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Promethazine Misuse among Methadone Maintenance Patients and Community-Based Injection Drug Users

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Abstract

Objective—Promethazine has been reported to be misused in conjunction with opioids in several settings. Promethazine misuse by itself or in conjunction with opioids may have serious adverse health effects. To date, no prevalence data for the nonmedical use of promethazine has been reported. This study examines the prevalence and correlates of promethazine use in two different populations in San Francisco, California, USA: methadone maintenance clinic patients and community-based injection drug users (IDUs).

Methods—We analyzed urine samples for the presence of promethazine and reviewed the clinical records for 334 methadone maintenance patients at the county methadone clinic. Separately, we used targeted sampling methods to recruit and survey 139 community-based opioid IDUs about their use of promethazine. We assessed prevalence and factors associated with promethazine use with bivariate and multivariate statistics.

Results—The prevalence of promethazine positive urine samples among the methadone maintenance patients was 26 percent. Only 15 percent of promethazine positive patients had an active prescription for promethazine. Among IDUs reporting injection of opiates in the community-based survey, 17 percent reported having used promethazine in the past month; 24 percent of the IDUs who reported being enrolled in methadone treatment reported using promethazine in the past month.

Conclusions—The finding that one quarter of methadone maintenance patients in a clinic or recruited in community settings have recently used promethazine provides compelling evidence of significant nonmedical use of promethazine in this patient population. Further research is needed to establish the extent and nature of nonmedical use of promethazine.

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Keywords

Promethazine; Methadone; Opiate Addiction; Opiate Substitution Treatment; Injection Drug User

INTRODUCTION

Known by the trade name Phenergan (Wyeth Pharmaceuticals, Philadelphia, PA, USA), promethazine is a phenothiazine derivative introduced in 1946 that acts as a histamine (H1) receptor antagonist, muscarinic (M1) antagonist and dopamine (D2) antagonist, but has relatively little dopamine antagonist activity compared to the phenothiazine antipsychotics. (Page et al., 2009) Promethazine is indicated for the treatment of allergic conditions, pre and post-operative sedation, nausea and vomiting, motion sickness, and adjunctive analgesia. (Sandoz Inc., 2006) The medical use of a combination of promethazine and opioids was first reported in 1949 as a "lytic cocktail," a combination of chlorpromazine, promethazine, and meperidine (and related compounds) that was noted to have an opioid sparing effect,(McGee and Weiss, 1956) allowing the use of lower doses of opioids to achieve sedation. In contemporary practice, the use of promethazine in combination with opioids for pre and post-operative sedation has declined due to adverse effects and lack of data supporting clinical efficacy.(Richter and Burk, 1992)

Non-medical use of prescription drugs is on the increase in the United States, with recent estimated prevalence of 7 million people. (SAMHSA, 2011) Little is known about the abuse potential of promethazine, but there is reason to believe that abuse may occur predominantly in combination with opioids. Popular press reports of abuse of cough syrup containing both promethazine and codeine began to appear in or around 2000, with an epicenter in Texas. (Klemme, 2001). Promethazine has also been reported to be present in fatal opioid overdoses. Promethazine was identified by post-mortem toxicology analysis in 25/176 (14.2%) of methadone toxicity fatalities in Kentucky from 2000–2004(Shields et al., 2007) and 39/1587 (2.5%) fatal overdose cases in Seattle from 1998 to 2004.(Banta-Green et al., 2004) In 2003 in the Seattle-King County area, promethazine was involved in 9/103 (8.7%) of overdose deaths that involved depressants, and "key informants note that promethazine is often used by those on methadone to potentiate the high."(Banta-Green et al., 2005) More recently, Clatts et al. documented intravenous promethazine use by new heroin injectors in Vietnam, who used it to augment an inadequate heroin dose or when heroin was not available.(Clatts et al., 2010) Cases of promethazine abuse in patients receiving buprenorphine treatment for opioid dependence have been reported in India and China. (Mendhekar et al., 1999; Zhou et al., 2008) In concordance with Banta-Green et al., we noted several reports of promethazine use by methadone maintenance patients to potentiate the "high" from methadone in our clinical practice (BJS).

