of 45, consistent with previous findings of greater illicit drug use and opioid abuse among younger adults.[18,22–29] Excessive days' supply of prescribed opioids was also a risk factor, suggesting the importance of prescriber attention to total days' supply of prescribed opioids. The odds of having a non-prescribed opioid detected were over twice as great for African-Americans as for whites; further research is needed to explore possible reasons.

In 12.3 % of UDTs, no opioid prescribed in the prior 90 days was detected. While the detection threshold was quite low, extremely low opioid levels could have been missed. Prescribed opioid non-detection could reflect no opioid use in the time period allowing detection. Indeed, prescribed opioid non-detection was more common among patients with low opioid doses, less-than-daily opioid supply (versus daily/near-daily), and only short-acting opioid prescriptions. The same proportion of UDTs negative for prescribed opioids (12 %) was reported at an urban teaching hospital pain clinic.[18] Unlike our study, this result was not associated with opioid type or dose, although their patient sample was smaller and average dose was much higher. Opioid non-detection could also reflect diversion. In our study, prescribed opioid non-detection was more common among patients under the age of 45 or with prior SUD diagnoses – both risk factors for substance abuse.

Table 4. Results of Regression Models Predicting Aberrant UDT Findings

	Any aberrant result		Prescribed opioid non-detection		THC, no illicit drug		Non-prescribed opioid		Illicit drug		Non-prescribed benzodiazepine		Dilute sample	
Predictor	**AOR**	**95 % CI**	**AOR**	**95 % CI**	**AOR**	**95 % CI**	**AOR**	**95 % CI**	**OR**	**95 % CI**	**OR**	**95 % CI**	**AOR**	**95 % CI**
Gender (ref. = Female)	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Male	**1.24**	**1.07, 1.43**	1.16	0.96, 1.40	**2.20**	**1.76, 2.75**	1.03	0.77, 1.38	0.87	0.41, 1.88	1.09	0.69, 1.73	**0.42**	**0.29, 0.59**
Age, yrs (ref. = 20–44)	–	–	–	–	–	–	–	–	–	–	–	–	–	–
45–64	**0.77**	**0.65, 0.92**	**0.79**	**0.63, 0.998**	**0.71**	**0.55, 0.94**	**0.52**	**0.38, 0.70**	**0.30**	**0.13, 0.69**	1.22	0.63, 2.39	1.08	0.74, 1.60
65+	**0.40**	**0.32, 0.50**	**0.44**	**0.32, 0.59**	**0.15**	**0.09, 0.24**	**0.44**	**0.30, 0.65**	**0.30**	**0.10, 0.91**	0.66	0.27, 1.62	1.09	0.69, 1.72
Race* (ref.= White)	–	–	–	–	–	–	–	–	–	–	–	–	–	–
African-American	1.13	0.81, 1.56	1.14	0.76, 1.72	1.41	0.88, 2.23	**2.07**	**1.16, 3.69**			0.25	0.04, 1.82	**0.18**	**0.04, 0.73**
Other	1.25	0.98, 1.59	**1.74**	**1.26, 2.39**	0.88	0.57, 1.35	1.29	0.80, 2.08			0.69	0.28, 1.72	0.90	0.54, 1.52
Missing data	1.25	0.51, 3.07	1.02	0.47, 2.23	0.77	0.24, 2.46	3.92	0.56, 27.5			1.37	0.55, 3.42	0.28	0.07, 1.11
Ethnicity* (ref. = Non-Hispanic)	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Hispanic	1.08	0.75, 1.54	0.83	0.50, 1.39	1.40	0.82, 2.39	0.90	0.45, 1.84			1.52	0.52, 4.49	0.47	0.20, 1.14
Missing data	1.04	0.45, 2.39	1.46	0.69, 3.09	1.70	0.57, 5.04	0.39	0.06, 2.59			1.45	0.58, 3.60	1.87	0.59, 5.89
Mental health diagnosis (ref. =No)	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Yes	1.11	0.96, 1.27	1.19	0.99, 1.44	1.05	0.84, 1.31	1.02	0.78, 1.34	0.87	0.43, 1.76	**1.82**	**1.10, 2.99**	0.94	0.69, 1.29
Alcohol use disorder diagnosis (ref. =No)	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Yes	0.84	0.64, 1.11	1.08	0.76, 1.53	0.79	0.52, 1.20	0.67	0.38, 1.19	1.58	0.48, 5.26	1.34	0.52, 3.47	0.72	0.39, 1.34
Substance use disorder diagnosis (ref. =No)	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Yes	**1.42**	**1.17, 1.72**	**1.70**	**1.31, 2.20**	**1.62**	**1.22, 2.16**	1.20	0.85, 1.69	**2.91**	**1.36, 6.25**	1.51	0.85, 2.67	0.86	0.55, 1.35
Current smoker (ref. = No)	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Yes	**1.50**	**1.30, 1.73**	1.20	0.99, 1.46	**1.97**	**1.58, 2.46**	0.95	0.72, 1.26	**2.22**	**1.04, 4.71**	1.45	0.90, 2.31	**1.44**	**1.07, 1.94**
Opioid daily MED (ref. =<40 mg)	–	–	–	–	–	–	–	–	–	–	–	–	–	–
40–<120 mg	**0.78**	**0.65, 0.95**	**0.52**	**0.39, 0.70**	0.89	0.66, 1.19	1.08	0.72, 1.60	0.73	0.31, 1.75	1.42	0.85, 2.37	1.14	0.79, 1.66
120+ mg.	0.83	0.60, 1.14	**0.22**	**0.11, 0.43**	0.66	0.42, 1.05	1.59	0.92, 2.73	0.53	0.12, 2.28	**2.26**	**1.22, 4.19**	1.80	0.92, 3.53
Days' supply (ref. =Less than daily)	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Daily/near-daily	0.88	0.75, 1.04	**0.78**	**0.63, 0.96**	**0.68**	**0.54, 0.86**	1.42	0.98, 2.05	1.69	0.46, 6.14	1.07	0.57, 2.03	1.42	0.95, 2.10
Excessive	0.98	0.80, 1.20	0.91	0.69, 1.21	0.74	0.54, 1.005	**1.59**	**1.03, 2.46**	1.52	0.38, 6.10	1.21	0.61, 2.40	1.51	0.94, 2.41
Opioid type (ref.=Short-acting)			–	–	–	–	–	–	–	–	–	–	–	–
Long-acting only	**0.72**	**0.55, 0.95**	**0.35**	**0.21, 0.57**	0.97	0.64, 1.46	1.02	0.62, 1.68	0.64	0.15, 2.75	1.42	0.69, 2.92	0.92	0.55, 1.55
Long-acting plus short-acting	**0.67**	**0.54, 0.83**	**0.35**	**0.24, 0.50**	1.04	0.76, 1.42	0.78	0.50, 1.20	0.82	0.34, 1.97	1.37	0.83, 2.27	0.74	0.47, 1.15

