

Observational Study

Repeated Quantitative Urine Toxicology Analysis May Improve Chronic Pain Patient Compliance with Opioid Therapy

Nebojsa Nick Knezevic, MD, PhD¹⁻³, Omar M. Khan, MD¹, Afsaneh Beiranvand, MD¹, and Kenneth D. Candido, MD¹⁻³

From: ¹Department of Anesthesiology, Advocate Illinois Masonic Medical Center, Chicago, IL; ²Department of Anesthesiology, University of Illinois, Chicago, IL; ³Department of Surgery, University of Illinois, Chicago, IL

Address Correspondence:
Nebojsa Nick Knezevic, MD
Department of Anesthesiology
Advocate Illinois Masonic
Medical Center
836 W. Wellington Ave. Suite 4815
Chicago, IL 60657
Email: nick.knezevic@gmail.com

Disclaimer: There was no external funding in the preparation of this manuscript. Conflict of interest: Each author certifies that he or she, or a member of his or her immediate family, has no commercial association (i.e., consultancies, stock ownership, equity interest, patent/licensing arrangements, etc.) that might pose a conflict of interest in connection with the submitted manuscript.

Manuscript received: 04-27-2016
Revised manuscript received:
07-27-2016
Accepted for publication:
08-04-2016

Free full manuscript:
www.painphysicianjournal.com

Background: Even though serious efforts have been undertaken by different medical societies to reduce opioid use for treating chronic benign pain, many Americans continue to seek pain relief through opioid consumption. Assuring compliance of these patients may be a difficult aspect of proper management even with regular behavioral monitoring.

Objective: The purpose of this study was to accurately assess the compliance of chronic opioid-consuming patients in an outpatient setting and evaluate if utilizing repeated urine drug testing (UDT) could improve compliance.

Study Design: Retrospective analysis of prospectively collected data.

Setting: Outpatient pain management clinic.

Methods: After Institutional Review Board (IRB) approval, a retrospective analysis of data for 500 patients was conducted. We included patients who were aged 18 years and older who were treated with opioid analgesic medication for chronic pain. Patients were asked to provide supervised urine toxicology specimens during their regular clinic visits, and were asked to do so without prior notification. The specimens were sent to an external laboratory for quantitative testing using liquid chromatography-tandem mass spectrometry.

Results: Three hundred and eighty-six (77.2%) patients were compliant with prescribed medications and did not use any illicit drugs or undeclared medications. Forty-one (8.2%) patients tested positive for opioid medication(s) that were not prescribed in our clinic; 8 (1.6%) of the patients were positive for medication that was not prescribed by any physician and was not present in the Illinois Prescription Monitoring Program; 5 (1%) patients tested negative for prescribed opioids; and 60 (12%) patients were positive for illicit drugs (8.6% marijuana, 3.2% cocaine, 0.2% heroin). Repeated UDTs following education and disclosure, showed 49 of the 77 patients (63.6%) had improved compliance.

Limitations: This was a single-site study and we normalized concentrations of opioids in urine with creatinine levels while specific gravity normalization was not used.

Conclusions: Our results showed that repeated UDT can improve compliance of patients on opioid medications and can improve overall pain management. We believe UDT testing should be used as an important adjunctive tool to help guide clinical decision-making regarding opioid therapy, potentially increasing future quality of care.

Key words: Urine toxicology analysis, chronic pain, opioids, compliance, pain management, urine drug testing, urine drug screening

Pain Physician Opioid Special Issue 2017; 20:S135-S145

The number of patients experiencing chronic pain increases annually, as well as the associated health care costs and the costs from lost productivity. Gaskin and Richard (1) collected data from a 2008 Medical Expenditure Panel Survey which Manchikanti et al (2) further analyzed and estimated that the total annual financial cost of pain management in the United States is approximately \$100 billion. These estimates included health care costs as well as costs from lost productivity (1,2). As further estimated by Manchikanti et al, there are approximately 44 million Americans who deal with moderate and severe chronic pain (2). It is estimated that 40% of all visits to primary care physicians are related to chronic pain (3).

Opioid analgesic therapy provides treatment for chronic severe pain and is shown to have short-term benefits (4). However, long-term opioid treatment is unproven and also comes with a risk of physiological dependence, tolerance, misuse, abuse, and development of an opioid use disorder. Birnbaum et al (5) reported that the calculated U.S. societal costs for abuse of prescription opioids in 2007 was \$55.7 billion, which included loss of productivity costs, health care costs, and criminal justice costs.

The Drug Awareness Warning Network Report (DAWN) showed that there were 1,244,872 emergency department visits due to nonmedical use of pharmaceutical drugs of which 366,181 were due to nonmedical use of opioids in 2011 (6). Overdose deaths due to prescription opioids are now at a higher rate than overdose deaths due to cocaine and heroin combined (7). The compliance and adherence of the opioid-consuming patient is an integral yet difficult aspect of proper management in the outpatient setting (8). Individuals who deal with opioid use disorder tend not to be truthful in self-reporting out of fear that they will not receive their desired medication if they express adverse events (i.e., constipation, etc.) or lack of efficacy. Data shows that self-reported drug use is unreliable (9,10). In a study conducted by Manchikanti et al (11), it was shown that 27% of patients had incorrectly reported their opioid use. Sometimes patients with chronic pain will resort to doctor shopping for their opioid medication. Physicians who may be concerned about factors such as misuse, abuse, opioid-related fatalities, and opioid use disorder, may lead to under dosing of opioids and therefore to inadequate pain control. Furthermore, physicians may also be deterred from prescribing opioids due to fear of being prosecuted under drug trafficking laws if a patient diverts their pain medication (12).

Many practitioners continue to rely solely upon patient self-reporting and behavioral observations in assessing aberrant drug related behavior (13). Despite the fact that written agreements are becoming more commonplace between physicians and patients, illicit drug use is usually not voluntarily disclosed by patients (14). The use of urine drug testing (UDT) may increase patient compliance and thus improve pain management by helping elucidate objective results that can be discussed with patients (educational process) as a prelude to implementing an analgesic protocol on their behalf (action plan). However, at the other end of the spectrum, physicians may also inappropriately utilize such tests for financial gain (15,16).

The purpose of this study was to accurately assess the compliance of chronic opioid-consuming patients in an outpatient pain management setting by utilizing repeated UDTs.

