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Promethazine use among chronic pain patients

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Abstract

Background—Concomitant use of opioids and promethazine has been reported in various subpopulations, including methadone maintenance patients, injection drug users, and at-risk teenagers. Promethazine is thought to potentiate the “high” from opioids. However, to date, the prevalence of promethazine use has not been determined among patients prescribed opioids for chronic pain.

Methods—Urine samples from 921 patients prescribed opioids for chronic pain were analyzed for promethazine. Demographic data, toxicology results, and opioid prescription information were obtained through medical record abstraction. We assessed the prevalence and factors associated with promethazine use with bivariable and multivariable statistics.

Results—The prevalence of promethazine-positive urine samples among chronic pain patients was 9%. Only 50% of promethazine-positive patients had an active prescription for promethazine. Having benzodiazepine-positive urine with no prescription for a benzodiazepine was statistically associated with promethazine use. Also, having a prescription for methadone for pain or being in methadone maintenance for the treatment of opioid dependence were both statistically associated

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with promethazine use. Chronic pain patients prescribed only a long-acting opioid were more likely to have promethazine-positive urines than patients prescribed a short-acting opioid.

Conclusions—The study provides compelling evidence of significant promethazine use in chronic pain patients. Promethazine should be considered as a potential drug of abuse that could cause increased morbidity in opioid-using populations.

Keywords

prescription drug abuse; opioids; promethazine; chronic pain; pain management

1. INTRODUCTION

Prescription drug misuse among chronic pain patients is a topic of great concern in the medical community worldwide (Adams et al., 2004; Manchikanti et al., 2006; Martell et al., 2007). According to the 2012 United States National Survey on Drug Use and Health, an estimated 4.9 million persons age 12 or older had used opioid pain medication non-medically in the past month and 1.9 million people met criteria for abuse or dependence on prescription opioids (Anonymous, 2013). The misuse of prescription opioids is the leading cause of accidental overdose (Compton and Volkow, 2006) and the practice of co-administration with other drugs is known to contribute significantly to overdose risk (Hall et al., 2008; Dunn et al., 2010). A study of opioid-related mortality reported that most deaths (80%) involving prescription opioids identified other contributing drugs in the bloodstream on autopsy (Hall et al., 2008). In a community-based cohort of people who inject drugs, 20.9% reported non-medical prescription drug use in the prior 6 months and of those, 57% reported co-administration of more than one prescription drug in combination (Khosla et al., 2011). These emerging trends suggest the need to broaden the focus of research on the nonmedical use of prescription drugs beyond controlled substances and to monitor high risk populations as sentinels for the emergence of new drug use practices.

Over the last two decades, there have been sporadic reports of concomitant use of opioids with promethazine (Wairagkar et al., 1994; Lam et al., 1996; Mattoo et al., 1997; Sharma and Mattoo, 1999; Elwood, 2001; Shek and Lam, 2006; Peters et al., 2007; Clatts et al., 2010; Agnich et al., 2013; Shapiro et al., 2013). Promethazine, a phenothiazine derivative, is routinely prescribed for the treatment of nausea, vomiting, and motion sickness. It is also FDA approved for the treatment of allergic conditions and for pre- and post-operative sedation (Sharma and Hamelin, 2003; Page et al., 2009). Starting in the late 1990's, there were reports that teenagers in Texas were drinking cough syrup containing codeine and promethazine to get "high" (Mattoo et al., 1997, 1999; Elwood, 2001; Peters et al., 2003, 2007). In one study, 25% of at-risk youth reported lifetime illicit use of cough syrup containing codeine and promethazine (Peters et al., 2003). Nonmedical use of promethazine has also been reported among heroin injectors in Vietnam who used it to augment an inadequate heroin dose (Clatts et al., 2010) and among individuals that abuse buprenorphine in India (Singh et al., 1992; Sharma and Mattoo, 1999). Recently, it was reported that the "South Asian Cocktail" which contains buprenorphine, diazepam, promethazine, and/or other substances, is the predominant drug of choice in Nepal (Ojha et al., 2014). Nonmedical use of promethazine has also been reported in other areas of the United States, Hong Kong,

and India (Wairagkar et al., 1994; Lam et al., 1996; Shek and Lam, 2006; Agnich et al., 2013).