Promethazine use by itself or in conjunction with opioids may have serious adverse health effects including apnea and respiratory depression, hematologic complications, injection site reactions and soft tissue injury, jaundice, and neuroleptic malignant syndrome. (Sandoz, Inc. 2006) Promethazine may potentiate sedation from opioids, and the package insert recommends reducing the dose of concomitantly administered opioids.(Sandoz, Inc. 2006) Promethazine prolongs the QT interval,(Jo et al., 2009) an electrocardiographic measurement of the duration of the repolarization of the heart. Prolongation of the QT interval has been associated with a potentially fatal, cardiac arrhythmia called torsade de pointes.(Antzelevitch, 2007) Methadone, one of the primary pharmacologic treatments for opioid dependence, also prolongs the QT interval and appears to be associated with torsade de pointes.(Stringer et al., 2009) Torsade de pointes is a rare event in methadone maintenance patients. Patients are at increased risk if they have electrolyte abnormalities;

personal or family history of structural heart disease; liver disease; or other medications that can prolong the QT interval.(Mayet et al., 2011) Isolated promethazine overdose is associated with delirium without reports of fatality.(Page et al., 2009)

The present study aims to estimate the prevalence of and factors associated with promethazine use among opioid users by evaluating two different populations in San Francisco: patients at a county hospital based methadone maintenance clinic and injection drug users (IDUs) recruited and surveyed in community settings.

METHODS

Procedures for the Methadone Patient Study

Institutional review board approval was obtained to perform urine analysis for promethazine and medical records review for patients at the county hospital methadone clinic. All non-pregnant patients enrolled in methadone maintenance treatment at the central clinic site on January 26, 2011 were included in the study. All patients in the study received routine clinical care including collection of at least one random urine sample per month by clinic staff in accordance with clinic, state, and federal regulations.

Urine samples were submitted by the clinic in standard fashion to San Diego Reference Laboratory (SDRL) for urine toxicology analysis, which included screening by immunoassay and confirmation by thin layer chromatography of the presence of methadone, methadone metabolite (EDDP), benzodiazepines, cocaine, amphetamine, methamphetamine, opioids (methodology does not detect some synthetic opioids including oxycodone), barbiturates, and phencyclidine (PCP). During the month of February 2011, one milliliter of urine from each patient was separately analyzed for promethazine and metabolite as described below.

Epidemiologic data, methadone treatment data, and the results of the SDRL urine toxicology analysis were obtained from the clinic's electronic medical record system. The San Francisco Department of Public Health's Lifetime Clinical Record (LCR) is a comprehensive clinical database used by San Francisco Department of Public Health clinics for medication management and prescribing. The LCR contained prescription information for 94% of the patients in the methadone patient study and was reviewed for the presence or absence of a prescription for promethazine.

Analysis of Promethazine in Urine

All urine samples were stored at −20° C, then brought to room temperature and thoroughly mixed prior to analysis for promethazine. The samples were tested using a liquid chromatography tandem mass spectrometry (LC-MS/MS) method. An assay was designed to detect promethazine and its primary metabolite, promethazine sulfoxide. For this method, the lower limits of detection for promethazine and promethazine sulfoxide are 1.25 ng/mL and 80 pg/mL, respectively. These concentrations were used as the 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.

Procedures for the Survey of Community-Based Injection Drug Users

Two hundred injection drug users (IDUs) were recruited through targeted sampling methods(Kral et al., 2010; Watters and Biernacki, 1989) in January and February 2011. Prior to data collection, the research team developed a targeted sampling plan by (1) collecting indicator data about the location of IDUs in San Francisco using hospital data, drug