METHODS

After Advocate Healthcare Institutional Review Board (IRB) approval, a retrospective analysis of prospectively collected data for 500 opioid-consuming patients was conducted. We included patients who were aged 18 years and older with chronic severe pain ($\geq 8/10$ on a numeric rating scale [NRS]) who were treated with opioid medication for at least one month. These patients were treated since September 2012 at Advocate Illinois Masonic Pain Clinic. Patients who had acute pain conditions or pain resulting from cancer were excluded from this study.

All of the patients who participated in this study signed the Pain Management Center's Consent and Treatment Agreement prior to receiving any opioid prescription medication. By signing this agreement, patients acknowledged that they have never been diagnosed, treated, or arrested for substance abuse or opioid use disorder; that they have never been involved in the sale, illegal possession, and distribution, or diversion of a controlled substance; that they agreed to only take medication prescribed by the physician from our clinic, and that if they were ever to give, sell, or misuse the medication(s), that their treatment would be immediately discontinued ("Zero Tolerance Policy"). The agreement also contains a list of possible risks associated with opioid use, which by signing, the patient certified that they understand and agree to be compliant. By employing such agreements, the physician is assured that the patient has consented to treatment and understands the listed terms of opioid use.

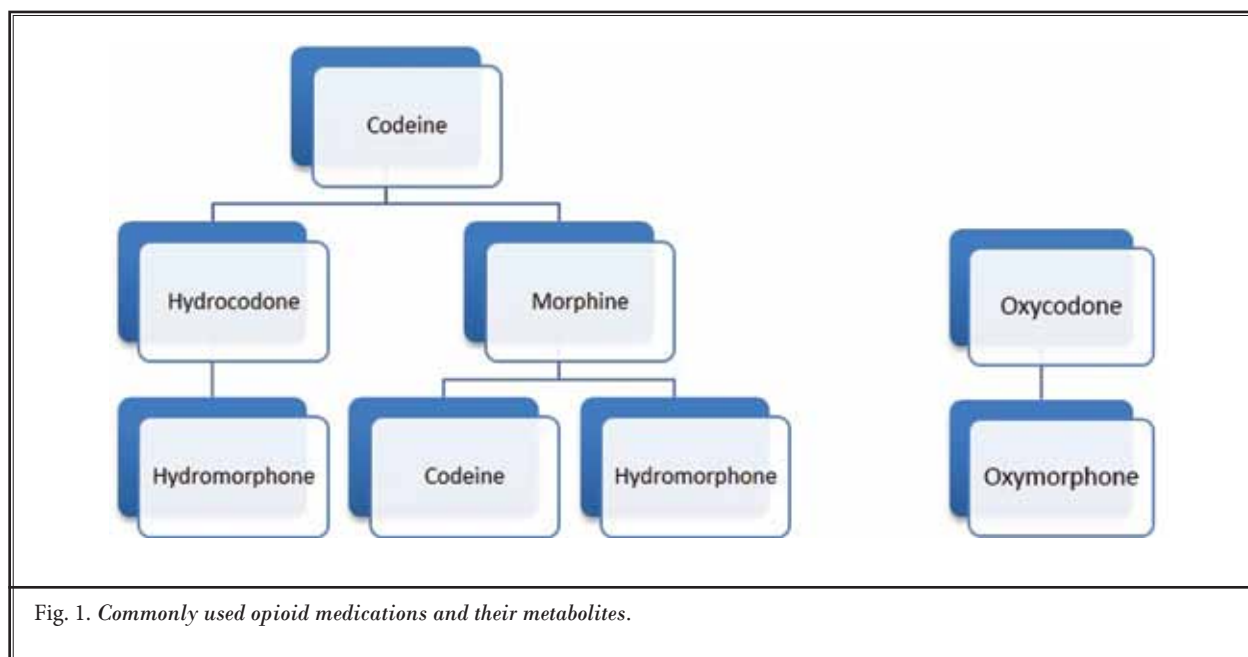


Fig. 1. Commonly used opioid medications and their metabolites.

Patients who were being treated with opioid medications were asked to provide supervised urine toxicology specimens during their regular clinic visits, and were asked to do so without prior notification. Before providing a urine sample, patients were asked when they had last taken their opioid medication to assure that the medication use was within the window of detection. A specimen collector would escort the patient to the restroom without their belongings (including coats, hats, and handbags) and would provide instructions, including “no use of the sink, and no toilet flushing” before handing over the specimen. The collected urine specimens were sent to an external laboratory for testing. The laboratory then conducted quantitative testing using liquid chromatography-tandem mass spectrometry (LC-MS/MS) to analyze for the presence or absence of specific drugs and their metabolites including opioids, sedative hypnotics, benzodiazepines, amphetamines, and illicit drugs including cocaine, cannabinoids, and phencyclidine. Commonly used opioids and their metabolites are shown in Fig. 1. The cutoff levels that we used, as well as the trade and brand names, and approximate detection times are listed in Table 1. Furthermore, creatinine levels were measured to detect a potentially diluted urine sample in addition to our on-site urine temperature monitoring to assure that specimens were made contemporaneous to the visit, and were not those from pre-voided specimens, for

example. We used creatinine to normalize concentrations of opioid metabolites by dividing the urine drug concentration (ng/mL) by the creatinine concentration (mg/dL) (17).

The quantitative results were cross-referenced with patient charts for prescribed medications and with the Illinois Prescription Monitoring Program (IPMP). The algorithm we created and used in this process is presented as Fig. 2. Patients were considered compliant if the urine sample was only positive for opioid medications that were prescribed by our pain clinic without the identified presence of any illicit drug. If the medication that our Pain Management Center prescribed was not present, it would suggest non-compliance and UDT was repeated at the next clinic visit, to assure that laboratory error or specimen contamination of some kind was not responsible for the identified result(s). If there was a presence of any other pain medication we would then cross reference with the IPMP to confirm whether the medication was prescribed by a physician at another institution. Any discrepancy with the above guidelines would be discussed with the patient during their follow-up clinic visit when UDT would be repeated. Lastly, if there were any positive results for illicit drugs, the patient was discharged from the Pain Management Center, as that would indicate a violation of our consent and treatment agreement signed by the patient prior to opioid treatment. Actual dis-

Table 1. Tested medications, their metabolites, and illicit drugs and their cut off level.

