Evaluation of Concomitant Methylphenidate and Opioid Use in Patients with Pain

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Methylphenidate is a central nervous system stimulant that is used for management of opioid-induced sedation. Sparse data exist regarding use patterns of methylphenidate and opioids in patients with pain. This retrospective data analysis evaluated concomitant methylphenidate and opioid use from physician-reported medication lists and in urine specimens of patients with pain. All specimens were analyzed and quantified with LC–MS-MS. Concomitant methylphenidate and opioid use (e.g., sample population) were compared with a baseline population of patients taking opioids. There were 3,326 patients with physician-reported use of methylphenidate. Of these, 1,089 patients were tested for the presence of methylphenidate in urine. Methylphenidate was positive in urine for 551 patients (detection rate of 50.6%). Ritalinic acid was positive in 776 patients (detection rate of 71.3%). The current study observed differences in the use pattern of methylphenidate based on opioid type. Physician-reported use revealed methadone had the highest percent difference between the sample and baseline populations (77%, $P \leq 0.05$). Fentanyl, morphine and hydromorphone also had higher percent differences of 19.6, 25.3 and 32.3%, respectively. Further studies need to examine the apparent discrepancies between the physician-reported medication lists and urine drug testing of concomitant methylphenidate and opioid use in patients with pain.

Introduction

Opioids are used to manage pain. Often, high doses or multiple opioids are needed for adequate pain control in patients with moderate-to-severe pain (1). Coupled with the analgesic benefits of opioids are the drawbacks of adverse effects. The incidence and severity of adverse effects associated with opioid use may be an important factor in achieving optimal pain management. Opioid-induced sedation and cognitive dysfunction occur in ~20–60% of patients and can lead to loss of daily functioning and decreased quality of life (2, 3). Opioid-induced sedation is dose-limiting, typically developing upon dose initiation or escalation, with most patients developing tolerance within a few days to weeks (4). However, some patients never develop tolerance to opioid-induced sedation (5). As such, opioid-induced sedation may limit opioid dose titration for adequate pain control (5, 6).

Methylphenidate, a piperidine derivative and a central nervous system stimulant, is considered the drug of choice for the management of attention deficit hyperactivity disorder (ADHD) in adults and children (7, 8). The mechanism of action has been attributed to its similarity to dopamine and the ability to compete with dopamine for its uptake binding site (9, 10). Methylphenidate has been shown to increase dopamine efflux in all major dopaminergic nerve terminal regions of the brain, leading to prolonged dopamine receptor interactions (9, 11, 12). These effects lead to an overall increase in alertness (12, 13). The stimulant properties of methylphenidate have resulted in clinical use to manage cancer-related fatigue and depression (12, 14). Methylphenidate is rapidly metabolized to ritalinic acid (inactive metabolite) via hydrolysis of the methyl ester linkage. Approximately 70% of the dose is eliminated in urine as ritalinic acid, thus providing a reliable indicator for monitoring drug usage (15).

Existing literature suggests that methylphenidate may improve opioid-induced sedation, with a significant reduction in drowsiness (1, 5, 16). Limited evidence also suggests that methylphenidate may potentiate the analgesic effects of opioids when used concurrently (17). However, as to which specific opioid is most and least commonly associated with methylphenidate use for opioid-induced sedation and/or analgesic effects is not known. Consequently, studies in the use patterns of methylphenidate and opioids in patients with pain are needed. The purpose of this retrospective data analysis was to evaluate concomitant methylphenidate and opioid use based on physician-reported medication lists and urine drug testing (UDT) in patients with pain. These observations may aid in the understanding of methylphenidate use in patients with pain and provide insight for UDT of methylphenidate.

Methods

Urine specimen selection

IRB-exempt status was granted by the University of California, San Diego, Human Research Protection Program. This retrospective analysis was conducted on a database of ~600,000 urine specimens from pain patients seen at pain physician practices during routine UDT between September 2011 and May 2012. Specimens with creatinine concentrations <20 mg/dL were excluded as these could be potentially tampered specimens lacking characteristics consistent with normal human urine (18). First visit, urine concentrations of opioids were normalized to correct for differences in hydration status using urine creatinine values (19). Final concentrations are presented in milligrams of drug per gram of creatinine (mg/g).