treatment data, and arrest data, (2) conducting ethnography, (3) and making a plan by estimating the size and demographic type of the drug using population in each geographic area. An outreach worker familiar with the neighborhoods and the study population then assisted with recruiting the sample. Along the way, we assessed how much our sample resembles the targeted plan, and made revisions in recruitment accordingly. For example, if we planned for 30% of the sample to be women, and only 25% of the first 100 study participants were women, we would increase our recruitment of women to make the targeted plan. Eligibility criteria included the following: (1) reported injecting illicit drugs within the past 30 days, (2) had visible signs of injection ("tracks"), (3) were at least 18 years of age, (4) were able to speak English, and (5) were able to provide informed consent. The study coordinator assessed eligibility and explained the study procedures to those participants who met eligibility criteria, and provided them with an appointment for their interview later that day. Interviews lasted 20–30 minutes and were administered by trained interviewers in private rooms in a building located in the center of the city, close to where many IDUs spend time. Responses to the questions were recorded on a paper form. In addition to questions about promethazine, other topics covered included demographic information, drug use, injection behaviors, perceptions of health services that could be offered in pharmacy settings, experiences purchasing syringes at pharmacies, and past and current involvement in drug treatment. Some of these topics were unrelated to this manuscript, but were part of the research of the overall study. Study protocols were approved by the Internal Review Board at RTI International. Participants were paid $15 for their contribution to the study.

Measures

The main outcome variable for the methadone patients was positive urine screen for promethazine, as defined by a positive result for promethazine and/or promethazine sulfoxide using the promethazine LC-MS/MS method described above. Independent variables included demographic variables (sex, race/ethnicity, age, marital status) as collected at methadone maintenance intake; HIV antibody status as collected through opt-out testing at intake, annually, and as clinically indicated; number of days since intake into methadone maintenance (calculated by subtracting the number of days between the urine specimen collection and the most recent intake date); methadone daily dose on February 1, 2011; and urine positive screens for cocaine, amphetamine, methamphetamine, morphine, benzodiazepines, barbiturates, codeine, and hydrocodone.

The main outcome variable in the survey of IDUs was reporting having taken Phenergan, which is the brand name of promethazine, in the past month as ascertained by the following question: "How many days in the past 30 days have you taken Phenergan?" This question was only asked of people who reported yes to the following question: "Have you ever used Phenergan that was not prescribed to you?" Independent variables included self-reported methadone treatment in the past 30 days (combining methadone maintenance and methadone detox); self-reported methadone dose in milligrams; self-reported buprenorphine treatment in past 30 days; demographic variables (sex, race/ethnicity, considers self homeless, age, income past 30 days, and number of years since first illicit injection of drugs); self-reported drug use variables (injection of methamphetamine, cocaine, heroin, or speedball [a combination of cocaine and heroin]; non-injected use of methamphetamine, cocaine, heroin, opiate prescription drugs, methadone, and benzodiazepines); self-reported HIV status; and self-reported healthcare utilization in past 6 months.

Analysis

Analysis of the data from methadone maintenance patients first consisted of frequencies and bivariate statistics. This included calculating the prevalence of urine samples positive for promethazine stratified by the independent variables. Statistics to assess significant

differences included chi square test for categorical variables in which all cells had at least five observations, Fisher's exact test for categorical variables in which any cells had less than five observations, and Wilcoxon two-sample non-parametric test for continuous variables, with $p<0.05$ indicating statistical association. Variables that had a $p<0.10$ in bivariate analysis were entered into forward and backward stepwise multiple logistic regression models of promethazine use to assess which factors were independently associated with its use. The final multivariate model only includes variables significant at the $p<0.05$ level.

Data entry of all IDU survey data were conducted twice by two different people into an Access database (Microsoft Access, Redmond, WA). Among 200 IDUs surveyed in the community, 139 reported past month use of heroin or a heroin-combination ("speedball") or being in methadone treatment. Given that this study is about promethazine use among opiate users, we limited our analysis to this subpopulation of 139 IDUs. Analysis of the data from the surveys of IDUs consisted of assessing the prevalence of reporting promethazine use in the past 30 days. We used the same statistical methods to assess the prevalence of and factors associated with promethazine use among IDUs as among methadone patients described above. All statistical analyses were conducted (by HYC) using SAS version 9.3 (SAS Institute Cary, NC).