Opioids (Metabolites)	Trade/Brand Names	Cut off level	Approximate detection time up to
Codeine	Tylenol + Codeine	25 ng/mL	1 – 4 days
Morphine	Avinza, MS Contin	25 ng/mL	1 – 4 days
Hydrocodone	Vicodin, Norco, Lorcet	25 ng/mL	1 – 4 days
Hydromorphone	Exalgo, Dilaudid	25 ng/mL	1 – 4 days
Oxycodone	OxyContin, OxyIR, Percocet	25 ng/mL	1 – 4 days
Oxymorphone	Opana, Opana IR	25 ng/mL	1 – 4 days
Buprenorphine	Buprenex, Suboxone	5 ng/mL	1 – 10 days
Norbuprenorphine (Buprenorphine metabolite)		5 ng/mL	1 – 10 days
Methadone	Dolophine, Methadose	50 ng/mL	1 – 10 days
EDDP (Methadone metabolite)		50 ng/mL	1 – 10 days
Tramadol	Ultram, Ultram ER, Ultracet	50 ng/mL	1 – 4 days
Meperidine	Demerol	50 ng/mL	1 – 4 days
Normeperidine (Meperidine metabolite)		50 ng/mL	1 – 4 days
Fentanyl	Duragesic, Actiq	0.20 ng/mL	1 – 4 days
Tapentadol	Nucynta	10 ng/mL	1 – 4 days
Desmethyltapentadol (Tapentadol metabolite)		10 ng/mL	1 – 4 days
Benzodiazepines (Metabolites)	Trade/Brand Names	Cut off level	Approximate detection time up to
7 aminoclonazepam (Clonazepam metabolite)		50 ng/mL	1 – 10 days
Hydroxyalprazolam (Alprazolam metabolite)		50 ng/mL	1 – 10 days
Lorazepam	Ativan	50 ng/mL	1 – 10 days
Temazepam (Restoril/Diazepam metabolite)		50 ng/mL	1 – 10 days
Nordiazepam (Diazepam metabolite)		50 ng/mL	1 – 10 days
Oxazepam (Diazepam metabolite)		50 ng/mL	1 – 10 days
Amphetamines (Metabolites)	Trade/Brand Names	Cut off level	Approximate detection time up to
Methamphetamine	Desosyn	100 ng/mL	1 – 5 days
Amphetamine	Adderall, Adderall XR, Vyvanse	100 ng/mL	1 – 5 days
MDA - Psychoactive drug (MDMA metabolite)		100 ng/mL	1 – 5 days
MDMA - Psychoactive drug		100 ng/mL	1 – 5 days
MDEA - Psychoactive drug		100 ng/mL	1 – 5 days
Illicit Substances	Trade/Brand Names (Metabolites)	Cut off level	Approximate detection time up to
Tapentadol	Nucynta	10 ng/mL	1 – 4 days
Desmethyltapentadol (Tapentadol metabolite)		10 ng/mL	1 – 4 days
Cannabinoids	THC	50 ng/mL	1 – 30 days
Cocaine	N/A	300 ng/mL	1 – 4 days
Benzoylcegonine (Cocaine metabolite)		50 ng/mL	1 – 4 days
6-Monoacetylmorphine (Heroin metabolite)			

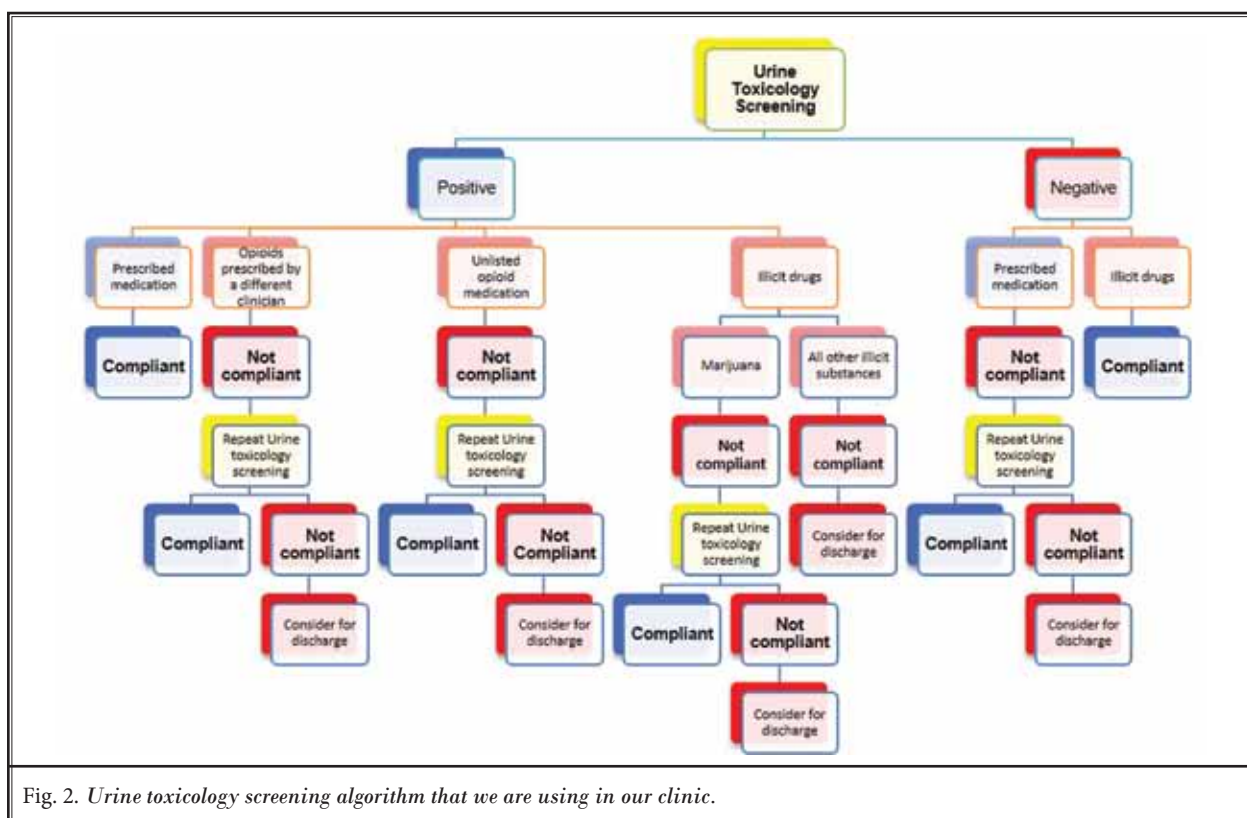


Fig. 2. Urine toxicology screening algorithm that we are using in our clinic.

charge consisted of patients being referred to addiction specialists or to other pain management centers and then were offered to return for tapering of analgesic medication. However, the patients that tested positive for marijuana were counseled and were given an opportunity to comply with protocol (no cannabis or derivatives) and UDT was repeated at the next clinic visit. If the results returned positive again on a repeated UDT for marijuana, pain management was then limited to interventional procedures only, without prescribing of any controlled substances.

