Medication and Illicit Substance Use Analyzed Using Liquid Chromatography Tandem Mass Spectrometry (LC-MS/MS) in a Pain Population

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Abstract

Background: Patients on chronic opioid therapy are often closely monitored to identify prescribed or non-prescribed medications and/or illicit substances and to identify medication use that may lead to adverse events. Monitoring is typically performed using a combination of clinical tools and assessment methods that often include patient medication histories, risk assessments, and medication monitoring with urine testing. The chronic pain population may be prescribed an average of three to five medications for pain and associated symptoms. In addition to prescribed therapies, this patient population often takes non-prescribed medications and/or illicit substances. Medication monitoring with Urine Drug Testing (UDT), particularly when performed using mass spectrometry, provides accurate information about medications and illicit substances present in the urine. Purpose of the study: To use LC-MS/MS analyses to describe the variety of medications and metabolites observed in urine specimens from individuals on opioid therapy.

Methods: Analytical procedures were developed using LC-MS/MS that could detect and differentiate between various opioids and their metabolites, other medications commonly prescribed for pain, and certain illicit substances. This retrospective analysis used approximately 340,000 de-identified specimens tested between November 2011 and February 2012 at Millennium Laboratories. Data was sorted to determine frequency of detection and concentrations of the excreted drugs and metabolites.

Results: The most frequently observed medications were hydrocodone and oxycodone, and their metabolites. The next most frequently observed medication was the benzodiazepine class followed by gabapentin, buprenorphine, and morphine. Additionally, illicit substances were detected in 15% of specimens; the most common illicit substances were cannabinoids and cocaine.

Conclusions: Urine drug testing, using LC-MS/MS technology with validated cutoff values for each analyte, provides objective data for providers to use when assessing medication use, potential drug-drug interactions, potential adverse events, and possible diversion. Specific identification of both the medication or substance and the associated metabolites allows for informed interpretation of UDT results. Understanding the medications and illicit substances found in UDT specimens from the pain population helps providers optimize medication monitoring for the best possible plan for pain management.

Keywords: Chronic pain; LC-MS/MS; Mass spectrometry; Urine drug testing; Illicit substances; Opiates; Pain medications

Introduction

The challenge in treating chronic pain with opioid therapy is balancing safety and efficacy; simultaneously responding to the need to relieve chronic pain while detecting and managing use, misuse, abuse and diversion of medications or illicit substances [1]. Urine Drug Testing (UDT) in the pain population is typically utilized to identify prescribed and non-prescribed medication and illicit substance use and analyze the test results for the risk for drug-drug interactions or adverse events and potential diversion or misuse. Monitoring is performed using a combination of clinical tools and assessment methods that often include patient medication histories, risk assessments, and medication monitoring with urine testing [2]. UDT continues to be the most common tool used for medication monitoring in this patient population [2]. UDT is only one component of a comprehensive risk mitigation plan which can include pill counts, state prescription drug monitoring programs, patient self-reports, treatment agreements, informed consent for high risk medications, and an effective patient-provider relationship [2].

Published studies have shown that patient self-reports regarding medication or illicit substance use are often unreliable [3-5]. Thus, other tools, such as UDT, are commonly used in conjunction with self-reports, and provide objective data when monitoring patients on chronic opioid therapy [2,6].

Urine drug testing has historically used immunoassay as a screening method before confirming using mass spectrometry [7]. Although in-office testing immunoassay technology allows for immediate in-office results, it is limited in usefulness, accuracy, and reliability [6,8]. One of the limitations is that an opiate immunoassay will identify whether the patient is positive for an opiate medication but will not specify which opiate is causing the positive result [8]. Furthermore, immunoassays are unable to identify the presence of opiate metabolites, which precludes the ability to determine if a patient is ingesting or properly metabolizing his or her medication [9]. A person who is unable to metabolize opiates or metabolizes them unusually slowly or rapidly

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or a lack of analgesia [10,11]. Immunoassays are also prone to false positive results from cross-reacting substances and common medications, and false negative results are due to the typically higher cutoffs compared to other technologies, such as liquid chromatography tandem mass spectrometry (LC-MS/MS). Additionally, immunoassays are often unable to identify adjuvant analgesics such as tapentadol or pregabalin.

