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Relationship Between Nonmedical Benzodiazepine Use and Psychiatric Disorders Among Rural Appalachian Drug Abusers

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RELATIONSHIP BETWEEN NONMEDICAL BENZODIAZEPINE USE AND PSYCHIATRIC DISORDERS AMONG RURAL APPALACHIAN DRUG ABUSERS

CAPSTONE PROJECT PAPER

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Abstract

Background: Inhabitants of Appalachian Kentucky are encumbered by tremendous health disparities, exhibit high rates of prescription drug abuse, and often co-present with psychiatric disorders. Compared to opioids, little research has focused on the nonmedical use of benzodiazepines.

Objective: To examine the association between nonmedical benzodiazepine use and major depressive disorder (MDD), generalized anxiety disorder (GAD), post-traumatic stress disorder (PTSD), and anti-social personality disorder (ASPD) in a population of opioid drug abusers.

Methods: Data for this cross-sectional study was obtained from the Social Networks among Appalachian People (SNAP) study. Contingency tables analysis and the X^2 statistic were used to examine the association between past 30 day benzodiazepine (i.e., alprazolam, clonazepam, diazepam) use and psychiatric diagnoses. The independent correlates of recent benzodiazepine use were determined using multiple logistic regression.

Results: 503 participants were included in this analysis. All reported a lifetime history of opioid drug abuse and 98% (n=493) reported use within the past 30 days. 71% (n=355) reported past 30 day benzodiazepine (i.e., alprazolam, clonazepam, or diazepam) use. The presence of MDD (Odds Ratio [OR]: 1.9, 95% Confidence Interval [CI]: 1.2-3.0) or GAD (OR: 1.9, 95% CI: 1.2-3.0) were significantly ($p<0.05$) associated with recent benzodiazepine use. Other variables associated with benzodiazepine use were: illicit methadone use (Adjusted OR [AOR]: 2.94, 95% CI: 1.9-4.56, marijuana use(AOR: 2.57, 95% CI: 1.64-4.01), oxycodone use (AOR: 2.52, 95% CI: 1.6-3.97), GAD (AOR: 1.67, 95% CI: 1.01-2.77), poor/fair health (AOR: 1.65, 2.6), and years living in eastern Kentucky (AOR: 1.03, 95% CI: 1.0-1.1).

Discussion: The results show a strong association between nonmedical benzodiazepine use and psychiatric disorders (i.e., MDD, GAD). A lack of accessible mental healthcare providers may be a contributing factor to the high rates of nonmedical benzodiazepine use found in this study. Longitudinal studies are needed to examine the effect of prescription drug monitoring programs on benzodiazepine abuse.

1. Introduction

Prescription drugs are the second most abused class of drugs in the United States. The prevalence of prescription drug abuse has rapidly increased over the past decade with one in every five Americans over the age of 12 now being able to report using a prescription drug for a nonmedical purpose at least once in their lifetime.[1] This epidemic has taken a toll not only on individual abusers, but the entire country. Prescription opioids are the most common class of medications abused with their total yearly economic cost of nonmedical use being more than $50 billion.[2] Accordingly, the majority of prescription drug abuse research has been focused on opioids. However, other prescription medications, such as benzodiazepines, are also frequently abused.

Benzodiazepines are Schedule IV medications and exert their pharmacologic effects by binding to receptors in the brain, which in turn increase the effects of gamma-aminobutyric acid (GABA). GABA is an inhibitory neurotransmitter that produces a calming and sedating effect. Benzodiazepines are approved for the short term treatment of anxiety but are also frequently prescribed long term and for uses other than their labeled indications.

Between 1998 and 2007, the number of alprazolam and clonazepam prescriptions dispensed through outpatient retail pharmacies increased 71% and 114% respectively.[3] One substantial issue in relation to prescription drug abuse is the treatment of patients with chronic pain. A common "drug cocktail" prescribed to patients with chronic pain consists of an opioid, benzodiazepine, and muscle relaxer. This combination of drugs is frequently prescribed to patients suffering from chronic pain despite a lack of proven clinical benefit. The prevalence of benzodiazepine prescribing has been increasing at a rate comparable to that of opioids[4], but

research investigating the factors associated with abuse and nonmedical use of benzodiazepines is lacking.