Aside from collecting UDTs, we also collected demographic data, location of moderate-to-severe pain, list of prescribed medications, and the average pain as measured by an 11-point (0 – 10) NRS.

Statistical analysis was performed using SPSS 20.0 software (IBM Corporation, Armonk, NY). For testing differences between variables we used Student’s T-test and Pearson Chi-square test. For testing the correlation between variables we used the Spearman rho coefficient. A *P* value less than 0.05 was considered to be statistically significant.

RESULTS

The study population consisted of 500 patients of which 230 (46%) were men and 270 (54%) were women. The age of the evaluated patients ranged from 24 years old to 92 years old with the average age of the patients being 53.93 ± 14.76 .

Results showed the female patient population was older than the male patient population with the average age of men being 52.51 ± 15.14 , and 55.01 ± 14.42 for women. However the difference in age was not of statistical significance ($P = 0.058$). Based on our findings, the average BMI in men was 28.24 ± 8.22 and in women it was 29.15 ± 8.41 and again there was no statistical significance ($P = 0.257$).

The most common chief complaint in our patient population was of lower back pain, with and without radicular pain, which 65% of patients complained of. The second most common complaint was for arthritis, joint, and musculoskeletal pain with 24.7% of patients represented, followed by cervical spondylosis related pain with 7.8% represented. The remainder complained of other types of pain including headache,

migraine, fibromyalgia, and complex regional pain syndrome (CRPS) (Table 2). There was no significant difference in the type of pain between men and women ($P = 0.539$). Results of our study showed that the male patient population was taking a significantly higher dosage of opioid pain medication as compared to the female patient population. The average daily morphine equivalent consumption was $38.86 \text{ mg} \pm 70.73 \text{ mg}$ for men and $23.32 \text{ mg} \pm 43.13 \text{ mg}$ for women. This difference was highly statistically significant ($P = 0.003$).

The most common opioid used amongst these patients was hydrocodone (61.1%) followed by tramadol (23%) and hydromorphone (14.4%) Fig. 3. Our results revealed that male patients were taking more oxycodone

done ($P = 0.021$) and fentanyl ($P = 0.039$) than were the female patients. There was no significant difference between men and women with regards to the other prescribed opioid pain medications.

Of the 500 patients, 386 (77.2%) were compliant with prescribed medication and did not use any illicit drugs or unlisted medication. Forty-one (8.2%) patients were positive for opioid medication that our pain clinic did not prescribe but were taking medication which was listed in the IPMP and which was prescribed by a clinician at a different clinic or hospital. Also, 8 (1.6%) of our patients had medication detected which was not prescribed by any physician nor was it present in the IPMP, and which was presumably obtained from either a relative or other third party. Five (1%) patients tested negative for prescribed opioids. Sixty (12%) patients were positive for illicit drugs, 43 (8.6%) of which were positive for marijuana, and 16 (3.2%) were positive for cocaine with one positive for heroin. (Fig. 4). Our results showed no significant difference between men and women in the initial compliance ($P = 0.108$).

Out of the 60 patients that tested positive for illicit drugs, 37 were men and 23 were women. There

Table 2. Frequency of chief complaint.

Reason	Percentage
Lower Back Pain	65%
Arthritis, Joint & Musculoskeletal Pain	24.7%
Cervical Pain	7.8%
Headache, Migraine, Fibromyalgia & CRPS	2.5%