Recent developments in methods of mass spectrometry analysis have been shown to clearly differentiate between medications within a class, enabling specific opiate identification [6]. The methods are free from interference of any other prescription medications, over-the-counter medications, herbal supplements, or other agents [12,13], thus virtually eliminating false positive results. Additionally, metabolites can be specifically identified, providing information to assist providers in determining the potential for deception (e.g., adding the medication directly to the urine to obtain a positive result) or the patient having slow or rapid metabolism which may be a concern [6]. For these reasons LC-MS/MS is now considered the gold standard for analysis of opioids and their metabolites [14-20].

This retrospective data analysis sought to examine the UDT results from a large cohort of individuals with chronic pain to better define the medications and metabolites observed in the urine of patients on opioid therapy. A secondary goal of this analysis was to assist in defining the optimal test menu required to monitor this patient population.

Methods

This analysis was approved by the Aspire IRB, 11491 Woodside Ave, Santee, CA 92071. Approximately 340,000 de-identified specimens collected between November 2011 and February 2012 were analyzed for commonly prescribed medications as well as illicit substances using validated methods at Millennium Laboratories [15,21-23]. All specimens were analyzed using (LC-MS/MS).

An Agilent® 1200 series binary pump SL Liquid Chromatography system, well plate sampler, thermostatted column compartment, paired with an Agilent® 6410 QQQ mass spectrometer and Agilent® Mass Hunter software was used for analysis of all drugs.

The lower limits of quantitation and the upper limits of linearity were obtained using the Agilent® Technologies QQQ LC-MS/MS system. The lower limits of quantitation for synthetic cannabinoids were set at 15 ng/mL. The coefficient of variation for all the analytes at the low and high ends of the quantitation curve were less than 10%. All quantitative data were obtained from calibration curves with R²> 0.95. Most were 0.99.

The number medications and illicit substances tested varied based on physician orders on the requisition. Specimen results were then sorted for each of the seventy medications, substances, and metabolites (Table 1). The percentage of positive tests for each medication or illicit substance and/or their metabolite(s) was then calculated. The mean, median, standard deviation and range of excrated drug concentrations for each medication or illicit substance and metabolite were also calculated.

Results

The prevalence and range of excretion values varied widely among the medications and substances (Table 1). The most frequently observed medications were hydrocodone and oxycodone, and their metabolites. The next most frequently detected analytes were the benzodiazepine class followed by gabapentin, buprenorphine, and morphine.

The prevalence of detection of the opioid analgesic medications varied. These medications also showed wide variation in concentrations. For example, morphine was found in 12.6% of the specimens (n=42,051; median concentration 10,069 ng/mL), methadone in 6.9% of specimens (n=21,483; median concentration 2,258 ng/mL), and fentanyl in 5.3% of specimens (n= 12,999; median concentration 35 ng/mL).

The benzodiazepines were the medication class that was most commonly observed after the opioids. Percentage positives within the class were as follows: alpha-hydroxyalprazolam 15.7% (n=49,952), 7-aminoconazepam 10% (n=31,798), diazepam metabolites 8.4-13.2% (oxazepam 13.2%, n=42,017; temazepam 11.2%, n= 35,501; and nordiazepam 8.4%, n= 26,783), lorazepam 4% (n= 12,579).

The metabolite of the muscle relaxant carisoprodol (meprobamate) was present in 9.3% of the tested specimens (n=20,032). The anticonvulsants gabapentin and pregabalin were shown in 16% (n=5,433) and 5.8% (n=2,059) of the specimens tested, respectively.

Of the antidepressant class, the tricyclic antidepressants represented about 4% of positive test results, the selective-serotonin re-uptake inhibitors (SSRIs) about 7% (fluoxetine 3.9%, norfluoxetine 4.6%, and paroxetine 2%), and the serotonin-norepinephrine reuptake inhibitors (SNRIs) were about 11% (duloxetine 6.4%, venlafaxine 3%, and O-desmethylvenlafaxine 4%).

Illicit substances appeared in about 15% of the specimens with the most commonly observed substance being marijuana metabolite at 10.6% (n=27,635). This was followed by cocaine metabolite at 3.1% (n= 9,942), the Spice compounds (i.e., synthetic cannabinoids) at approximately 0.9%, and methamphetamine and heroin each at 0.7%.