In the 1950s, the combination of promethazine and opioids was noted to have an opioid sparing effect and was used medically to allow for the use of lower doses of opioids to achieve sedation and analgesia (McGee and Weiss, 1956). Consuming large quantities of these two drugs prolongs and intensifies each drug's sedative effects and is also responsible for an increase in life-threatening events, such as delirium, respiratory depression, overdose, neuroleptic malignant syndrome, and prolongation of the QT interval (Owczuk et al., 2009; Jo et al., 2009, Gerostamoulos et al., 1996; Mattoo et al., 1997). In contemporary medical practice, the use of the two drugs in combination for sedation has declined due to these adverse effects and lack of data supporting clinical efficacy (Richter and Burk, 1992). Promethazine has also been reported to be present in fatal opioid overdoses. Promethazine was identified by postmortem toxicological analysis in 14.2% of methadone fatalities in Kentucky from 2000–2004 and 8.7% of fatal overdose cases that involved depressants in Seattle in 2003 (Shields et al., 2007; Banta-Green et al., 2005). In our recent study, we reported that one-quarter of methadone maintenance patients had promethazine in their urine samples, and 13% of people who inject heroin surveyed in the community reported nonmedical use of promethazine in the past month (Shapiro et al., 2013). Together, these data show that there are large proportions of teenagers, methadone maintenance patients, and people who inject heroin that use promethazine nonmedically, and that there appears to be a significant underground market for promethazine.

Chronic pain patients are another opioid using population with relatively high prevalence of nonmedical use of prescription drugs and other illicit drug use. Studies of patients taking opioids for chronic pain suggest that as many as 45% engage in aberrant drug-taking behaviors (Katz et al., 2003; Martell et al., 2007; Michna et al., 2007). Numerous investigations have found a high prevalence of opioid misuse (18% to 41%) and illicit drug use (48% to 50%) among patients receiving opioids for chronic pain (Katz et al., 2003; Manchikanti et al., 2005, 2006). A systematic review of patients in opioid treatment for chronic back pain estimated the prevalence of lifetime substance use disorders to range from 36% to 56% (Martell et al., 2007). We are not aware of any studies that have assessed whether chronic pain patients use promethazine nonmedically. While chronic pain patients could obtain promethazine from nonmedical sources, they could also obtain them directly from medical providers by feigning symptoms that are indications for promethazine. As such, even when chronic pain patients receive a valid promethazine prescription, it is possible that they are using it for nonmedical reasons.

Given the high prevalence of promethazine use among other opioid using populations, the high prevalence of illicit drug use among chronic pain patients, and the potential for life-threatening events with concomitant use, we sought to determine the prevalence of and factors associated with promethazine use among patients prescribed opioids for chronic pain.

2. METHODS

2.1 Study Sample and Chart Review

Institutional review board approval was obtained to perform urine analysis and medical records review for patients in five health clinics in the San Francisco Department of Public Health. The clinics were selected based on their diverse patient populations, high number of patients treated for chronic pain, high number of urine toxicology screens ordered, and having a chronic pain patient registry (Table 1). These clinics are all federally qualified health primary care clinics that primarily treat underserved patients. These clinics are representative of the patient population served at San Francisco General Hospital. In comparison to the demographics of the city of San Francisco as a whole, these clinics have a higher Black and Hispanic patient population and lower Asian population. All patients in these clinics who had a urine toxicology screen ordered by their medical provider and sent to the San Francisco General Hospital (SFGH) Clinical Laboratory during a six month time period (3/1/2012 – 8/31/2012) were included in the study. Only the urine from the first toxicology screen ordered for each patient (N=1208) during the study period was considered for inclusion in the study. All patients in the study received routine clinical care and the study data were not released to the patients or their medical providers.