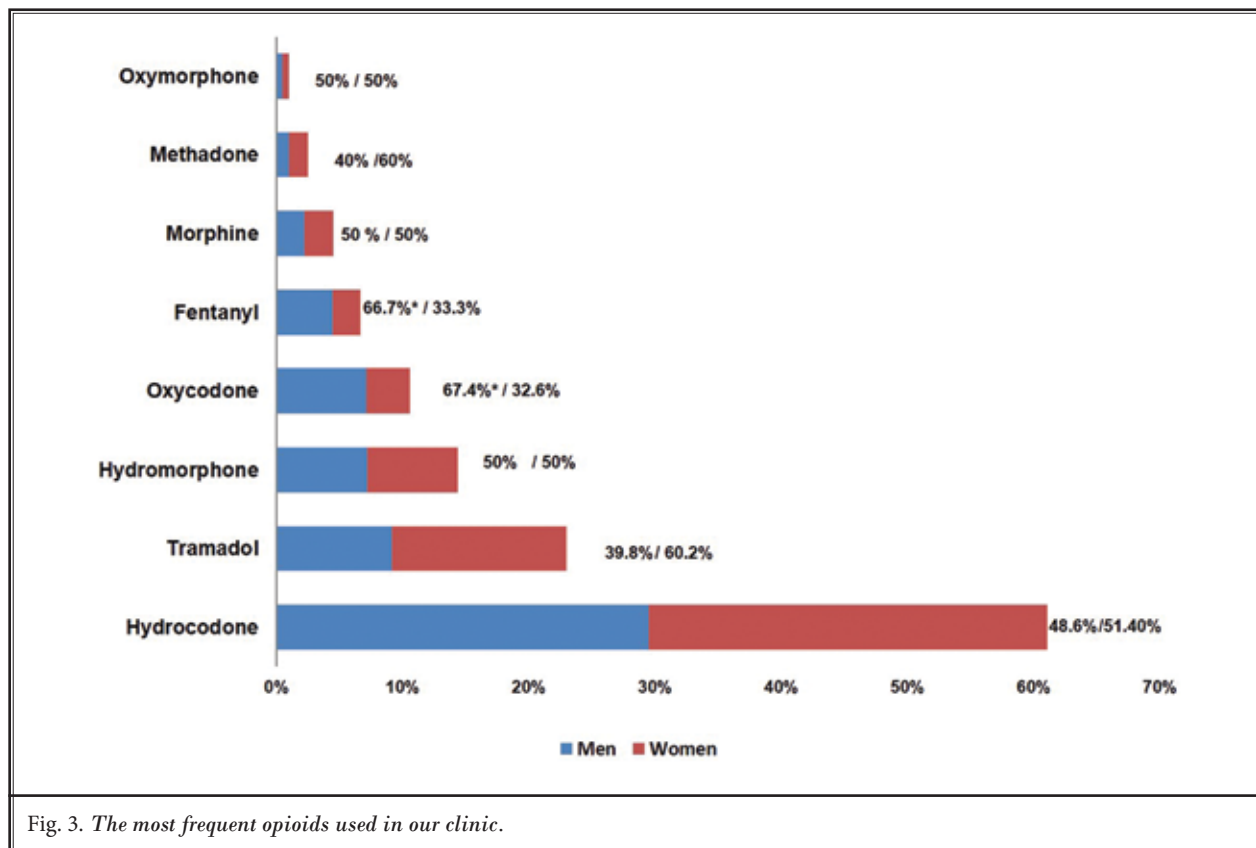


Fig. 3. The most frequent opioids used in our clinic.

was a statistical significance in the difference between the positive results of men and women ($P = 0.003$). Furthermore, 28% of these patients were negative for the prescribed opioid medication where 5% were positive for unlisted medications. Sixteen patients were positive for cocaine and one patient was positive for heroin metabolites. Due to our "zero tolerance" policy and agreement, patients were educated about their results, and were then immediately discharged from our clinic with referrals to an addiction specialist and other pain management centers and were offered to return for tapering of analgesic medication. Of all the patients who tested positive for cocaine and heroin, there were no statistical significances between men and women ($P = 0.405$). The remaining patients who had tested positive for illicit drugs were 28 men and 15 women that tested positive for marijuana. This difference was of statistical significance ($P = 0.014$).

We had repeated urine toxicology screenings in 77 patients out of 97 which required repeated UDTs for non-compliance (medications prescribed by other clinicians, positive for undisclosed medication, negative for prescribed opioids, and positive for marijuana). The 20 patients that remained to be re-tested did not return to the pain clinic for follow-up visits. Repeated UDTs showed that 49 of the 77 patients (63.6%) had improved compliance. Of the 49 patients that improved compliance, 56.25% were previously positive for marijuana, 37.5% were previously positive for medication that was prescribed by another physician, and 6.25% were previously positive for an undisclosed medication. Of the 28 that were noncompliant, 2/3 were positive for marijuana and 1/3 was positive for medication prescribed by another physician. Our results showed that compliance improved equally among both men and women ($P = 0.383$). Patients who were non-compliant on repeated UDTs were offered only interventional procedures and non-opioid analgesic treatments for their chronic pain conditions.

Discussion

Results of our study showed that 77.2% of our patients were compliant with prescribed opioid medications. Our results showed higher rates of compliance than other published studies (18- 20). Michna et al showed that 45% of their patients had abnormal UDT results (18), Matteliano and Chang found 54% of their patients appeared non-compliant to their prescribed opioid regimen (19), and an even more staggering figure was found in a retrospective study conducted by

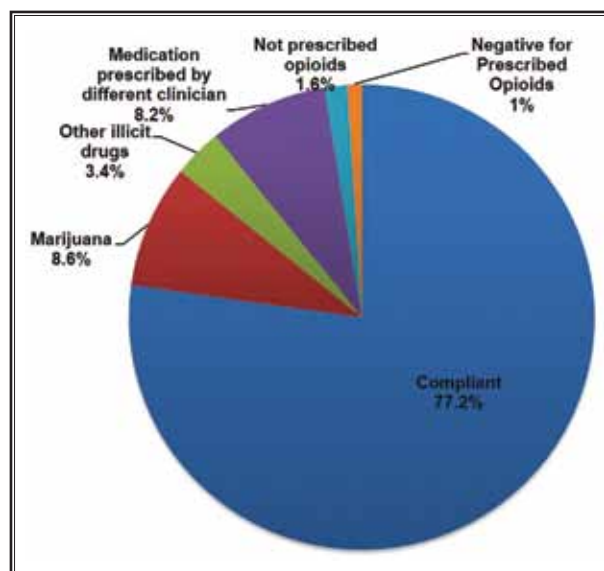


Fig. 4. Patients' compliance.

Couto et al, which showed that 75% of patients from the Ameritox database were non-compliant with prescribed medication (20) (Table 3). A reason for higher rates of compliance in our study may be due to a stricter discharge policy for non-compliant patients in conjunction with our dedicated patient educational process undertaken for every potential candidate for this type of therapy.

In our study, 54 out of the 500 patients (10.8%) were either positive for an opioid medication that was prescribed by a different clinic, or an opioid medication not present in the IPMP, or tested negative for prescribed opioids. A similar finding was present in Michna et al's study (10.2%) (18). Matteliano and Chang's study (19) showed a higher percentage of similar non-compliance where 23% of their patients had absence of one or more of their prescribed opioids and 12.5% had presence of non-prescribed medication. Also Couto et al's study (20) found that 38% of the patients did not have the prescribed medication present and 29% had non prescribed medication present (Table 3). Expecting a patient to accurately report medication use and self-report their aberrant use or frank drug abuse has already shown to be quite unreliable (21,22). Our numbers may be lower than similar studies because we avoided overlapping into multiple categories, such as patients testing positive for an illicit drug, which were only kept in that category.

Twelve percent of our patients were positive for illicit substances; 8.6% of which were positive for mari-

Table 3. Summary of reviewed studies that utilized urine toxicology testing.