UDT urine drug test, THC tetrahydrocannabinol, AOR adjusted odds ratio, ref. reference category, MED morphine-equivalent dose

*Note: **Bolded values** indicate statistically significant at P< 0.05. In predicting THC, the odds ratios in the multivariable model were slightly lower than in the bivariate analyses, but patterns of statistical significance were the same. In the multivariable regression analyses predicting prescribed opioid non-detection and dilute sample, results were similar to bivariate results, with the following minor exceptions: In predicting prescribed opioid non-detection, current smoker and excessive days' supply were significant in the bivariate, but not the multivariable, models, and substance use disorder diagnosis was significant in the multivariable, but not the bivariate, model. For prediction of dilute samples, the ORs for days' supply 84–96 and ≥97 were significant relative to 70–83 in the bivariate, but not the multivariable, analyses. In each case, differences in ORs were minor, but minor differences in the 95 % CI resulted in changes in statistical significance.*

* *Race and ethnicity could not be included in model predicting detection of illicit drugs due to insufficient subgroup sizes*

UDTs negative for prescribed opioids require discussion between prescriber and patient to identify reasons and appropriate response.

Benzodiazepines were detected in 12 % of UDTs; 1.7 % of UDTs detected benzodiazepines in patients without recent benzodiazepine prescriptions. Because benzodiazepines are associated with increased risk of opioid overdose,[46] UDTs have value for informing opioid prescribers previously unaware of concomitant benzodiazepine use.

Dilute urine samples, present in 4.8 % of tests, were significantly less common among men and African-Americans. Dilute urine may result from multiple causes (e.g., attempts to avoid drug detection, diuretic use, diet, fluid consumption, race, genetics), and requires interpretation by patients' physicians.[47]

Regarding study limitations, the smoking and diagnosis information in the EHR may under-represent true rates of smoking and of mental health, alcohol use disorders, and other substance use disorders. The study was conducted in a single healthcare system, and most patients were on low–moderate opioid doses and on short-acting opioids only; results may not generalize to other settings. UDT aberrancies among COT patients are likely to be more common in pain clinics and other settings with a higher prevalence of substance abuse. Some patients may have obtained medications from non-GH pharmacies, but this would have been more expensive, and previous research indicates that GH members obtain nearly all of their prescription medications from GH pharmacies.[48] Study strengths include the large primary care population-based sample data on UDTs, patient diagnoses, and prescribed opioids, as well as the use of multivariable models to predict specific types of UDT aberrancies.