The opioids examined in this analysis were: oxycodone (OXY), oxymorphone (OXM), hydrocodone (HYD), hydromorphone (HYM), morphine (MOR), fentanyl (FEN) and methadone (MTD). These are commonly used opioids for pain management found in the 2009 Medical Treatment Utilization Schedule for chronic pain treatments (20).

LC–MS–MS analysis

All specimens were analyzed and quantified using LC–MS-MS (21, 22) by Millennium Laboratories (San Diego, CA, USA). An
Agilent 1200 series binary pump SL LC system, well-plate sampler and thermostatted column compartment paired with an Agilent triple Quadrupole mass spectrometer and Agilent Mass Hunter software were used for analysis of methylphenidate and ritalinic acid. Chromatographic separation was performed using an acetonitrile formic acid water gradient running at 0.4 mL/min and a 2.1 × 50 mm², 1.8 μm Zorbax SB C 18 column. Mobile phase A = +0.1% formic acid in water, B = 0.1% formic acid in acetonitrile and column temperature was set to 50°C. Samples were prepared for injection by incubating 25 μL of urine with 50 Units of β-glucuronidase Type L-II from Patella vulgata (keyhole limpet) Sigma Product number G 8132 (Sigma–Aldrich Corp, St. Louis, MO, USA) in 50 μL 0.4 M acetate buffer (pH 4.5) for 3 h at 45°C. Five microliters of the solution were injected for each sample.

Opioids were analyzed as part of a multiplex pain medication assay. The samples were hydrolyzed, then incubated with a β-glucuronidase enzyme prior to analysis. Total drug concentrations (free and glucuronidated forms) were measured as part of a multiplex pain medication assay that is described in detail elsewhere (21, 22). All spectra were collected using positive electrospray ionization. The optimized instrumental parameters were as follows: gas temperature, 350°C; drying gas, 12 L/min; nebulizer gas (nitrogen), 35 psi (~24,100 Pa); capillary voltage, 3,000 V; and fragmenter voltage, 60 V. Multiple reaction monitoring (MRM) mode was used for quantitation. Scan time was set to 500 ms. In MRM mode, two transitions were used to identify and quantitate a single compound. Data were acquired running the QQQ in MRM mode, using transitions methylphenidate-D9: 243.2 → 93, methylphenidate: 234.2 → 84.1, 234.2 → 56.2, ritalinic acid-D10: 230.2 → 93.1, ritalinic acid: 220.1 → 84.1, 220.1 → 56.1, OXY: 316.2 → 256.1, 316.2 → 241.1, OXY-d6: 322.2 → 247.1, OXM: 302.3 → 227, 302.3 → 198, OXM-d6: 305.3 → 201.1, noroxycodone: 302.2 → 284, 302.2 → 187, HYD: 300.2 → 199, 300.2 → 128, HYD-d6: 306.2 → 202.2, HYM: 286.2 → 185, 286.2 → 128.1, HYM-d6: 292.2 → 128.1, norhydrocodone: 286.1 → 199.1, 286.1 → 115.1, MOR: 286.2 → 165.1, 286.2 → 152.1, MOR-d6: 292.2 → 165.1, MTD: 310.2 → 265.1, 310.2 → 105, MTD-d3: 313.2 → 105, EDDP-d3: 234.1 → 186, EDDP-d3: 281.2 → 234.1, FEN: 337.2 → 234.1, FEN-d5: 337.2 → 234.1, FEN: 322.2 → 105.1, FEN-d5: 322.2 → 105.1, norfentanyl: 233.2 → 84.1, 233.2 → 56, norfentanyl-d5: 238.2 → 84.1. A quantitative transition was used to calculate concentration based on the quantifier ion and a second transition was used to ensure accurate identification of the target compound based on the ration of the quantifier ion to the quantifier ion.