Author	Type of study	Total number of patients	Non-compliant	Absence of prescribed medication	Non-prescribed medication	Illicit drug	Marijuana	Cocaine
Michna et al (18)	Retrospective	470	45%	10.2%	NA	20%	NA	NA
Matteliano and Chang (19)	Retrospective	120	54%	23%	12.5%	32.5%	24.2%	11.7%
Cuoto et al (20)	Retrospective	938,586	75%	38%	29%	11%	NA	NA
Morasco et al (24)	Retrospective	406	42%	NA	10.5%	31.4%	28.8%	2.5%
Katz et al (14)	Retrospective	122	43%	NA	14%	21.3%	16.4%	4.9%

juana, 3.2% were positive for cocaine, and one patient was positive for heroin. The difficulties of heroin detection should be taken into consideration, because even its metabolite 6-monoacetylmorphine (6-MAM) is only detectable in urine for up to 8 hours after heroin use (23). Similarly, studies that Fishbain et al (13) included in their review showed that 3.2% – 18.9% of chronic pain patients had a prevalence of drug abuse, addiction, and dependence. Ameritox's data analysis found that 11% of the patients tested in their database were positive for illicit drugs (20). According to Matteliano and Chang's data (19), they had a higher rate of positive results for illicit drugs (marijuana 24.2%, and cocaine 11.7%). As for a study conducted by Katz et al (14), 26 (21.3%) of the 122 patients tested were positive for illicit drugs (marijuana 16.4% and cocaine 4.9%). Lastly, Morasco et al (24) found 28.8% of their patients were positive for marijuana and 2.5% were positive for cocaine (Table 3). The range of positive results for illicit substances could be due to different patient populations (suburban vs. urban) included in the studies as well as differences in medical marijuana laws in various states (24). Even though medical marijuana is approved in 23 states, it is still against laws of the federal government to consume it for recreational or non-recreational (i.e., "medical") purposes, and this causes some ambiguity for pain physicians when attempting to treat patients who may be using marijuana for medicinal purposes. There is currently a debate over whether THC should be routinely tested for in chronic pain patients, but studies seem to show that illicit drug use and opioid misuse are often associated with marijuana use, which some classify as a "gateway drug" (25,26).

When reporting on toxicology results of 226 chronic pain patients, Fishbain et al (21) concluded that a significant percentage (8.8%) provided incorrect information on current illicit drug use. In a similar study, Melanson et al (27) found during a 3 month testing

period that 28.7% of their patients were positive for non-prescribed medications or illicit drugs and 14.7% of their patients were possibly diverting medication.

Our results showed that 28% of our patients, who were positive for illicit drugs, were also negative for prescribed opioids. Pesce et al (28) reviewed nearly 400,000 urine specimens in a retrospective study and concluded that patients testing positive for their prescribed medication were less likely to present with illicit drugs in their urine samples. In instances when patients tested negative for their prescribed medications, it was found they would be more likely to present with a positive test results for illicit drugs, with a possible hypothesis being that patients are using illicit drugs in place of prescribed medication (28).

Furthermore, Matteliano and Chang (19) found that the patient's gender, race, and pain level were not associated with UDT results. However our results showed statistically significant gender difference. Our results also revealed that there were more men than women that tested positive for marijuana ($P = 0.014$).

Recently, Back et al (29) showed that significantly more men than women displayed lifetime (15.9% vs 11.2%) as well as past year (5.9% vs 4.2%) non-medical use of prescription opioids. This study concluded that an estimated 33 million individuals report lifetime non-medical use of opioids with 13% of current users abusing or becoming dependent. Within the same study, while using data from the 2006 National Survey on Drug Use and Health survey (NSDUH), it was estimated that 12 million people within the U.S. had misused or abused prescription pain medications (29). However, data from the 2014 NSDUH survey estimates that only 4.3 million people aged 12 and older were using pain medication for nonmedical purposes (30).

In another retrospective study, Banta-Green et al (31) found that 704 pain patients were examined in an integrated medical practice of which men were more

likely than women to display addictive behaviors such as early refill requests; used the medication for symptoms other than their intended use such as sleep and anxiety; and had a doctor on record who had refused to prescribe medication due to concerns of abuse. In a similar study by Carise et al (32), where 27,816 individuals from 157 addiction treatment programs were analyzed, it was found that men were 1.46 times more likely than women to abuse oxycodone.

We had repeated UDTs in 77 patients and our data showed that 64% of them demonstrated improvement in compliance following education and discussion with those individuals. Repeated quantitative urine analysis and opioid concentration monitoring allowed for improvement in overall pain management. Urine opioid concentrations were normalized by the creatinine level because drinking large amounts of fluid may dilute the urine sample and alter its results (33). However, this method assumes the production and excretion of creatinine are constant, thereby accounting for changes in the amount of water.

Urine toxicology screening, behavioral observation, self-reporting questionnaires, review of medical charts, and oversight of the prescription monitoring program may allow physicians to better recognize which patient is misusing opioid as well as non-opioid prescription medication. A hope is that a combination of all of these processes could lead to a higher quality of life for the patient. Adherence monitoring has shown to be associated with a decrease in 50% of opioid abuse in chronic pain patients (34). Owen et al (35) conducted a 20-item survey of Texas Pain Society members and recommendations were made based on this survey as well as various published guidelines in regards to opioid use for chronic pain patients, suggesting that all patients being treated with opioids be tested with UDT and that the high-risk patients should be tested more frequently (36,37).

According to the latest published the Center for Disease Control and Prevention (CDC) opioid guidelines, urine toxicology has been identified as an important tool for providing information about opioid use and misuse. All experts agreed that UDT should be performed prior to initiating treatment with opioids and at least annually. However, not all experts could agree on how frequently these tests should be done. Experts suggested that patients should not be tested for tetrahydrocannabinol (THC) as they believe it does not affect patient management (38). We respectfully disagree with that point because if patients are using medical marijuana to reduce pain, one would assume

that those patients would require less opioids; have lower pain scores; and/or a better quality of life; and therefore its use would affect patient pain management. Furthermore, marijuana is still federally categorized as a Schedule I drug and requires physicians to be diligent, as there is some suggestion it may potentially be a "gateway drug."

The American Society of Interventional Pain Physicians (ASIPP) concluded that there is good evidence to support that UDT is useful in detecting illicit drug use and prescription opioid misuse, and it a useful tool for use in chronic pain management. Their guidelines also instruct clinicians to implement urine drug testing prior to initiating opioid therapy with subsequent monitoring, without specifying its frequency (39,40).

It is very difficult to make strict guidelines on how frequently UDT should be repeated. In our practice, we repeat tests 2 – 4 times per year for compliant patients. We believe that the final decision on frequency of testing should be determined by the treating physician on a case by case basis, taking into consideration various factors such as behavioral changes and classification of high risk patients. Creating an exact schedule for testing (for example: every 3, 4, or 6 months) may present an obvious timetable that can be manipulated by patients who are prone to be non-compliant.

There are some concerns that physicians may overutilize UDTs because Medicare data shows an increase in drug test reimbursements from 101 tests in 2000 to 3.2 million tests in 2009 (12). Millennium Laboratories and Ameritox in recent years have paid fines of \$256 million and \$16.3 million, respectively, for false billing and kickbacks (41,42).