Metabolites were typically identified in the presence of the following parent medications (metabolite appears in parenthesis): codeine (morphine), hydrocodone (norhydrocodone, hydromorphine), oxycodone (noroxycodone, oxymorphine), fentanyl (norfentanyl), buprenorphine (norpseudoephedrine), methadone (EDDP), carisoprodol (meprobamate), venlafaxine (O-demethylvenlafaxine), and fluoxetine (norfloxetine).

Discussion

Monitoring patient medication and substance use is critical in achieving a balance between optimal analgesia and minimizing adverse effects, misuse, and diversion. Quantitative laboratory testing provides reliable and accurate information for treating clinicians. However, little is published regarding the range of excrated concentrations for individual medications, substances, or their metabolites in the chronic pain population. This retrospective data analysis demonstrated numerous medications and/or substances that are used by the chronic pain population and also demonstrated wide variability in excrated concentrations for medications, substances, and their metabolites.

In the opioid class, oxycodone and hydrocodone represented the greatest percentage of positive test results, each at approximately 30%. This result was expected because these drugs are the most widely prescribed opiate medications.

Morphine positive results were observed in 12.6% of the specimens. The median concentration value of morphine was higher than median concentrations of other opiates.

Codeine was present in only 2% of the specimens because codeine is known to be a poor analgesic compared with other opioids and is therefore not often prescribed for chronic pain [24].
## Analytes Cutoff (ng/mL) N Tested N Positive % Positive Mean (ng/mL) Median (ng/mL) SD ×/÷ Minimum (ng/mL) Maximum (ng/mL)