Chronic pain registry lists and electronic medical records (EMR) were reviewed to determine whether patients were in treatment for chronic pain at the time of the urine toxicology sample collection. Patients were excluded from the study if they were neither listed on their clinic's pain patient registry nor documented to have chronic pain, chronic pain syndrome, or a pain disorder in their problem list or billing diagnoses.

The remaining patients' EMRs were reviewed to determine if they had been prescribed an opioid at the time of the urine toxicology screen. The opioid prescriptions included were; codeine, morphine, hydrocodone, hydromorphone, oxycodone, fentanyl, tramadol, buprenorphine for pain, and methadone for pain. Patients were excluded from the study if they; 1) did not have any opioid prescriptions, 2) were only prescribed buprenorphine for the treatment of opioid dependence, or 3) were enrolled in methadone maintenance for the treatment of opioid dependence but were not prescribed any additional opioids for pain. Prescription information for opioids, benzodiazepines, and promethazine were recorded in the study database. In cases where the prescribing records were unclear, two physician investigators performed in-depth chart reviews, obtaining information from progress notes and discharge summaries to develop an accurate record of prescribing at the time of the urine toxicology screen.

Of the 1208 unique subjects who had a urine toxicology screen ordered, 125 did not have urine remaining for additional testing, 29 did not meet the chronic pain criteria, and 133 where not prescribed opioids for chronic pain bringing the total number of subjects included in the study to 921.

2.2 Toxicology Testing

Urine samples were submitted by the clinics to the SFGH Clinical Laboratory for routine urine toxicology analysis, which included screening by immunoassay for amphetamines/

MDMA cocaine, benzodiazepines, methadone metabolite, opioids, and oxycodone. Confirmatory analysis was performed by gas chromatography mass spectrometry for opioids (codeine, morphine, hydrocodone, and hydromorphone) and liquid chromatography mass spectrometry for amphetamines (amphetamine, methamphetamine, and MDMA). The urine remaining after routine testing was aliquoted and stored at −20°C for additional testing. All samples were tested for fentanyl, tramadol, and buprenorphine by liquid-chromatography mass spectrometry since these opioids are not detected using the routine toxicology drug screen.

2.3 Promethazine Testing

All urine samples were stored at −20°C and then brought to room temperature before analysis for promethazine. The samples were tested using a liquid chromatography tandem mass spectrometry (LC-MS/MS) method (Shapiro et al., 2013). The assay was designed to detect promethazine and its primary metabolite, promethazine sulfoxide. For this method, the lower limit of detection for promethazine and promethazine sulfoxide are 1.25 ng/mL and 80 pg/mL, respectively. These concentrations were used as cut-off values for determining if a sample was positive or negative for promethazine and promethazine sulfoxide. If a sample contained promethazine and/or promethazine sulfoxide, it was reported as promethazine positive.

2.4 Measures

The main outcome variable for the study was a positive urine screen for promethazine, as defined by a positive result for promethazine and/or promethazine sulfoxide. Independent variables included demographic variables (sex, race/ethnicity, age), opioid prescription by drug, prescription for short-acting opioid, prescription for long-acting opioid, enrollment in methadone maintenance, and urine toxicology results.

2.5 Analysis

All statistics were calculated using SAS version 9.3.1. First, we calculated frequencies for the outcome variable and independent variables. Then, we conducted bivariable analyses between the independent variables and the outcome variable (positive urine screen for promethazine) using logistic regression, calculating odds ratios and 95 percent confidence intervals. Finally, we conducted a multivariable analysis of the outcome using logistic regression analysis. However, no more than one variable was statistically significantly associated with the outcome when adjusting for other variables, so these models are not presented. In preliminary analyses, these adjustments of the inferential statistics included race, sex, age, and clinic location.

