Urine Specimen Detection of Concurrent Nonprescribed Medicinal and Illicit Drug Use in Patients Prescribed Buprenorphine

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Patients being treated with buprenorphine usually have a history of opioid dependence and may be predisposed to misuse of drugs. Concurrent drug misuse increases the risk of life-threatening drug interactions. This retrospective data analysis observed which nonprescribed and illicit drugs were most commonly detected in the urine of patients from pain management clinics taking buprenorphine with or without a prescription. GC, LC/MS and LC–MS-MS were used to quantify 20,929 urine specimens. The most prevalent illicit drug used in both the groups (prescribed and nonprescribed buprenorphine) was marijuana, followed by cocaine. The most prevalent nonprescribed medications abused by both the groups were benzodiazepines, followed by oxycodone and hydrocodone. The overall prevalence of illicit and nonprescribed drug use was significantly higher in subjects who used buprenorphine without a prescription versus prescribed use. Of the concurrent use of marijuana and cocaine with buprenorphine, cocaine is most concerning since it decreases exposure to buprenorphine (lower area under the concentration–time curve and maximum concentration). The concurrent use of nonprescribed benzodiazepines with buprenorphine can cause excess sedation leading to respiratory depression and even death. These findings highlight the importance of educating patients about these potential toxicities. Furthermore, pain providers should consider expanding the spectrum of drugs that they monitor in patients under treatment.

Introduction

Buprenorphine is a semisynthetic opioid derived from the opium alkaloid thebaine. Its chemical structure is similar to morphine and thus, exhibits some of the characteristics of morphine along with its own unique pharmacological features (1). It is a partial μ-opioid receptor agonist (i.e., high affinity, low-intrinsic activity and slow dissociation) and a κ-opioid receptor antagonist, giving it a unique mechanism of action that results in low respiratory depression risk, fewer autonomic signs of opioid withdrawal and fewer psychomimetic or dysphoric effects relative to other mixed agonist–antagonist medications (2). Buprenorphine is primarily metabolized into norbuprenorphine by Cytochrome P450 (CYP) 3A4 and 2C8, which is further metabolized by a host of Uridine 5’-diphospho-glucuronosyltransferase enzymes (3). Both buprenorphine and norbuprenorphine have distinct pharmacological effects and half-lives of >24 h. Buprenorphine’s better safety profile, low physical dependence and flexibility in dose scheduling make it an attractive alternative to methadone in the treatment of opioid dependence (2, 4, 5).

Buprenorphine at low doses is effective in the treatment of acute and chronic pain, whereas at higher doses its use is reserved for the office-based treatment of opioid addiction (6, 7). For the treatment of opioid dependence, buprenorphine is available as sublingual tablets (Subutex®) and also in combination with naloxone in sublingual tablets and films (Suboxone®). Some patients being treated with buprenorphine have a history of opioid dependence and as a result, may be predisposed to taking drugs abnormally, specifically abusing nonprescribed or illicit drugs. Buprenorphine has its own abuse potential due to its potentially euphoric effects, lending itself to diversion. The crushing of buprenorphine tablets and their subsequent snorting or injection are common methods of abuse (8). Because of its efficacy as an alternative to methadone, the number of buprenorphine patients worldwide is increasing, making it important to investigate the concurrent drug use patterns associated with buprenorphine.

To date, few data examine the prevalence of concomitant misuse of drugs with buprenorphine. This is the first study to observe the prevalence of buprenorphine use with benzodiazepines in a large population. Drug abuse prevalence in chronic pain patients on opioids ranges from 18 to 41%. Illicit drug use in patients with controlled substance abuse has been reported as high as 34% (9). A previous study by Cone et al. (10) characterized the drug disposition patterns of urine specimens from a large population of pain patients. They found that opioids and benzodiazepines were the most frequently encountered licit drugs, whereas 10.9% of specimens tested positive for illicit drugs, with marijuana and cocaine being the most frequent (10).

The goal of this retrospective study was to observe the nonprescribed and illicit drug use patterns associated with buprenorphine use and to compare these patterns with those found by Cone et al. (10) in the general chronic pain population. This study also sought to see if the abuse of buprenorphine was associated with that of any other type of drug. This study also examines the abuse patterns of buprenorphine in a large population of pain patients by observing data collected from urine drug testing. Knowledge of concurrent drug use patterns with buprenorphine may lead to better patient outcomes and help clinicians determine whether their patients are at an increased risk of potentially fatal drug interactions.