### Opiates

**Codeine**  50 334,248 6,539 2.0% 922.1 807.2 6.2 50 446,192

**Morphine**  50 334,248 42,051 12.6% 6,359.1 10,068.7 9.4 50 2,161,530

**Hydrocodone**  50 334,247 101,224 30.3% 923.3 979.9 4.3 50 240,498

**Norhydrocodone**  50 334,247 106,614 31.9% 1,011.8 1,075.0 4.2 50 261,278

**Hydromorphone**  50 334,245 286.3 245.8 3.3 50 292,724

### Oxycodone

**Oxycodone**  50 329,790 99,354 30.1% 2,376.3 2,480.5 6.1 50 7,344,920

**Noroxycodone**  50 329,786 105,576 32.0% 2,761.2 3,097.6 9.6 50 1,598,650

**Oxymorphone**  50 329,790 107,419 32.6% 1,299.3 1,259.3 5.5 50 566,387

### Buprenorphine

**Buprenorphine**  10 203,157 24,902 12.3% 130.6 123.5 4.3 10 203,157

**Norbuprenorphine**  20 203,157 25,558 12.6% 343.2 370.0 3.5 20 25,393

### Fentanyl

**Fentanyl**  2 244,612 12,999 5.3% 35.9 35.1 4.6 2 244,612

**Norfentanyl**  8 244,612 13,575 5.5% 216.7 235.4 4.4 8 244,612

### Meperidine

**Meperidine**  50 116,446 245 0.2% 1,008.6 937.2 6.4 51 129,922

**Normeperidine**  50 116,273 362 0.3% 2,868.9 3,076.4 7.2 52 289,751

### Methadone

**Methadone**  100 313,417 21,483 6.9% 2,152.1 2,257.5 4.4 100 328,786

**EDDP**  100 313,416 21,825 7.0% 3,064.0 3,536.2 4.7 100 255,380

### Propoxyphene

**Propoxyphene**  100 60,751 58 0.1% 481.8 339.3 3.9 100 18,497

**Norpropoxyphene**  100 60,750 150 0.2% 1,425.3 1,081.0 5.4 100 152,388

### Tapentadol

**Tapentadol**  50 123,626 1,952 1.6% 7,133.3 11,325.4 5.8 51 720,475

### Barbiturates

**Butalbital**  200 167,333 3,838 2.3% 1,071.5 993.6 2.6 200 339,238

**Phenobarbital**  200 167,332 664 0.4% 3,330.6 3,455.9 4.3 200 98,911

**Secobarbital**  200 167,332 3 < 0.1% 554.6 551.9 2.2 258 1,200

### Benzodiazepines

**Alpha-hydroxyalprazolam**  20 317,340 49,952 15.7% 200.4 183.2 3.6 20 34,118

**7-Amino-clonazepam**  20 317,340 31,798 10.0% 278.5 281.8 3.7 20 43,176

**Lorazepam**  40 317,340 12,579 4.0% 631.3 644.7 3.9 40 80,050

**Nordiazepam**  40 317,340 32,348 10.4% 323.4 301.3 3.5 40 26,496

**Oxazepam**  40 317,340 42,017 13.2% 517.9 496.6 4.5 40 412,887

**Temazepam**  50 317,340 35,501 11.2% 937.9 783.6 6.2 50 333,611

### Muscle Relaxers

**Carisoprodol**  100 215,751 10,486 4.9% 542.9 440.5 3.9 100 953,981

**Meprobamate**  100 215,751 20,032 9.3% 11,379.3 15,463.3 5.6 100 1,144,930

**Cyclobenzaprine**  50 164,101 8,800 5.4% 140.7 120.8 2.2 50 105,432

**Tricyclic Antidepressants**

**Amitriptyline**  50 164,101 5,265 3.2% 259.7 228.8 2.9 50 240,468

**Nortriptyline**  50 164,101 6,477 3.9% 314.6 278.2 3.2 50 27,119

**Imipramine**  50 164,100 293 0.2% 399.9 409.5 3.2 51 14,189

**Desipramine**  50 164,100 190 0.1% 638.0 706.5 3.8 51 7,585
Table 1: Analyte statistics.

<table>
<thead>
<tr>
<th>Analytes</th>
<th>Cutoff (ng/mL)</th>
<th>N Tested</th>
<th>N Positive</th>
<th>% Positive</th>
<th>Mean (ng/mL)</th>
<th>Median (ng/mL)</th>
<th>SD ×/÷</th>
<th>Minimum (ng/mL)</th>
<th>Maximum (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Selective Serotonin Reuptake Inhibitors</strong></td>
<td></td>
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<tr>
<td>Fluoxetine</td>
<td>25</td>
<td>11,984</td>
<td>472</td>
<td>3.9%</td>
<td>789.1</td>
<td>936.9</td>
<td>4.4</td>
<td>29</td>
<td>19,817</td>
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<tr>
<td>Norfluoxetine</td>
<td>25</td>
<td>11,984</td>
<td>552</td>
<td>4.6%</td>
<td>673.4</td>
<td>900.8</td>
<td>4.4</td>
<td>26</td>
<td>17,868</td>
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<tr>
<td>Paroxetine</td>
<td>25</td>
<td>11,912</td>
<td>237</td>
<td>2.0%</td>
<td>289.4</td>
<td>269.5</td>
<td>3.7</td>
<td>26</td>
<td>10,809</td>
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<td><strong>Serotonin Norepinephrine Reuptake Inhibitors</strong></td>
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<tr>
<td>Duloxetine</td>
<td>25</td>
<td>20,510</td>
<td>1,315</td>
<td>6.4%</td>
<td>151.0</td>
<td>135.7</td>
<td>3.0</td>
<td>25</td>
<td>30,197</td>
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<td>Venlafaxine</td>
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<td>11,688</td>
<td>352</td>
<td>3.0%</td>
<td>5,789.7</td>
<td>6,499.9</td>
<td>4.9</td>
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<td>Desmethylvenlafaxine</td>
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<td>11,688</td>
<td>471</td>
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<td>15,080.3</td>
<td>16,130.5</td>
<td>2.9</td>
<td>101</td>
<td>139,150</td>
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<td><strong>Alcohol</strong></td>
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<tr>
<td>Ethyl glucuronide</td>
<td>500</td>
<td>146,228</td>
<td>20,250</td>
<td>13.8%</td>
<td>8,524.4</td>
<td>6,578.3</td>
<td>6.5</td>
<td>501</td>
<td>3,613,660</td>
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<td>Ethyl sulfate</td>
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<td>146,228</td>
<td>16,680</td>
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<td>4,228.9</td>
<td>3,201.3</td>
<td>4.7</td>
<td>500</td>
<td>903,593</td>
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<td><strong>Antiepileptics</strong></td>
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<tr>
<td>Gabapentin</td>
<td>100</td>
<td>34,027</td>
<td>5,433</td>
<td>16.0%</td>
<td>137,999.1</td>
<td>222,540.0</td>
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<tr>
<td>Pregabalin</td>
<td>100</td>
<td>35,617</td>
<td>2,059</td>
<td>5.8%</td>
<td>71,331.7</td>
<td>99,040.4</td>
<td>6.9</td>
<td>100</td>
<td>12,001,600</td>
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<td><strong>Ketamine</strong></td>
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<tr>
<td>Ketamine</td>
<td>50</td>
<td>24,270</td>
<td>19</td>
<td>0.1%</td>
<td>440.0</td>