3. RESULTS

Among the 921 subjects included in the study, 65% were male, 47% were black, 40% were white, the remaining were of other race/ethnicity, and the median age was 52 years (range 17–79). Table 2 shows the prescription information for the study population. Oxycodone was the most commonly prescribed medication (45%) followed by morphine (34%). Almost half of the study subjects were prescribed only a short-acting opioid for their chronic pain

(45%). Twenty-seven percent were receiving only a long-acting opioid, and 28% were receiving both a short-acting and long-acting opioid.

Drug testing results showed that 72% were positive for opioids, 26% were positive for cocaine, and 22% for benzodiazepines (Table 3). The confirmatory drug testing results revealed that morphine (32%), methadone (30%), and oxycodone (27%) were the most prevalent opioids found in the patient urines (Table 3). Similarly, these three opioids were the most commonly prescribed or administered (in the case of methadone maintenance). Nine percent of the patients tested positive for promethazine. Among the 82 patients who were promethazine positive, only 41 (50%) had an active prescription for promethazine.

In bivariable analysis, demographic variables (race, age, sex) and clinic location were not statistically significantly associated with promethazine positive urines (Table 4). Benzodiazepine-positive urines were statistically associated with promethazine-positive urines (Odds Ratio [OR]=2.33; 95% confidence interval [CI]=1.43–3.64). There was no statistical association between being prescribed a benzodiazepine (daily and/or as needed prescription) and promethazine-positive urines (Table 4). However, having a benzodiazepine-positive urine with no prescription for a benzodiazepine was statistically associated with promethazine-positive urines (OR=1.95; CI=1.14–3.63).

Methadone-positive urines were also statistically significantly associated with promethazine-positive urines (OR=3.13; 95% CI=1.97–4.81). Similarly, having a prescription for methadone for pain (OR=1.91; CI=1.13–3.38) or being in methadone maintenance for the treatment of opioid dependence (OR=2.72; CI=1.53–4.64) were both statistically associated with promethazine-positive urines. The prevalence of promethazine-positive urines in subjects not in methadone maintenance was 7.5% whereas the prevalence was 18% in subjects being treated with methadone for opioid dependence. The prevalence of promethazine-positive urines in subjects not prescribed methadone for pain was 8%, whereas the prevalence was 14% in subjects prescribed methadone for pain.

Of the opioids other than methadone prescribed to the patients, only having a prescription for hydrocodone was statistically associated (negatively) with having a promethazine-positive urine (OR=0.57; CI=0.31–0.98). All other opioid prescriptions were not associated with promethazine-positive urines. Chronic pain patients prescribed only a long-acting opioid had higher odds of having promethazine positive urines than patients prescribed a short-acting opioid, either alone or in combination with a long acting opioid (OR=1.97, 95% CI=1.87–3.00). Those prescribed a short acting opioid alone were less likely to use promethazine (OR=0.66, 95% CI 0.42–0.92) than others.

4. DISCUSSION

This study represents the first report of which we are aware that assessed the prevalence of promethazine use in patients prescribed opioids for chronic pain. The finding that nearly one-tenth of chronic pain patients who are prescribed opioids had promethazine detected in their urine provides compelling evidence of significant promethazine use in this population. Half of the chronic pain patients with promethazine-positive urines did not have a prescription for promethazine, indicating illicit use, and even those with prescriptions may

be using promethazine in ways that the prescribers did not intend. Promethazine use by itself or in conjunction with opioids can have serious adverse health effects, including delirium, respiratory depression, overdose, neuroleptic malignant syndrome, and prolongation of the QT interval (especially in conjunction with methadone; Owczuk et al., 2009; Jo et al., 2009). Further, it can potentiate sedation from opioids; the package insert recommends reducing the dose of concomitantly administered opioids. Opioid users have indicated that taking promethazine in conjunction with opioids produces a high that is distinct from opioid use alone. In follow-up debriefs, many describe being profoundly disoriented and incapacitated during the period of concomitant use. The combination of opioids and promethazine has been reported to be highly addictive (Peters et al., 2007). Promethazine could enhance the addiction potential of opioids prescribed for chronic pain, contributing to the increasingly common and dangerous problem of prescription drug misuse.