Methods

Between March 2008 and August 2011, 1,268,537 urine specimens from patients being seen by pain management physicians as part of routine clinical monitoring were collected and quantified by Millennium Laboratories (San Diego, CA, USA). All study data were de-identified prior to retrospective analysis, and Institutional Review Board–exempt status was granted by the
Urine specimens of subjects who took buprenorphine with or without a prescription were analyzed and quantified by using GC, LC–MS and LC–MS–MS (the method and details of each assay are described elsewhere) (11–14). Prior to analysis, samples were prepared for injection by incubating 25 mL of urine with 50 units of β-glucuronidase Type L-II from Patella vulgata (keyhole limpet), Sigma product number G8132 (Sigma-Aldrich Corp., St. Louis, MO, USA), in 50 mL 0.4 M acetate buffer (pH 4.5) for 2 h at 60°C. For each specimen, data included the medications that each subject was prescribed (as reported by their physician) and the drugs and metabolites that were detected in their urine. The drugs, metabolites and their limits of detection are listed in Table I.

Only urine samples meeting specific criteria were included in the study, and the selection process is outlined in Figure 1. Specimens with creatinine concentrations <20 ng/mL were excluded from the study as these could be potentially tampered specimens and do not have characteristics consistent with normal human urine (15). Only the first specimen taken from each subject was used in analyses to prevent bias toward subjects with multiple samples. To be included in an analysis, each subject had to have been tested for every drug in the analysis’s drug panel. Parent drugs and their metabolites were grouped into categories (Table I). Subjects with parent drug or metabolite urine concentrations higher than the limit of detection were reported as having taken the drug. Instances of a drug being detected in a subject’s specimen that was not reported in their medication list by their physician were considered instances of nonprescribed use of a drug. Subjects using buprenorphine without a prescription were included in each analysis to compare the drug abuse patterns of a population that was prescribed buprenorphine with a population that used buprenorphine without a prescription.

Data were analyzed using Microsoft Excel 2010 (Microsoft Corp., Redmond, WA, USA). Drug usage and prescription rates are presented as percentages. Z-tests were performed to detect statistical differences in concomitant drug usage rates between populations. Statistical significance was defined as P < 0.05.

### Table I

<table>
<thead>
<tr>
<th>Category name</th>
<th>Legal status</th>
<th>Parent drugs included in detection assay (limit of detection in ng/mL)</th>
<th>Metabolites included in detection assay (limit of detection)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buprenorphine</td>
<td>Prescription</td>
<td>Buprenorphine (5)</td>
<td>Norbuprenorphine (10)</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>Prescription</td>
<td>Hydrocodone (25), hydromorphone (25)</td>
<td>Norhydrocodone (25)</td>
</tr>
<tr>
<td>Dicyclomine</td>
<td>Prescription</td>
<td>Dicyclomine (25), oxymorphone (25)</td>
<td>Noroxycodeine (25)</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>Prescription</td>
<td>Lorazepam (20), oxazepam (20), temazepam (25)</td>
<td>Nordiazepam (20), alpha-hydroxyalprazolam (10), 7-amino-clonazepam (10)</td>
</tr>
<tr>
<td>Morphine</td>
<td>Prescription</td>
<td>Morphine (25)</td>
<td>None</td>
</tr>
<tr>
<td>Methadone</td>
<td>Prescription</td>
<td>Methadone (50)</td>
<td>2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (50)</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>Prescription</td>
<td>Fentanyl (1)</td>
<td>Norfentanyl (4)</td>
</tr>
<tr>
<td>Codeine</td>
<td>Prescription</td>
<td>Codeine (25)</td>
<td>None</td>
</tr>
<tr>
<td>Amphetamine</td>
<td>Prescription</td>
<td>Amphetamine (50)</td>
<td>None</td>
</tr>
<tr>
<td>Methamphetamine</td>
<td>Prescription/Ilicit</td>
<td>Methamphetamine (50)</td>
<td>None</td>
</tr>
<tr>
<td>THC (Marijuana)</td>
<td>Prescription/Ilicit</td>
<td>Dronabinon (N/A)</td>
<td>cTHC (7.5)</td>
</tr>
<tr>
<td>Cocaine</td>
<td>Ilicit</td>
<td>Cocaine (N/A)</td>
<td>Benzylecgonine (25)</td>
</tr>
<tr>
<td>Heroin</td>
<td>Ilicit</td>
<td>Heroin (N/A)</td>
<td>6-monoacetylmorphine (5)</td>
</tr>
</tbody>
</table>

Nonprescribed use of methamphetamine or THC was considered illicit. Samples were analyzed with glucuronidase, and therefore, all samples report the concentration of glucuronidated and nonglucuronidated drug combined.
73.34% had at least one other controlled substance detected in their urine.

