Drug and Alcohol Dependence 150 (2015) 92–97

Contents lists available at ScienceDirect

Drug and Alcohol Dependence

journal homepage: www.elsevier.com/locate/drugalcdep

Promethazine use among chronic pain patients

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ARTICLE INFO

Article history:
Received 30 September 2014
Received in revised form 24 January 2015
Accepted 14 February 2015
Available online 26 February 2015

Keywords:
Prescription drug abuse
Opioids
Promethazine
Chronic pain
Pain management

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 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.

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 (Substance Abuse and Mental Health Services Administration, 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).

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http://dx.doi.org/10.1016/j.drugalcdep.2015.02.023
0376-8716/

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 1990s, 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 to 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 (18–41%) and illicit drug use (48–50%) 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.