Analysis of factors associated with promethazine use revealed that unprescribed benzodiazepine use was a strong correlate. In our previous work, we found the same association to be true in methadone maintenance patients (Shapiro et al., 2013). Like unprescribed use of benzodiazepines, promethazine use may be a marker for more severe underlying substance use and psychiatric disorders. The clinical practice of prescribing benzodiazepines along with opioids for chronic pain patients has been discouraged due to increased risk for fatal and non-fatal overdose (McLellan and Turner, 2010). Similar cautions regarding prescribing promethazine and further investigation of adverse effects associated with the combination of promethazine and opioids may be warranted.

The current study shows that promethazine use is not only associated with methadone maintenance therapy but also with having a methadone prescription for pain. The prevalence of promethazine use in subjects not prescribed methadone for pain was 8% whereas the prevalence was 14% in subjects prescribed methadone for pain. Further studies are needed to determine if this is due to patients perceived to be higher risk for opioid misuse being preferentially prescribed methadone for pain or if the slow onset and minimal euphoria associated with methadone leads patients to desire adjunctive medications to potentiate its euphoric effects. The latter theory is supported by the finding that patients prescribed only long-acting opioids without a short-acting adjunct were twice as likely to have promethazine in their urine as patients with a prescription for a short-acting opioid. This suggests that patients who seek the acute euphoria of a short-acting opioid, when denied that option by their prescriber, will look for an alternative in promethazine. This would be consistent with the principle that simply reducing access to one class of drugs (short acting opioids) is not likely to stem the use of dangerous substances overall.

Prescribers, pain experts, medical examiners, toxicology laboratories, pharmacists, harm reduction counselors, and other healthcare providers may be unaware that promethazine could be used and diverted for the purpose of enhancing the opioid “high”. In addition, they may underestimate or not fully understand the potential dangers of concurrent opioid and promethazine use. Our research suggests that prescribers may wish to be more cautious in prescribing promethazine to patients who are also prescribed opioids, regardless of other signs of medication misuse or illicit drug use. Our data also suggest that screening for non-

prescribed promethazine use could provide clinicians with useful information about the risk of nonmedical use of prescription medications in chronic pain patients receiving opioids.

Generalizability of this study is limited by the observational study design, which collected data on patients within a single geographic area. Additionally all of the clinics whose chronic pain patients were included in the study were federally qualified health primary care clinics that primarily treat underserved patients. Medication records were obtained through electronic medical record review. While all patients included in the study receive their primary care in the San Francisco Department of Public health, we cannot rule out the possibility that some patients may have received additional prescription opioids or promethazine from a prescriber outside of the system. Promethazine use may have been underestimated because of the limited detection window in urine. Finally, this study does not establish that any specific harm (or benefit) has occurred from promethazine use.

These results demonstrate that promethazine needs to be investigated as a potential drug of abuse in opioid using populations and that further research is needed to establish the extent and nature of promethazine misuse in other geographical areas. Our studies indicate widespread nonmedical use of promethazine among methadone maintenance patients, heroin injection drug users and opioid-prescribed chronic pain patients (Shapiro et al., 2013). The nonmedical use of promethazine with opioids has also been reported in other areas of the United States, Hong Kong, Vietnam and India, however, more systematic studies are needed to assess how geographically dispersed its use is (Singh et al., 1992; Wairagkar et al., 1994; Lam et al., 1996; Sharma and Mattoo, 1999; Shek and Lam, 2006; Clatts et al., 2010; Agnich et al., 2013). More research is needed to explore the motivations for, context of and patterns of nonmedical use of promethazine among opioid users, as well as the contribution of promethazine to morbidity and mortality associated with opioid use and misuse.