**Discussion**

**Illicit drug use**

This study was the first to look at the illicit drug use patterns in patients who are also taking buprenorphine. The illicit drugs of highest prevalence in subjects prescribed or taking nonprescribed buprenorphine were THC and cocaine. This trend agrees with the findings of Cone *et al.* (10), where THC and cocaine were the most prevalent drugs detected in a chronic pain population. There are no known safety issues with the concurrent use of THC with buprenorphine. Cocaine, however, has been shown to alter exposure to buprenorphine in the blood. A study by McCance-Katz *et al.* (16) showed that chronic and heavy cocaine use decreased pharmacokinetic exposure to buprenorphine (lower area under the concentration–time curve and maximum concentration), while occasional use showed little effect. This decreased exposure could be due to vasoconstriction caused by cocaine, which would decrease absorption of buprenorphine, or to the induction of CYP or P-glycoprotein in the intestines or liver (16). Decreased exposure to buprenorphine could increase the risk of the precipitation of withdrawal...
symptoms or could lead to poor clinical outcomes of opioid replacement therapy.

This study shows that there is a prevalence of illicit drug use in patients taking buprenorphine with and without a prescription that pain clinicians need to be aware of. These results provide further support for the conclusion made by Pesce et al. (17) that physicians prescribing opioids should consider urine testing in their patients for illicit drugs. The increased likelihood of cocaine use in subjects who obtained and abused buprenorphine without a prescription highlights the importance of urine drug testing in ensuring the appropriate use of opioid replacement therapy and preventing the diversion of buprenorphine.

The prevalence of illicit drug use within the population who was prescribed buprenorphine was higher than that found in the chronic pain population in the study by Cone et al. (10) (34.4 versus 10.9%). This high rate of illicit drug use within subjects on buprenorphine is alarming and indicates that there may be a need for additional or more repeat testing to monitor for illicit drugs. Continued urine drug testing may decrease illicit drug use over time among pain patients (18). According to the urine drug testing data, not all subjects who were prescribed buprenorphine were tested for all common drugs of abuse on a consistent basis. Practitioners do not always order illicit drug tests for their patients on buprenorphine, but it may be beneficial for them to routinely include these tests in their monitoring of buprenorphine use.

Nonprescribed drug use

The rate of poly-drug use in patients prescribed buprenorphine was found to be 73.54% and is consistent with the high rates found in another study (19). Benzodiazepines were the most widely abused prescription drugs in subjects prescribed buprenorphine and those taking nonprescribed buprenorphine. This finding is consistent with previous studies, which found a high prevalence of benzodiazepine use in buprenorphine patients (20). Subjects may have been using benzodiazepines without a prescription to ameliorate withdrawal symptoms associated with opioid replacement therapy such as sleeplessness, agitation and anxiety (21). The possibility that they were being abused without physician supervision for intoxication purposes must not be ruled out (22). There exists a potential risk of excess sedation leading to respiratory depression when benzodiazepines are used concurrently with buprenorphine (23). When taken alone, buprenorphine has been shown to have a limited effect on respiratory depression. However, studies in rats have shown that the co-administration of buprenorphine with benzodiazepines caused buprenorphine to act like a full opioid agonist and lose its respiratory depression ceiling effect, with both drugs acting in a synergistic fashion to depress ventilation (24). A study in humans showed that therapeutic doses of diazepam used with buprenorphine did not significantly affect respiratory function (22), although the abuse of these drugs for intoxication purposes may involve doses that are significantly higher.

Because buprenorphine and benzodiazepines both undergo extensive metabolism by CYP3A4, metabolic interactions between the two drugs may contribute to the risk of using both drugs concurrently. To date, there is little clinical data regarding the interaction between buprenorphine and benzodiazepines. Chang and Moody (25) found that midazolam is a moderate inhibitor of CYP3A4-mediated N-dealkylation of buprenorphine, although this was the only benzodiazepine found to do so. Midazolam is not available in outpatient settings and is unlikely to be implicated in the toxicity of concurrent benzodiazepine and buprenorphine use. Indeed, more clinical studies that observe the pharmacological interaction between benzodiazepines and buprenorphine are necessary.