RESULTS

Among 373 methadone maintenance patients at the county methadone clinic, 334 (90%) provided urine for drug screening during February 2011. There was no statistically significant difference between the patients who provided urine for the study and those who did not provide urine for the study in terms of sex, race/ethnicity, marital status, or HIV status ($p>0.05$). Among the 334 who provided urine for drug screening, over one-third were women, over half were white, nearly one quarter were African American, over one-fifth were of other race/ethnicity, the median age was 50.0 (range 24, 82), over a quarter were HIV antibody positive, and the median number of days since intake was 1,599 (range 12, 9,754)[Table 1]. Twenty-six percent of urines tested positive for promethazine. Among the 87 patients who had promethazine positive urines, only 13 (15%) had an open prescription for promethazine per the LCR database. Only 5 (5.7%) of these patients did not have prescription data available in the LCR. In bivariate analysis, none of the demographic variables, HIV status, or number of days since methadone maintenance intake was statistically associated with promethazine positive urines. Of eight different classes of substances for which we tested urines, only benzodiazepine positive urines were statistically associated with promethazine positive urines (53% vs 21%; $p <0.0001$). Methadone dose in milligrams was also statistically associated with promethazine positive urines (median of 90mg among positive and 85mg among negative urines; $p<0.02$) in bivariate analysis. When entering benzodiazepine positive urine and methadone dose into forward and backward stepwise logistic regression models of promethazine positive urine, only benzodiazepine remained as a statistically significant variable in the model, at $p<0.05$.

Among the 139 IDUs who reported heroin or speedball (heroin and cocaine combination) use or being in methadone treatment, 28 percent were women, 42 percent were white, 32 percent were African American, 26 percent were of other race/ethnicity, 68 percent considered themselves to be homeless, percent reported being HIV antibody positive, and the median age was 48. Overall, 17 percent reported having used promethazine in the past month (Table 2). Among those who reported being in methadone treatment, 24 percent (14/59) reported having used promethazine in the past month. Among those who reported not being in methadone treatment, 13 percent (10/80) reported having used promethazine in the past month. Among those who reported using heroin or speedball in past month but not

being in methadone treatment, 13 percent reported having used promethazine in the past month. Only 4/24 (17%) reported having a current prescription for promethazine. In bivariate analysis, the following variables were significantly associated with self-reported promethazine use in the past 30 days: crack cocaine smoking past 30 days, non-injection and injection of speedballs in past 30 days, benzodiazepine use in past 30 days, and illicit methadone use past 30 days. In a multivariate model with promethazine use as the outcome variable using logistic regression analysis, reporting use of non-prescribed opiate pills in past 30 days (adjusted odds ratio=4.6; 95% confidence level=1.3, 16.9) and reported injection of speedballs in past 30 days (adjusted odds ratio=3.8; 95% confidence level=1.2, 12.1) were independently associated with reporting promethazine use in the past month.

DISCUSSION

This study represents the first report of which we are aware that assessed the prevalence of promethazine use in samples of methadone patients and community-based heroin IDUs. The findings that one quarter of methadone maintenance patients had promethazine detected in their urine samples and that a similar percentage of community-based IDUs in methadone maintenance treatment reported promethazine use in the past month provide compelling evidence of promethazine use in this patient population. Eighty-five percent of the methadone clinic patients with promethazine positive urines did not have active prescriptions for promethazine, indicating illicit use. Awareness of nonmedical use of promethazine appears to be minimal among physicians. It is not scheduled as a controlled substance by the United States Drug Enforcement Administration, and the package insert contains no information related to potential misuse or abuse.(Sandoz, Inc. 2006)

Analysis of factors associated with promethazine positive urines demonstrated no significant association with a number of factors including race, gender, age, time in methadone treatment, and HIV status. The presence of promethazine in urine was strongly correlated only with benzodiazepine positive urine toxicology. This is noteworthy because the abuse of non-opioid drugs by opioid dependent people both in and out of methadone treatment is a significant public health problem and can worsen treatment outcomes.(DeMaria et al., 2000) Like benzodiazepine use, promethazine use may be a marker for more severe underlying substance use and psychiatric disorders. The only substance with a statistically significant association with promethazine in the methadone maintenance patients was benzodiazepines. Abuse of benzodiazepines in methadone maintained patients has been associated with more severe psychopathology, worse treatment outcomes, and greater use of cocaine, cannabis, and heroin.(Bleich et al., 1999) More research will be necessary to determine if promethazine is also a marker for more severe underlying substance use and psychiatric disorders.