HPLC grade water, acetonitrile, methanol and formic acid were obtained from VWR (Westchester, PA, USA). Methylphenidate and ritalinic acid were obtained from Cerrilant Corp (Round Rock, TX, USA). The deuterated internal standards were diluted to 1,000 ng/mL by adding them to synthetic urine (Microgenics Corp., Fremont, CA, USA). Quantitative analysis was performed using Agilent Mass Hunter Quantitative Analysis software. A four-point calibration curve was created by using a linear fit and forcing the line to go through the origin. Accepted accuracy for calibrators was ±20% of the target value and the coefficient of determination (R²) was required to be ≥0.99 as verification of linearity and goodness of fit.

The upper limits of linearity for methylphenidate and ritalinic acid were 100,000 ng/mL. The lower limits of quantification for methylphenidate and ritalinic acid were 50 ng/mL. The opioid lower limits of quantitation were: 50 ng/mL for OXY, OXM, noroxycodone, HYD, HYM, norhydrocodone and MOR; 2 ng/mL for FEN; 8 ng/mL for norfentanyl; and 100 ng/mL for MTD and EDDP.

Data and statistical analysis
Data were de-identified and collected into an MS Excel™ database that included a study-specific subject identification number, specimen identification number, urine creatinine concentration, physician-reported medication list and urine concentration of opioids, methylphenidate and ritalinic acid. A physician-reported medication list was provided for each urine sample sent to Millennium Laboratories for analysis. Any medication documented on the medication list was manually entered into the MS Excel™ database. Data were separated into a baseline population and sample population (Figure 1). The baseline population represented patients who were taking an opioid. The sample population included patients who were concomitantly taking methylphenidate and an opioid.

The prevalence of physician-reported medication use in the baseline population was calculated as the number of subjects at first visit on a specific opioid divided by total number of subjects at first visit reported to be on any opioid (n = 463,371). The prevalence of physician-reported medication use in the sample population was calculated as the number of subjects at first visit reported to be on methylphenidate and a specific opioid divided by the total number of subjects at their first visit reported to be on methylphenidate (n = 3,326). The percent (%) difference between populations was determined by the following equation:

\[
\text{\% Difference} = \left(\frac{\text{Sample prevalence} - \text{Baseline prevalence}}{\text{Baseline prevalence}}\right) \times 100
\]

Regarding the evaluation of urine specimens, data included the number of specimens tested and the number of positive specimens in the baseline and sample populations. Detection rates in urine were the number of specimens with detectable drug divided by the number of specimens tested for that particular drug (specimens were tested because subjects were reportedly using that specific drug). Frequencies were calculated using specimens collected from a subject’s first visit only. Data were analyzed using Microsoft Excel 2010 (Microsoft Corporation, Redmond, WA, USA) and OriginPro 8.6 (23). Z tests with Yates correction were performed to determine if there were differences in prevalence or opioid detection rates between baseline and sample populations (24). Statistical significance was defined as P ≤ 0.05.

Results
Detection rates of methylphenidate and ritalinic acid from UD
There were 1,089 patients that were tested for presence of methylphenidate in urine. Methylphenidate was positive in urine for 551 patients (baseline detection rate of 50.6%). Ritalinic acid was positive in 776 patients (baseline detection rate of 71.3%). All specimens that were positive for methylphenidate were also positive for ritalinic acid. Thus, the overall detection rate
(methylphenidate or ritalinic acid) was 71.3%. Table I summarizes the detection rates of methylphenidate and ritalinic acid in the sample population. The methylphenidate detection rate was highest for urine specimens positive for MOR (63.5%) and lowest for HYD (12%). For ritalinic acid, detection rate was highest in specimens positive for MTD (81.7%) and MOR (81%) and lowest for OXM (57.1%; Table I).

**Physician-reported methylphenidate and opioid use**

There were 3,326 patients with physician-reported use of methylphenidate. Physician-reported opioid use in the baseline and sample populations is summarized in Table II. Oxycodone and HYD were the most common physician-reported opioids in both populations. There were differences in the reported prevalence of all opioids tested between the baseline and sample populations (Table II). Methadone had the greatest percent difference (77%; \( P \leq 0.05 \)) from baseline (Figure 2). Fentanyl, MOR and HYM also had higher percent differences of 19.6, 25.3 and 32.3%, respectively (Figure 2). Hydrocodone, OXM and OXY had a lower prevalence in the sample population compared with the baseline population.