Numerous cases of death resulting from the concomitant use of benzodiazepines with buprenorphine have been documented in previous studies. In a study conducted by Kintz (26), over 75% of the observed fatalities from buprenorphine involved the concurrent use of benzodiazepines. In a study that observed buprenorphine-related deaths in Singapore, Lai et al. (27) found that benzodiazepines were detected in the autopsies of 19 of 21 subjects. Selden et al. found that co-ingestion of hypnotics and sedatives with buprenorphine was found in 75% of buprenorphine-related deaths in their study, suggesting that these drugs interact with buprenorphine to produce toxic effects that buprenorphine alone would not have produced (19). Fatal poisonings from the use of buprenorphine alone are not common, but have also been reported (19, 28). These studies highlight the potentially lethal consequences of the co-administration of benzodiazepines with buprenorphine. While our findings do not imply a causative relationship between concomitant benzodiazepine and buprenorphine use and mortality, they could support the existing literature that links buprenorphine-related deaths with benzodiazepines.

Relatively, the high prevalence of nonprescribed oxycodone and hydrocodone use compared with their prescription prevalence suggests that subjects may be having difficulties with opioid replacement therapy. Buprenorphine use without a prescription seems to be linked to an increase in drug-seeking behavior (29). One reason for this could be that those who are prescribed buprenorphine are making more of an effort to decrease their substance abuse than those who are not being treated for opioid dependence, but are being monitored by a clinician for their chronic pain management. The prevalence of buprenorphine use without a prescription and its association with the abuse of other controlled substances suggests that
clinicians should consider regularly including buprenorphine in the routine urine drug testing of chronic pain patients. Furthermore, these results highlight the critical role of routine urine drug testing in ensuring the appropriate use of a drug regimen while minimizing drug diversion.

**Prescription rates of buprenorphine and concomitant medications**

Benzodiazepines were the most widely prescribed drugs in the whole study population, outnumbering the prescription rates of all other drugs in the study combined (20.56 versus 19.65%). They are often prescribed as ancillary medications to treat withdrawal symptoms (19). The high prevalence of benzodiazepine use in this study may also be due to the high incidence of psychiatric co-morbidities in the chronic pain population (23).

**Buprenorphine metabolite**

The detection rate of buprenorphine and its metabolite in subjects who were prescribed the drug was 90.11%. The prevalence of subjects testing positive for buprenorphine but not norbuprenorphine should not be ignored. Buprenorphine undergoes extensive metabolism in the liver to norbuprenorphine. The absence of norbuprenorphine in the urine may suggest that the subject is a slow metabolizer, although the more likely case is that the subject is attempting to test positive for buprenorphine without having taken the drug for the purpose of drug diversion. A further discussion and investigation between the prescriber and patient needs to be explored.

**Limitations**

The nature of the data collection procedure for urine drug testing in pain management offices did not allow for the collection of certain types of information for this study. Although our data were collected from pain management clinics, buprenorphine has FDA-approved indications for both pain and opioid dependence and the data collection method for this study did not distinguish the indication for each subject’s use of buprenorphine. Another limitation of this study is the incomplete reporting of medications being used prior to data collection. Each subject’s pain clinician listed their current medications at the time of sample collection, although there is a possibility that the clinician was not able to report all the medications if the subject was seeing more than one doctor. This may have altered the prevalence percentages seen in the nonprescribed drug use analysis.

Buprenorphine is a drug that can be prescribed for both pain and opioid dependence treatment, but in this study there was no way to distinguish this for each subject who was prescribed buprenorphine. Opioid dependence can have a large impact on the drug use or abuse patterns of an individual.

**Conclusion**

Among the illicit drugs included in this study, buprenorphine was most commonly used concurrently with marijuana and cocaine. Previous studies have shown that cocaine could potentially lead to undesirable therapeutic outcomes. Among the nonprescribed drugs included in this study, buprenorphine was most commonly concurrently used with benzodiazepines, followed by oxycodone and hydrocodone. Co-administration of buprenorphine with benzodiazepines may lead to morbidity and possibly mortality. Subjects using buprenorphine without a prescription were more likely to use other nonprescribed and illicit drugs than those who were prescribed buprenorphine. This evidence suggests that pain physicians should consider including buprenorphine in the routine drug tests that they order to gain insights into a patient’s propensity for drug abuse and to mitigate diversion. Given the high prevalence of concurrent controlled substance and illicit drug use with buprenorphine, care must be taken to avoid potentially dangerous drug interactions that may occur through drug abuse. These findings highlight the importance of prescribers being aware of and educating their patients on the potential toxicity of buprenorphine when administered concomitantly with other illicit and nonillicit drugs.

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