Further research is needed in several other areas related to the high prevalence of promethazine use among methadone maintenance patients and heroin users. There is a need to further elucidate the epidemiology of promethazine use: its geographic distribution, characteristics of users, common sources, reasons for use, and specific practices. Investigation is also needed to determine promethazine's contribution to drug related morbidity and mortality and its prevalence in other opiate using populations including chronic pain patients treated with opioids, buprenorphine treated patients, and prescription opioid abusers not in treatment. Pharmacokinetic interactions between promethazine, methadone, and benzodiazepines have not been characterized. Variations in CYP450 2D6 genotype alter promethazine metabolism,(Foster et al., 2007) and could result in a pharmacogenomic predisposition to or protection from promethazine misuse. Reports of abuse of other medications not widely perceived to have abuse potential like clonidine, (Beuger et al., 1998) quetiapine,(Tcheremissine, 2008) and gabapentin(Reccoppa et al.,

2004) suggest the need to broaden the focus of research on nonmedical use of prescription drugs and to monitor high risk populations as sentinels for the emergence of new drug use practices.

Generalizability of this study is limited by the use of non-random patient samples and a single geographic area (San Francisco). The survey of IDUs relies on unverified self-report and is subject to response bias. This is ameliorated to some degree by the concordance of results between the survey and the urine toxicology data from a separate but related population. The use of a cross-sectional methodology does not allow determination of causation. Promethazine use may have been underestimated by urine toxicology due to a limited detection window and by survey responses due to under-reporting related to social desirability. The number of methadone patients with a promethazine prescription may have been underestimated because some patients may have had a medical provider outside of the San Francisco Department of Public Health system, although our analysis suggests that this number is likely to be small. Similarly, the number of IDUs in the survey who reported phenergan use may have been underestimated, as the lead-in question was limited to those who had ever used phenergan without prescription. 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 patients with opioid dependence, and that further research is needed to establish the extent and nature of promethazine misuse.

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Table 1

Factors Associated with Promethazine Positive Urine Specimen among Methadone Maintenance Patients, 2011 (N=334).

Risk Factor	Promethazine Positive n/n (%)	p value*
Total	87/334 (26)	
Female	37/130 (28)	0.42
Male	50/204 (25)	
White	48/184 (26)	
African American	21/79 (27)	0.99
Other race/ethnicity	18/71 (25)	
Married/Domestic partner	8/32 (25)	0.41
Never married	39/130 (30)	
Other	40/172 (23)	
HIV antibody positive	21/89 (24)	0.54
HIV antibody negative	66/245 (27)	
Cocaine positive urine	39/143 (27)	0.66
Cocaine negative urine	48/191 (25)	
Amphetamine positive urine	10/35 (29)	0.72
Amphetamine negative urine	77/299 (26)	
Methamphetamine positive urine	10/31 (32)	0.41
Methamphetamine negative urine	77/303 (25)	
Morphine positive urine	12/50 (24)	0.72
Morphine negative urine	75/284 (26)	
Benzodiazepine positive urine	29/55 (53)	0.0001
Benzodiazepine negative urine	58/279 (21)	
Barbiturate positive urine	0/1 (0)	1.00
Barbiturate negative urine	87/333 (26)	
Codeine positive urine	4/9 (44)	0.25
Codeine negative urine	83/325 (26)	
Hydrocodone positive urine	1/3 (33)	1.00
Hydrocodone negative urine	86/331 (26)	
Median age among promethazine positive urine	47.0 years	0.08
Median age among promethazine negative urine	51.0 years	
Median number days since methadone maintenance intake among promethazine positive urine	1,599 days	0.24
Median number days since methadone maintenance intake among promethazine negative urine	1,453 days	
Median daily methadone dose among promethazine positive urine	90 milligrams	0.02
Median daily methadone dose among promethazine negative urine	85 milligrams	

*For categorical variables, p values were calculated with chi square test unless any cell contained less than 5 observations, in which cases we used Fishers exact test of significance. For continuous variables, the Wilcoxon two-sided two-sample test was used to calculate p value.

Table 2

Factors Associated with Self-Reported Promethazine Use in Past 30 days among Community-Recruited Injection Heroin Drug Users in San Francisco, 2011 (N=139).