<td>289.5</td>
<td>5.4</td>
<td>68</td>
<td>30,172</td>
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<tr>
<td>Norketamine</td>
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<td>24,270</td>
<td>19</td>
<td>0.1%</td>
<td>291.8</td>
<td>194.3</td>
<td>4.0</td>
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<td>7,263</td>
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<tr>
<td>Naltrexone</td>
<td>10</td>
<td>17,253</td>
<td>79</td>
<td>0.5%</td>
<td>388.8</td>
<td>543.5</td>
<td>5.9</td>
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<td>Naltrexol</td>
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<td>17,252</td>
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<td>0.5%</td>
<td>809.3</td>
<td>951.0</td>
<td>8.3</td>
<td>9</td>
<td>88,704</td>
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<tr>
<td>Zolpidem</td>
<td>10</td>
<td>40,927</td>
<td>1,341</td>
<td>3.3%</td>
<td>36.1</td>
<td>29.2</td>
<td>2.9</td>
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<td>Carboxy-zolpidem</td>
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<td>3,548</td>
<td>8.7%</td>
<td>1,155.9</td>
<td>1,838.1</td>
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<td><strong>Stimulants</strong></td>
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<tr>
<td>Amphetamine</td>
<td>100</td>
<td>316,507</td>
<td>13,639</td>
<td>4.3%</td>
<td>2,801.8</td>
<td>3,105.3</td>
<td>5.2</td>
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<td>Methamphetamine</td>
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<td>2,247</td>
<td>0.7%</td>
<td>3,402.9</td>
<td>3,016.4</td>
<td>7.1</td>
<td>101</td>
<td>605,736</td>
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<tr>
<td>Methylphenidate</td>
<td>50</td>
<td>40,364</td>
<td>451</td>
<td>1.1%</td>
<td>502.5</td>
<td>489.0</td>
<td>3.6</td>
<td>50</td>
<td>53,838</td>
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<tr>
<td>Ritalinic acid</td>
<td>50</td>
<td>40,364</td>
<td>702</td>
<td>1.7%</td>
<td>7,085.8</td>
<td>10,521.2</td>
<td>6.0</td>
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<td>169,000</td>
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<td><strong>Cannabinoids</strong></td>
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<tr>
<td>Carboxy-THC</td>
<td>15</td>
<td>260,078</td>
<td>27,635</td>
<td>10.6%</td>
<td>177.7</td>
<td>159.6</td>
<td>4.2</td>
<td>15</td>
<td>40,370</td>
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<tr>
<td>JWH-018A</td>
<td>15</td>
<td>63,281</td>
<td>527</td>
<td>0.8%</td>
<td>94.9</td>
<td>74.4</td>
<td>3.4</td>
<td>15</td>
<td>2,136</td>
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<tr>
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<td>15</td>
<td>63,281</td>
<td>521</td>
<td>0.8%</td>
<td>91.2</td>
<td>77.2</td>
<td>3.5</td>
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<td>63,281</td>
<td>107</td>
<td>0.2%</td>
<td>31.5</td>
<td>26.3</td>
<td>1.8</td>
<td>15</td>
<td>382</td>
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<tr>
<td>JWH-073B</td>
<td>15</td>
<td>63,281</td>
<td>563</td>
<td>0.9%</td>
<td>100.9</td>
<td>81.5</td>
<td>3.6</td>
<td>15</td>
<td>2,298</td>
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<td><strong>Illicit Substances</strong></td>
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<tr>
<td>6-Acetylmorphine</td>
<td>10</td>
<td>216,670</td>
<td>1,505</td>
<td>0.7%</td>
<td>246.9</td>
<td>255.1</td>
<td>6.6</td>
<td>10</td>
<td>153,236</td>
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<tr>
<td>Benzoylecgonine</td>
<td>50</td>
<td>325,124</td>
<td>9,942</td>
<td>3.1%</td>
<td>1,006.1</td>
<td>507.9</td>
<td>11.1</td>
<td>50</td>
<td>495,250</td>
</tr>
<tr>
<td>MDMA</td>
<td>100</td>
<td>316,507</td>
<td>26</td>
<td>&lt; 0.1%</td>
<td>1,414.5</td>
<td>987.9</td>
<td>5.4</td>
<td>101</td>
<td>51,693</td>
</tr>
<tr>
<td>Phencyclidine</td>
<td>10</td>
<td>196,732</td>
<td>73</td>
<td>&lt; 0.1%</td>
<td>172.8</td>
<td>142.7</td>
<td>6.4</td>
<td>10</td>
<td>6,447</td>
</tr>
<tr>
<td><strong>Cathinones</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MDPV</td>
<td>10</td>
<td>60,990</td>
<td>29</td>
<td>&lt; 0.1%</td>
<td>131.5</td>
<td>61.9</td>
<td>7.7</td>
<td>13</td>
<td>33,932</td>
</tr>
<tr>
<td>Mephedrone</td>
<td>10</td>
<td>60,990</td>
<td>3</td>
<td>&lt; 0.1%</td>
<td>123.3</td>
<td>142.9</td>
<td>2.5</td>
<td>47</td>
<td>279</td>
</tr>
<tr>
<td>Methylone</td>
<td>10</td>
<td>60,990</td>
<td>29</td>
<td>&lt; 0.1%</td>
<td>114.5</td>
<td>52.8</td>
<td>10.5</td>
<td>10</td>
<td>72,973</td>
</tr>
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</table>
As the detection of analytes varied by medication or illicit substance, the quantitative values also showed significant variability for the parent compounds as well as their metabolites. The morphine, tramadol and tapentadol median excretion concentrations were the highest of the opioid drug class, each with a median value of approximately 10,000 ng/mL. The median value for oxycodone was approximately 2,500 ng/mL. The hydrocodone median value was approximately 1,000 ng/mL. However, all the medication or illicit substances examined showed a wide range of excretion values, with some extreme cases of concentrations greater than 1,000,000 ng/mL of excreted medication or illicit substance. Reasons for the wide variance include differences in medication doses, metabolic variations from person to person, and specimens that had been altered by the patient in an attempt to deceive the physician. In cases with extremely high concentrations, the patient who was not actually ingesting the medication would likely have “shaved” the medication directly into the urine collection cup to produce a positive test result.