Our findings may be useful for making decisions with regard to UDT frequency and protocol for COT patients in settings with a low prevalence of drug abuse. The costs, physician and patient burden, rarity of illicit drug detection, ability of some patients to purposely avoid illicit drug detection, uncertainty regarding responses to aberrant results, and potential harms of UDTs (e.g., incorrectly assuming illicit drug use or diversion) must be weighed against potential benefits in deterrence of diversion or illicit drug use and in providing an objective reference of COT compliance, illicit drug use, and use of medications (e.g., non-prescribed opioids, benzodiazepines) that increase COT risks. Systematic reviews have noted the paucity (especially in primary care settings) and poor quality of studies of clinical outcomes associated with UDTs for COT patients.[2,49–51] Clearly, more research is needed concerning the impact of UDTs on patient and public health safety and the cost-effectiveness of specific UDT guidelines in various settings. Different patient population scenarios may need different guidelines.

In the absence of adequate data, a policy of occasional random urine drug testing for all COT patients, with testing frequency based on known safety and abuse risk factors, might be reasonable. Physician prediction of individual patient risk for aberrant results is likely to be imprecise, and a policy of routine urine drug testing may be easier to administer, may mitigate the possible negative impact of selective UDTs on provider-patient relationships, and may discourage drug abusers from seeking COT. Our results suggest that it might be prudent to order UDTs more frequently for patients under the age of 45, smokers, and those with a history of SUD.

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Corresponding Author: *Judith A. Turner, PhD; Department of Psychiatry and Behavioral Sciences, University of Washington, Seattle, WA, USA (e-mail: jturner@uw.edu).*

REFERENCES

1. **Kirschner N, Ginsburg J, Sulmasy LS.** Prescription drug abuse: a policy position paper from the American College of Physicians. Ann Intern Med. 2014;160:198–200.
2. **Starrels JL, Becker WC, Alford DP, Kapoor A, Williams A, Turner BJ.** Systematic review: treatment agreements and urine drug testing to reduce opioid misuse in patients with chronic pain. Ann Intern Med. 2010;152:712–20.
3. **Warner M, Chen LH, Makuc DM, Anderson RN, Minino AM.** Drug poisoning deaths in the United States, 1980–2008. NCHS data brief, no. 81. National Center for Health Statistics. 2011 [Accessed August 13, 2014]. Available at: http://www.cdc.gov/nchs/data/databriefs/db81.htm.
4. **Starrels J, Becker W, Weiner M, Li X, Heo M, Turner B.** Low use of opioid risk reduction strategies in primary care even for high risk patients with chronic pain. J Gen Intern Med. 2011;26:958–64.
5. **Bohnert ASB, Valenstein M, Bair MJ, et al.** Association between opioid prescribing patterns and opioid overdose-related deaths. JAMA. 2011;305(13):1315–21.
6. **Volkow ND, McLellan TA.** Curtailing diversion and abuse of opioid analgesics without jeopardizing pain treatment. JAMA. 2011;305(13):1346–7.
7. **Rolfs RT, Johnson E, Williams NJ, Sundwall DN.** Utah Clinical Guidelines on Prescribing Opioids for Treatment of Pain. J Pain Palliat Care Pharmacother. 2010;24(3):219–35.
8. **Chou R, Fanciullo GJ, Fine PG, et al.** Clinical guidelines for the use of chronic opioid therapy in chronic noncancer pain. J Pain. 2009;10(2):113–30.
9. **Manchikanti L, Abdi S, Atluri S, et al.** American Society of Interventional Pain Physicians (ASIPP) Guidelines for Responsible Opioid Prescribing in Chronic Non-Cancer Pain: Part 2-Guidance. Pain Physician. 2012;15:S67-S116.
10. Department of Veterans Affairs, Department of Defense. VA/DoD Clinical practice guideline for management of opioid therapy for chronic pain. Department of Veterans Affairs, Department of Defense. 2010 [Accessed August 13, 2014]. Available at: http://www.healthquality.va.gov/guidelines/Pain/cot/.