Risk Factor	Used Promethazine n/n (%)	p value*
Total	24/139 (17)	
Female	8/39 (21)	0.53
Male	16/100 (16)	
White	12/58 (21)	
African American	8/45 (18)	0.46
Other race/ethnicity	4/36 (11)	
Considers self homeless	18/95 (19)	0.44
Considers self not homeless	6/44 (14)	
Self-reported HIV positive	3/17 (18)	1.00
Self-reported HIV negative	20/120 (17)	
Self-reported currently enrolled in methadone treatment	14/59 (24)	0.09
Self-reported currently not enrolled in methadone treatment	10/80 (13)	
Self-reported currently enrolled in buprenorphine treatment	4/14 (22)	0.52
Self-reported currently not enrolled in buprenorphine treatment	20/121 (17)	
Self-reported in healthcare past 6 months	19/110 (17)	0.99
Self-reported not in healthcare past 6 months	5/29 (17)	
Self-reported non-injection powder cocaine use past 30 days	10/46 (22)	0.33
Self-reported no non-injection powder cocaine use past 30 days	14/93 (15)	
Self-reported injection cocaine use past 30 days	5/36 (14)	0.48
Self-reported no injection cocaine use past 30 days	19/99 (19)	
Self-reported crack cocaine smoking past 30 days	23/107 (22)	0.02
Self-reported no crack cocaine smoking past 30 days	1/32 (3)	
Self-reported injection crack cocaine use past 30 days	12/50 (24)	0.12
Self-reported no injection crack cocaine use past 30 days	12/89 (13)	
Self-reported non-injection methamphetamine use past 30 days	12/76 (16)	0.61
Self-reported no non-injection methamphetamine use past 30 days	12/63 (19)	
Self-reported injection methamphetamine use past 30 days	10/69 (14)	0.39
Self-reported no injection methamphetamine use past 30 days	14/70 (20)	
Self-reported non-injection heroin use past 30 days	24/130 (18)	0.16
Self-reported no non-injection heroin use past 30 days	0/9 (0)	
Self-reported injection heroin use past 30 days	23/129 (18)	1.00
Self-reported no injection heroin use past 30 days	1/10 (10)	
Self-reported non-injection speedball (heroin and cocaine mix) use past 30 days	20/80 (25)	0.006
Self-reported no non-injection speedball (heroin and cocaine mix) use past 30 days	4/59 (7)	
Self-reported injection speedball (heroin and cocaine mix) use past 30 days	20/79 (25)	0.006
Self-reported no injection speedball (heroin and cocaine mix) use past 30 days	4/59 (7)	
Self-reported non-injection benzodiazepine use past 30 days	18/65 (28)	0.003
Self-reported no non-injection benzodiazepine use past 30 days	6/72 (8)	

Risk Factor	Used Promethazine n/n (%)	p value*
Self-reported injection benzodiazepine use past 30 days	1/8 (13)	1.00
Self-reported no injection benzodiazepine use past 30 days	23/129 (18)	
Self-reported non-injection opiate pill use past 30 days	21/83 (25)	0.003
Self-reported no non-injection opiate pill use past 30 days	3/55 (5)	
Self-reported injection opiate pill use past 30 days	9/49 (18)	0.71
Self-reported no injection opiate pill use past 30 days	14/88 (16)	
Self-reported illicit methadone use past 30 days	13/45 (29)	0.02
Self-reported no illicit methadone use past 30 days	11/94 (12)	
Median age of IDUs who self-report recent promethazine use	48.5 years	0.70
Median age of IDUs who self-report no recent promethazine use	47.0 years	
Median monthly income of IDUs who self-reported recent promethazine use	$914	0.55
Median monthly income of IDUs who self-reported no recent promethazine use	$870	
Median number of years since initiating injection drug use among IDUs who report recent promethazine use	25.0 years	0.72
Median number of years since initiating injection drug use among IDUs who report no recent promethazine use	24.0 years	
Median daily methadone dose among IDUs who self-report promethazine use	90 milligrams	0.19
Median daily methadone dose among IDUs who self-report no promethazine use	80 milligrams	

* For categorical variables, p values were calculated with chi square test unless any cell contained less than 5 observations, in which cases we used Fishers exact test of significance. For continuous variables, the Wilcoxon two-sided two-sample test was used to calculate p value.