In an effort to curb the overutilization and overbilling of UDTs and drug test reimbursements, Medicare is proposing changes that could cap billing for urine drug tests. They are proposing a tiered billing structure that would be based on how many drugs are being tested, which would include lump-sum payments rather than separate payments for individually tested substances and would be capped off at \$250 (43,44). We believe that once these changes become effective and the proper patient selection for urine toxicology is implemented (Fig. 2), this will help curb the overall expenses.

There are some limitations in this study. This was a single site retrospective study and further analysis would be beneficial with a larger population as well as for multiple sites. Another limitation is that we used creatinine normalization and not specific gravity normalization.

Urine drug testing is not without expenses related to collection and analysis of specimens. Saliva, hair, blood, nails, and sweat are alternative sources that can be utilized for drug testing (15). However, urine drug testing is more affordable and can be easily collected and analyzed. While these costs might still deter some clinicians from embracing conceptually UDT, the cost of untreated or worse still, unidentified iatrogenic opioid addiction is many-fold higher. Missing opportunities to identify, objectively, those abusing their medications can have catastrophic consequences, including death,

in addition to financial and occupational mishaps.

Previously conducted studies showed that UDT can be used as a tool for discovering misuse of opioid medications. Our results showed that repeated UDT can improve compliance of patients on opioid medication and can improve overall pain management. Though our study was conducted in an outpatient pain management center, we believe that UDT should be utilized not exclusively by pain physicians but also by primary care clinicians who are prescribing opioids, in order to improve future quality of care.

REFERENCES

- Gaskin DJ, Richard P. The economic costs of pain in the United States. *J Pain* 2012; 13:715-724.
- Manchikanti L, Atluri S, Candido KD, Boswell MV, Simopoulos TT, Grider JS, Falco FJE, Hirsch JA. Zohydro™ approval by Food and Drug Administration: Controversial or frightening? *Pain Physician* 2014; 17:E437-E450.
- Arning K, Baron R. Evaluation of symptom heterogeneity in neuropathic pain using assessments of sensory functions. *Neurotherapeutics* 2009; 6:738-748.
- Furlan A, Chaparro LE, Irvin E, Mailis-Gagnon A. A comparison between enriched and nonenriched enrollment randomized withdrawal trials of opioids for chronic noncancer pain. *Pain Res Manag* 2011; 16:337-351.
- Birnbaum H, White A, Schiller M, Waldman T, Cleveland J, Roland C. Societal costs of prescription opioid abuse, dependence, and misuse in the United States. *Pain Med* 2011; 12:657-667.
- The CBHSQ Report - Short Report of Drug Abuse Warning Network (DAWN) findings on Emergency Department Visits Involving Narcotic Pain Relievers: www.samhsa.gov/data/sites/default/files/report_2083/ShortReport-2083.pdf
- Paulozzi LJ, Jones C, Mack K, Rudd R. Centers for Disease Control and Prevention (CDC). Vital signs: Overdoses of prescription opioid pain relievers—United States, 1999-2008. *Morb Mortal Wkly Rep* 2001; 60:1487-1492.
- Fishman SM, Wilsey B, Yang J, Reisfeld GM, Bandman TB, Borsook D. Adherence monitoring and drug surveillance in chronic opioid therapy. *J Pain Symptom Manage* 2000; 20:293-307.
- Katz N, Fanciullo GJ. Role of urine toxicology testing in the management of chronic opioid therapy. *Clin J Pain* 2012; 18:S76-S82.
- Preston KL, Silverman K, Schuster CR, Cone EJ. Comparison of self-reported drug use with quantitative and qualitative urinalysis for assessment of drug use in treatment studies. *NIDA Res Monogr* 1997; 167:130-145.
- Manchikanti L, Damron KS, McManus CD, Barnhill RC. Patterns of illicit drug use and opioid abuse in patients with chronic pain at initial evaluation: A prospective, observational study. *Pain Physician* 2004; 7:431-437.
- Kaye AD, Marshall ZJ, Lambert SM, Trescot AM, Prabhakar A, Elhassan AO, Urman RD. Ethical perspectives on urine drug screening for pain physicians. *Pain Physician* 2014; 17:E559-E564.
- Fishbain DA, Rosomoff HL, Rosomoff RS. Drug abuse, dependence and addiction in chronic pain patients. *Clin J Pain* 1992; 8:77-85.
- Katz NP, Sherburne S, Beach M, Rose RJ, Vielguth J, Bradley J, Fanciullo GJ. Behavioral monitoring and urine toxicology testing in patients receiving long-term opioid therapy. *Anesth Analg* 2003; 97:1097-1102.
- Christo PJ, Manchikanti L, Ruan X, Bottros M, Hansen H, Solanki D, Jordan AE, Colson J. Urine drug testing in chronic pain. *Pain Physician* 2011; 14:123-143.
- Weaver C, Mathews AW. Doctors Cash In on Drug Tests for Seniors, and Medicare Pays the Bill. *The Wall Street Journal*. November 10, 2014. www.wsj.com/articles/doctors-cash-in-on-drug-tests-for-seniors-and-medicare-pays-the-bill-1415676782
- Cone EJ, Caplan YH, Moser F, Robert T, Shelby MK, Black DL. Normalization of urinary drug concentrations with specific gravity and creatinine. *J Anal Toxicol* 2009; 33:1-7.
- Michna E, Jamison RN, Pham LD, Ross EL, Janfaza D, Nedeljkovic SS, Narang S, Palombi D, Wasan AD. Urine toxicology screening among chronic pain patients on opioid therapy: Frequency and predictability of abnormal findings. *Clin J Pain* 2007; 23:173-179.
- Matteliano D, Chang YP. Describing prescription opioid adherence among individuals with chronic pain using urine drug testing. *Pain Manag Nurs* 2014; 16:51-59.
- 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; 12:185-190.
- Fishbain DA, Cutler RB, Rosomoff HL, Rosomoff RS. Validity of self-reported drug use in chronic pain patients. *Clin J Pain* 1999; 15:184-191.
- Ready LB, Sarkis E, Turner JA. Self-reported vs. actual use of medications in chronic pain patients. *Pain* 1982; 12:285-294.
- Mayo Clinic Mayo Medical Laboratories – Opiates Interpretation: www.mayomedicallaboratories.com/test-info/drug-book/opiates.html
- Morasco BJ, Krebs EE, Cavanagh R, Hyde S, Crain A, Dobscha SK. Treatment changes following aberrant urine drug test results for patients prescribed chronic opioid therapy. *J Opioid Manag* 2015; 11:45-51.
- Reisfeld GM, Wasan AD, Jamison RN. The prevalence and significance of cannabis use on patients prescribed chronic