11. **Nuckols TK, Anderson L, Popescu I, et al.** Opioid prescribing: a systematic review and critical appraisal of guidelines for chronic pain. Ann Intern Med. 2014;160:38–47.
12. **Peppin JF, Passik SD, Couto JE, et al.** Recommendations for urine drug monitoring as a component of opioid therapy in the treatment of chronic pain. Pain Med. 2012;13:886–96.
13. Colorado Division of Workers' Compensation. Chronic Pain Disorder Medical Treatment Guidelines 2011 [Accessed August 13, 2014]. Available at: http://www.colorado.gov/cs/Satellite?blobcol=urldata&blobheader=application%2Fpdf&blobkey=id&blobtable=MungoBlobs&blobwhere=1251894637011&ssbinary=true.
14. **Kahan M, Mailis-Gagnon A, Wilson L, Srivastava A.** Canadian guideline for safe and effective use of opioids for chronic noncancer pain: clinical summary for family physicians. Part 1: general population. Can Fam Physician. 2011;57:1269–76.
15. **Turner JA, Saunders K, Shortreed SM, et al.** Chronic opioid therapy risk reduction initiative: impact on urine drug testing rates and results. J Gen Intern Med. 2014;29:305–11.
16. **Couto JE, Romney MC, Leider HL, Sharma S, Goldfarb NI.** High rates of inappropriate drug use in the chronic pain population. Popul Health Manag. 2009;12(4):185–90.
17. **Manchikanti L, Manchukonda R, Pampati V, et al.** Does random urine drug testing reduce illicit drug use in chronic pain patients receiving opioids? Pain Physician. 2009;9(2):123–9.
18. **Michna E, Jamison RN, Pham L-D, et al.** Urine toxicology screening among chronic pain patients on opioid therapy: frequency and predictability of abnormal findings. Clin J Pain. 2007;23:173–9.
19. **Morasco BJ, Duckart JP, Dobscha SK.** Adherence to clinical guidelines for opioid therapy for chronic pain in patients with substance use disorder. J Gen Intern Med. 2011;26(9):965–71.
20. **Morasco BJ, Duckart JP, Carr TP, Deyo RA, Dobscha SK.** Clinical characteristics of veterans prescribed high doses of opioid medications for chronic non-cancer pain. Pain. 2010;151:625–32.
21. **Trescott CE, Beck RM, Seelig MD, Von Korff M.** Group Health's initiative to avert opioid misuse and overdose among patients with chronic noncancer pain. Health Aff. 2011;30:1420–4.
22. **Turk DC, Swanson KS, Gatchel RJ.** Predicting opioid misuse by chronic pain patients: a systematic review and literature synthesis. Clin J Pain. 2008;24:497–508.
23. **Ives T, Chelminski P, Hammett-Stabler C, et al.** Predictors of opioid misuse in patients with chronic pain: a prospective cohort study. BMC Health Services Research. 2006;6(1):46.
24. **Katz NP, Sherburne S, Beach M, et al.** Behavioral monitoring and urine toxicology testing in patients receiving long-term opioid therapy. Anesthesia & Analgesia. 2003;97:1097–102.
25. **Edlund MJ, Steffick D, Hudson T, Harris KM, Sullivan M.** Risk factors for clinically recognized opioid abuse and dependence among veterans using opioids for chronic non-cancer pain. Pain. 2007;129(3):355–62.
26. **Reid MC, Engles-Horton LL, Weber MB, Kerns RD, Rogers EL, O'Connor PG.** Use of opioid medications for chronic noncancer pain syndromes in primary care. J Gen Intern Med. 2002;17:173–9.
27. **White AG, Birnbaum HG, Schiller M, Tang J, Katz NP.** Analytic models to identify patients at risk for prescription opioid abuse. Am J Manag Care. 2009;15:897–906.
28. **Sullivan MD, Edlund MJ, Fan M-Y, DeVries A, Brennan Braden J, Martin BC.** Risks for possible and probable opioid misuse among recipients of chronic opioid therapy in commercial and Medicaid insurance plans: The TROUP Study. Pain. 2010;150(2):332–9.
29. **Edlund MJ, Martin BC, Fan M-Y, Devries A, Braden JB, Sullivan MD.** Risks for opioid abuse and dependence among recipients of chronic opioid therapy: Results from the TROUP Study. Drug Alcohol Depend. 2010;112(1–2):90–8.
30. **Michna E, Ross EL, Hynes WL, et al.** Predicting aberrant drug behavior in patients treated for chronic pain: importance of abuse history. J Pain Symptom Manage. 2004;28(3):250–8.
31. **Wasan AD, Butler SF, Budman SH, Benoit C, Fernandez K, Jamison RN.** Psychiatric history and psychologic adjustment as risk factors for aberrant drug-related behavior among patients with chronic pain. Clin J Pain. 2007;23:307–15.