### Table I

<table>
<thead>
<tr>
<th>Opioid</th>
<th>Number of specimens tested</th>
<th>Methylphenidate</th>
<th>Ritalinic acid</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Number of positive specimens</td>
<td>Detection rates (%)</td>
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<tr>
<td>Oxycodone</td>
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<td>117</td>
<td>53.4</td>
</tr>
<tr>
<td>Oxymorphone</td>
<td>14</td>
<td>4</td>
<td>28.6</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>217</td>
<td>26</td>
<td>12.0</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>35</td>
<td>19</td>
<td>54.3</td>
</tr>
<tr>
<td>Morphine</td>
<td>63</td>
<td>40</td>
<td>63.5</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>35</td>
<td>22</td>
<td>62.9</td>
</tr>
<tr>
<td>Methadone</td>
<td>60</td>
<td>37</td>
<td>61.7</td>
</tr>
</tbody>
</table>

**Detection rates of opioids from UDT**

Table III summarizes the urine drug test results of opioids in the baseline and sample populations. In the baseline and sample populations, MTD had the highest detection rates (88.3 and 93.5%, respectively), whereas HYD had the lowest detection rates (67 and 71.1%). There were no differences in detection rates of OXY, OXM, HYM and MOR concentrations between populations. In contrast, significant differences in the detection rates between populations were observed for HYD, FEN and MTD (\( P \leq 0.05 \)). All evaluated opioids had a higher detection rate in the sample population compared with the baseline population (Figure 3).

### Discussion

**Detection rates of methylphenidate and ritalinic acid from UDT**

This study evaluated methylphenidate and ritalinic acid detection rates in urine specimens from a pain patient population.
In the sample population, the detection rates of methylphenidate and ritalinic acid during concomitant opioid use was 12–63.5% and 57.1–81.7%, respectively. Detection rates of methylphenidate and ritalinic acid were variable based on opioid type. One explanation for the variable detection rates for methylphenidate and ritalinic acid is the short elimination half-lives of ~2–5 h (25). The rapid elimination of methylphenidate and ritalinic acid from the body may contribute to the lower detection rates, especially if the time of the urine drug test does not correlate with when the patient has consumed the dose or with the frequency of methylphenidate use if taken on an as needed basis. A limitation of this study was that information regarding methylphenidate dose, time of administration and frequency of use (e.g., scheduled or as needed basis) was not documented in the current study.

Morphine, MTD and FEN had the highest number of positive methylphenidate specimens, whereas HYD has the lowest number of positive specimens (Table I). We speculate that this finding may be due to opioid potency, with HYD considered an opioid with weak potency, whereas MOR, MTD and FEN are opioids with strong potency. However, future research is needed to confirm these findings. Future research should also examine detection rates with opioids and other medications that have been used for opioid-induced sedation such as dextroamphetamine, donepezil, modafinil and caffeine.

![Figure 2. Percent difference of prevalence between baseline and sample population of physician-reported opioid use. OXY, oxycodone; OXM, oxymorphone; HYD, hydrocodone; HYM, hydromorphone; MOR, morphine; FEN, fentanyl; MTD, methadone.](image)

**Physician-reported methylphenidate and opioid use**

Physician-reported use of methylphenidate and MTD had the highest percent difference of prevalence in the sample population versus baseline population (Figure 2). Morphine, FEN and HM also showed a higher prevalence of concomitant use with methylphenidate. These results seem to suggest that these opioids are mostly commonly associated with methylphenidate use. In patients who become tolerant to the analgesic properties of opioids, higher doses are required for adequate pain control. Increasing opioid doses can lead to a higher incidence of opioid-induced sedation (20, 26). This may explain why HYD, an opioid with weak potency, was found to have a lower percent difference in prevalence, and thus a lower co-prescribing frequency (Figure 2).