- opioid therapy: A review of the extant literature. *Pain Med* 2009; 10:1434-1441.
26. Pesce A, West C, Rosenthal M, West R, Crews B, Mikel C, Almazan P, Latyshev S, Horn PS. Marijuana correlates with use of other illicit drugs in a pain patient population. *Pain Physician* 2010; 13:283-287.
 27. Melanson, SE, Tanasijevic, MJ, Snyder, ML, Darragh, A, Quade, C, Jarolim P. Significant cost savings achieved by in-sourcing urine drug testing for monitoring medication compliance in pain management. *Clin Chim Acta* 2013; 422:10-14.
 28. Pesce A, West C, Gonzales E, Rosenthal M, West R, Mikel C, Almazan P, Latyshev S, Horn P. Illicit drug use correlates with negative urine drug test results for prescribed hydrocodone, oxycodone, and morphine. *Pain Physician* 2012; 15:E687-E692.
 29. Back SE, Payne RL, Simpson AN, Brady KT. Gender and prescription opioids: Findings from the National Survey on Drug Use and Health. *Addict Behav* 2010; 35:1001-1007.
 30. Substance Abuse and Mental Health Services Administration – Behavioral Health Trends in the United States: www.samhsa.gov/data/sites/default/files/NSDUH-FRR1-2014/NSDUH-FRR1-2014.pdf
 31. Banta-Green CJ, Merrill JO, Doyle SR, Boudreau DM, Calsyn DA. Opioid use behaviors, mental health and pain – development of a typology of chronic pain patients. *Drug Alcohol Depend* 2009; 104:34-42.
 32. Carise D, Dugosh KL, McLellan AT, Camilleri A, Woody GE, Lynch KG. Prescription OxyContin abuse among patients entering addiction treatment. *Am J Psychiatry* 2007; 164:1750-1756.
 33. Jaffee WB, Trucco E, Levy S, Weiss RD. Is this urine really negative? A systemic review of tampering methods in urine drug screening and testing. *J Subst Abuse Treat* 2007; 33:33-42.
 34. Manchikanti L, Manchukonda R, Damron KS, Brandon D, McManus CD, Cash KA. Does adherence monitoring reduce controlled substance abuse in chronic pain patients? *Pain Physician* 2006; 9:57-60.
 35. Owen GT, Burton AW, Schade CM, Passik S. Urine drug testing: Current recommendations and best practices. *Pain Physician* 2012; 15:ES119-ES133.
 36. Cone EJ, Caplan YH. Urine toxicology testing in chronic pain management. *Postgrad Med* 2009; 121: 91-102.
 37. Nuckols, TK, Anderson, L, Popescu, I, Diamant AL, Doyle B, Di Capua P, Chou R. Opioid prescribing: A systematic review and critical appraisal of guidelines for chronic pain. *Ann Intern Med* 2014; 160:38-47.
 38. Center for Disease Control and Prevention – CDC Guideline for Prescribing Opioids for Chronic Pain: www.cdc.gov/mmwr/volumes/65/rr/rr6501e1.htm
 39. Manchikanti L, Abdi S, Atluri S, Balog CC, Benyamin RM, Boswell MV, Brown KR, Bruel BM, Bryce DA, Burks PA, Burton AW, Calodney AK, Caraway DL, Cash KA, Christo PJ, Damron KS, Datta S, Deer TR, Diwan S, Eriator I, Falco FJ, Fellows B, Geffert S, Gharibo CG, Glaser SE, Grider JS, Hameed H, Hameed M, Hansen H, Harned ME, Hayek SM, Helm S, 2nd, Hirsch JA, Janata JW, Kaye AD, Kaye AM, Kloth DS, Koyyalagunta D, Lee M, Malla Y, Manchikanti KN, McManus CD, Pampati V, Parr AT, Pasupuleti R, Patel VB, Sehgal N, Silverman SM, Singh V, Smith HS, Snook LT, Solanki DR, Tracy DH, Vallejo R, Wargo BW. American Society of Interventional Pain Physicians (ASIPP) guidelines for responsible opioid prescribing in chronic non-cancer pain: Part I – evidence assessment. *Pain Physician* 2012; 15:S1-S65.
 40. Manchikanti L, Abdi S, Atluri S, Balog CC, Benyamin RM, Boswell MV, Brown KR, Bruel BM, Bryce DA, Burks PA, Burton AW, Calodney AK, Caraway DL, Cash KA, Christo PJ, Damron KS, Datta S, Deer TR, Diwan S, Eriator I, Falco FJ, Fellows B, Geffert S, Gharibo CG, Glaser SE, Grider JS, Hameed H, Hameed M, Hansen H, Harned ME, Hayek SM, Helm S 2nd, Hirsch JA, Janata JW, Kaye AD, Kaye AM, Kloth DS, Koyyalagunta D, Lee M, Malla Y, Manchikanti KN, McManus CD, Pampati V, Parr AT, Pasupuleti R, Patel VB, Sehgal N, Silverman SM, Singh V, Smith HS, Snook LT, Solanki DR, Tracy DH, Vallejo R, Wargo BW. 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.
 41. The United States Department of Justice – Millennium Health Agrees to Pay \$256 Million to Resolve Allegation of Unnecessary Drug and Genetic Testing and Illegal Remuneration to Physicians: www.justice.gov/opa/pr/millennium-health-agrees-pay-256-million-resolve-allegations-unnecessary-drug-and-genetic
 42. Danielson, R. Drug-testing company to pay \$16.3 million to settle kickback claims. *Tampa Bay Times*. November 16, 2010. www.tampabay.com/news/business/corporate/drug-testing-company-to-pay-163-million-to-settle-kickback-claims/1134676
 43. Weaver C, Mathews AW. Lab Nears Settlement Over Pricey Medicare Drug Tests. *The Wall Street Journal*. June 14, 2015. www.wsj.com/articles/lab-nears-settlement-over-pricey-medicare-drug-tests-1434326131
 44. Addiction Professional – Urine drug testing model likely to roll out nationwide: www.addictionpro.com/article/urine-drug-testing-model-likely-roll-out-nationwide