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Table 1

Characteristics of the Public Health Clinics included in the study

	Clinic 1	Clinic 2	Clinic 3	Clinic 4	Clinic 5
Clinic Characteristics					
Clinic/patient description	primarily homeless	underserved primary care	marginally housed	underserved primary care	HIV positive
Approximate patient visits per year	48,450	30,000	13,200	47,000	15,815
Approximate number of patients	9,067	6,500	1,100	10,000	2,543
Toxicology screens ordered per year	1724	1144	579	547	382
Patient Demographics (%)					
White	40	20	30	15	53
Black	33	21	40	12	24
Hispanic	18	28	20	41	17
Asian	5	28	>1	26	5
Other	4	3	10	6	1
Primary language is English	88	40	95	50	93
Homeless	25	2	10	1	5
Public insurance	58	>80	95	70	72
Uninsured	42	2 – 20	5	30	27

Table 2

Patient Prescription Information (N=921)

Prescription	***N***	***%***
promethazine	41	4%
benzodiazepines	174	19%
morphine	312	34%
oxycodone	416	45%
hydromorphone	35	4%
hydrocodone	185	20%
codeine	97	11%
buprenorphine	44	5%
fentanyl	29	3%
tramadol	5	1%
methadone	240	26%
maintenance	122	13%
pain	127	14%
unknown	1	0%
short-acting opioid only	415	45%
long-acting opioid only	245	27%
both short- and long-acting opioid	261	28%

Table 3

Drug Testing Results (N=921)

Drug or drug class (positive)	***N***	***%***
Promethazine	82	9%
Cocaine	246	27%
Benzodiazepines	200	22%
Amphetamines	90	10%
Opioids (any opioid)	666	72%
morphine	293	32%
oxycodone	246	27%
hydromorphone	76	8%
hydrocodone	68	7%
codeine	64	7%
buprenorphine	37	4%
fentanyl	19	2%
tramadol	7	1%
methadone	274	30%

Table 4

Factors Associated with a Positive Promethezine Urine Specimen Among Chronic Pain Patients (N=921)*

Demographics	***OR***	***95% CI***
Sex		
Male	Reference	
Female	1.12	0.70–1.74
Race		
White	Reference	
Black	0.61	0.43–1.01
Hispanic	0.62	0.21–1.42
Other	0.63	0.20–2.23
Age		
17–36	Reference	
36–50	1.44	0.52–3.71
51–60	1.33	0.54–3.47
61+	1.57	0.62–4.03
Clinic		
Clinic 1	Reference	
Clinic 2	0.81	0.46–1.45
Clinic 3	0.53	0.23–1.12
Clinic 4	1.00	0.52–1.93
Clinic 5	0.81	0.43–1.88

Drug Testing Results (positive)	***OR***	***95% CI***
Cocaine	1.32	0.71–2.02
Benzodiazepines	2.33	1.43–3.64
Amphetamines	0.56	0.24–1.32
Morphine	1.19	0.66–1.71
Oxycodone	0.76	0.46–1.20
Hydromorphone	1.03	0.59–2.49
Hydrocodone	0.81	0.33–2.16
Codeine	1.52	0.72–3.34
Buprenorphine	1.63	0.60–4.33
Methadone	3.13	1.97–4.81

Prescription Information	***OR***	***95% CI***
Morphine	1.02	0.60–1.69
Oxycodone	0.94	0.60–1.44
Hydromorphone	1.06	0.52–2.44
Hydrocodone	0.57	0.31–0.98
Codeine	1.12	0.52–2.27
Buprenorphine	1.73	0.62–4.16
Fentanyl	0.83	0.21–3.25

Prescription Information	***OR***	***95% CI***
Methadone Maintenance	2.72	1.53–4.64
Methadone Prescription for Pain	1.91	1.13–3.38
Benzodiazepine (daily and/or as needed)	1.43	0.82–2.45
Daily Benzodiazepine Prescription	1.63	0.86–2.97
No Benzodiazepine Prescription and Positive Screen	1.95	1.14–3.63
Short-acting opioid only**	0.66	0.42–0.92
Long-acting opioid only***	1.97	1.87–3.00
Both short- and long-acting opioid	1.28	0.72–2.23

* each main effect for drug use exposure was estimated as a bivarable model

** referent is long acting and/or short and long acting

*** reference it short acting and/or short and long acting