However, these results are to be interpreted with caution as one study limitation was that the indication for which methylphenidate was prescribed was not known. It may be possible that the observation of higher physician-reported methylphenidate use was not for management of opioid-induced sedation but for other indications such as ADHD. In addition, physician-reported medication lists may be inaccurate due to patients not disclosing methylphenidate and/or opioid use to their pain physician, inadvertent omission of documentation of methylphenidate on the medication list or lack of knowledge of methylphenidate use by the pain physician if prescribed by another physician/provider. However, medication history is an acceptable method to evaluate concurrent medication use and potential for clinically significant drug–drug interactions. In one study of immunosuppressant drugs, which have a narrow therapeutic window, concurrent medication use was identified via medication history in the absence of qualitative and/or quantitative analysis (27). Regarding the current study, the extent of contribution regarding inaccurate physician-reported medication lists is unknown. Rather a multiple method approach of medication list documentation, UDT, as well as other methods (e.g., pill counts, prescription drug monitoring), are critical to confirm appropriate opioid use.

**Detection rates of opioids from UDT**

The current study observed opioid detection rates of 67–88.3% in the baseline population and of 71.1–93.5% in the sample population (Table III). These results are consistent with another study that examined similar opioids (HYD, MTD, MOR and OXY) in urine specimens from pain patients and reported detection rates ranging from 74 to 91% (28). Detection rates were higher for all the opioids examined in the sample population.

**Table III**

<table>
<thead>
<tr>
<th>Opioid</th>
<th>UDT in baseline population</th>
<th>UDT in sample population</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of specimens tested</td>
<td>Number of positive specimens</td>
<td>Detection rates (%)</td>
</tr>
<tr>
<td>Oxydone</td>
<td>158,200</td>
<td>114,564</td>
<td>72.4</td>
</tr>
<tr>
<td>Oxymorphone</td>
<td>14,931</td>
<td>12,513</td>
<td>83.8</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>183,956</td>
<td>123,186</td>
<td>67.0</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>14,445</td>
<td>11,297</td>
<td>78.2</td>
</tr>
<tr>
<td>Morphine</td>
<td>38,094</td>
<td>31,893</td>
<td>83.7</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>21,449</td>
<td>17,755</td>
<td>82.6</td>
</tr>
<tr>
<td>Methadone</td>
<td>25,370</td>
<td>22,406</td>
<td>88.3</td>
</tr>
</tbody>
</table>

*Z-test with Yates Correction comparing prevalence between baseline and sample populations.
who were taking methylphenidate (Table III), with significant differences in rates for HYD, FEN and MTD. Whether such differences between populations are due to scheduled, around-the-clock opioid dose administration or higher daily opioid doses is unknown and a further area of investigation. We speculate that the observed increase in detection rates of methylphenidate and opioid use may also be observed with other medications used for opioid-induced sedation. Additional studies utilizing different and external urine data are needed to confirm the current study findings of the increased detection of methylphenidate with HYD, FEN and MTD.

Conclusions

To the best of our knowledge, this is the first analysis in a pain population evaluating concomitant methylphenidate and opioid use by examining physician-reported medication lists and UDT. These results highlight the differences in the use patterns of methylphenidate with different opioids. Further studies should be conducted to validate current study findings, to elucidate the causes of these differences and to examine the apparent discrepancies between physician-reported and UDT of these medications in patients with pain. As urine specimens continue to be collected for methylphenidate and ritalinic acid, it would also be of interest to examine methylphenidate and ritalinic acid urine concentration variability and the effect of confounding factors such as age, sex and urine pH, which are known to influence urine drug concentrations (29, 30).

Acknowledgments

The authors thank Dr Amadeo Pesce for his expert advice and guidance in this project. Urine specimens were tested and provided by Millennium Laboratories. Dr Joseph D. Ma is a paid consultant of Millennium Laboratories, Inc.

Funding

This work was supported, in part, by an education grant provided to the University of California, San Diego (UC San Diego) Skaggs School of Pharmacy and Pharmaceutical Sciences from an unrestricted gift from the Millennium Research Institute (to J.Y.J.).

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