The illicit substances most often found were (from most common to least common): marijuana, cocaine, synthetic cannabinoids, methamphetamine, heroin, MDMA, PCP, and synthetic cathinones. Methamphetamine was accompanied by amphetamine more than 95% of the time. Heroin, as determined by the 6-acetylmorphine metabolite, was accompanied more than 92% of the time by the presence of codeine, which has been shown to be an impurity in the manufacturing process [25,26].

For some medications, the presence or absence of the metabolite may be characteristic for that medication. Consistent with previous studies, the metabolite hydromorphone was not always found with morphine [27]. In some cases, the metabolite was observed in absence of the parent drug (e.g. meprobamate was observed without carisoprodol about 41% of the time) [19]. As the results demonstrated, the inclusion of metabolites in the test menu can allow for informed interpretation of results, and to help identify patients attempting deception, as well as those with atypical metabolism.

Conclusions

The guidelines for monitoring patients on chronic opioid therapy are designed to identify prescribed analgesic medications taken by those patients, and to reduce risk for abuse, morbidity, and mortality. LC-MS/MS technology used with validated cutoff levels for each analyte in a specific test menu provides objective data that may contribute to achieving those objectives. Understanding the medications and illicit substances found in UDT specimens from the pain population can help providers optimize medication monitoring for the best possible and safest plan to manage the patient’s pain.

References