32. **Liebschutz JM, Saitz R, Weiss RD, et al.** Clinical factors associated with Prescription Drug Use Disorder in urban primary care patients with chronic pain. J Pain. 2010;11(11):1047–55.
33. **Akbik H, Butler SF, Budman SH, Fernandez K, Katz NP, Jamison RN.** Validation and clinical application of the Screener and Opioid Assessment for Patients with Pain (SOAPP). J Pain Symptom Manage. 2006;32(3):287–93.
34. Public Health Service and Health Care Financing Administration. International classification of diseases, 9th revision, clinical modification. Washington, D. C.: Public Health Service; 1980.
35. **Elixhauser A, Steiner C, Palmer L.** Clinical Classifications Software (CCS), 2014. U.S. Agency for Healthcare Research and Quality. 2013 [Accessed August 13, 2014]. Available at: http://www.hcup-us.ahrq.gov/toolssoftware/ccs/ccs.jsp.
36. **Wiley LK, Shah A, Xu H, Bush WS.** ICD-9 tobacco use codes are effective identifiers of smoking status. J Am Med Inform Assoc. 2013;20(4):652–8.
37. **Raebel MA, Newcomer SR, Reifler LM, et al.** Chronic use of opioid medications before and after bariatric surgery. JAMA. 2013;310(13):1369–76.
38. **Von Korff M, Saunders K, Ray GT, et al.** De facto long-term opioid therapy for noncancer pain. Clin J Pain. 2008;24:521–7.
39. **Carson S, Thakurta S, Low A, Smith B, Chou R.** Drug class review: long-acting opioid analgesics: Final Update 6 Report. Portland, OR: Oregon Health & Science University. 2011 [Accessed August 13, 2014]. Available at: http://www.ncbi.nlm.nih.gov/books/NBK62335/.
40. **McCullagh P, Nelder JA.** Generalized Linear Models. London: Chapman & Hall; 1989.
41. **Liang JK-Y, Zeger SL.** Longitudinal data analysis using generalized linear models. Biometrika. 1986;73:13–22.
42. **Zeger SL, Liang JK-Y.** Longitudinal data analysis for discrete and continuous outcomes. Biometrics. 1986;42:121–30.
43. Substance Abuse and Mental Health Services Administration. Results from the 2012 National Survey on Drug Use and Health: Summary of national findings. NSDUH Series H-46, HHS Publication No. (SMA) 13–4795. Rockville, MD: Substance Abuse and Mental Health Services Administration. 2013 [Accessed August 13, 2014]. Available at: http://www.samhsa.gov/data/NSDUH/2012SummNatFindDetTables/NationalFindings/NSDUHresults2012.htm.
44. **Berg CJ, Wen H, Cummings JR, Ahluwalia JS, Druss BG.** Depression and substance abuse and dependency in relation to current smoking status and frequency of smoking among nondaily and daily smokers. Am J Addict. 2013;22:581–9.
45. **Fuster D, Cheng DM, Allensworth-Davies D, Palfai TP, Samet JH, Saitz R.** No detectable association between frequency of marijuana use and health or healthcare utilization among primary care patients who screen positive for drug use. J Gen Intern Med. 2014;29:133–9.
46. **Gudin JA, Mogali S, Jones JD, Comer SD.** Risks, management, and monitoring of combination opioid, benzodiazepines, and/or alcohol use. Postgrad Med. 2013;125:115–30.
47. **Chaturvedi AK, Sershon JL, Craft KJ, et al.** Effects of fluid load on human urine characteristics related to workplace drug testing. J Anal Toxicol. 2013;37(1):5–10.
48. **Saunders KW, Davis RL, Stergachis A.** Group Health Cooperative. In: Strom B, editor. Pharmacoepidemiology. 4th ed. West Sussex, England: John Wiley and Sons; 2005. p. 223–39.
49. **Chou R, Ballantyne JC, Fanciullo GJ, Fine PG, Miaskowski C.** Research gaps on use of opioids for chronic noncancer pain: findings from a review of the evidence for an American Pain Society and American Academy of Pain Medicine Clinical Practice Guideline. J Pain. 2009;10(2):147–59.
50. **Chou R, Fanciullo GJ, Fine PG, Miaskowski C, Passik SD, Portenoy RK.** Opioids for chronic noncancer pain: prediction and identification of aberrant drug-related behaviors: a review of the evidence for an American Pain Society and American Academy of Pain Medicine Clinical Practice Guideline. J Pain. 2009;10(2):131–46.
51. **Dupouy J, Mémier V, Catala H, Lavit M, Oustric S, Lapeyre-Mestre M.** Does urine drug abuse screening help for managing patients? A systematic review. Drug Alcohol Depend. 2014;136:11–20.