Residents of the Appalachian region of Kentucky suffer from severe health disparities and have rates of prescription drug abuse and mental health disorders that exceed national averages.[5] The self-medication hypothesis of addictive disorders, first described by Dr. Edward Khantzian, may explain this relationship.[6] This hypothesis suggests that individuals with psychiatric disorders crave certain drugs of abuse because of the specific pharmacologic properties of the drug. Thus, the primary objective of this study was to determine if a relationship exists between nonmedical benzodiazepine use and DMS-IV psychiatric disorders such as: major depressive disorder (MDD), generalized anxiety disorder (GAD), and post-traumatic stress disorder (PTSD) in a population of opioid drug abusers residing in Appalachian Kentucky. The hypothesis being that drug abusers with an underlying psychiatric illness may use benzodiazepines to self-medicate comorbid conditions. A secondary objective of this study was to identify the demographics associated with the nonmedical use of benzodiazepines, specifically alprazolam, clonazepam, and diazepam. The study also examined the correlation of other drugs of abuse with the nonmedical use of benzodiazepines. The final objective of this study is to categorize the sources from which users obtained their first time supply of a benzodiazepine for a nonmedical purpose.

2. Methods

This retrospective cross-sectional study analyzes data acquired from the Social Networks among Appalachian People (SNAP) study. SNAP is an ongoing longitudinal cohort study of social networks and HIV risk among rural Appalachian drug users who reside in Perry County, Kentucky. Perry County has a population of approximately 30,000 and is located in Southeastern

Kentucky. The vast majority of the population is white (97%), with an average yearly household income of $33,000, and with 26% of individuals living in poverty.[7] The SNAP study was approved by the Institutional Review Board (IRB) at the University of Kentucky.

SNAP study participants were recruited using Respondent Driven Sampling (RDS) which has been effectively utilized in previous studies of hard to reach populations such as rural drug users.[8] Initial recruits were identified via community outreach, word-of-mouth, and flyers. These initial recruits then solicited peers to participate in the study. Subjects were monetarily reimbursed for successfully recruiting additional eligible study participants. This process continued until the desired sample size was attained (n=503).

Trained non-clinician researchers conducted baseline interviews and used the Addiction Severity Index (ASI)[9] to determine illicit and prescription drug use. Psychiatric disorders were diagnosed using the Mini-International Neuropsychiatric Interview (MINI), version 5.0.[10] Demographic variables collected through completion of the ASI included age, gender, years of education, employment, financial status, health insurance status, health status, and a detailed history of both lifetime and past 30 day nonmedical substance use. The MINI was used to evaluate if Diagnostic and Statistical Manual of Mental Disorders criteria were met for current major depressive disorder (MDD), generalized anxiety disorder (GAD), post-traumatic stress disorder (PTSD), and/or antisocial personality disorder (ASPD). Additionally, participants were questioned regarding specific nonmedical drug sources (i.e., family member, friend, dealer). Participants were asked to provide specific drug names or street names in order to record lifetime and past 30 day use of substances for a nonmedical purpose (e.g., “to get high”). The correct categorization of substances reported was confirmed before data analysis. For the purposes of data analysis, only subjects that were categorized as using alprazolam, clonazepam, or diazepam

within the past 30 days were labeled as benzodiazepine users. All data capable of identifying individual participants was purged before analysis. The Institutional Review Board at the University of Kentucky granted an IRB exemption for this study.

Subjects were divided into two groups, "past 30 day users of benzodiazepines" and "past 30 day non-users", and the descriptive statistics were reported via a univariate analysis. The Chi-square test, Fisher's Exact test, and the Mann-Whitney rank-sum test for categorical and continuous variables were utilized to compare the demographic and substance abuse characteristics of each group respectively. The chi-square test was utilized to identify significant ($p<0.05$) differences in the prevalence of MDD, GAD, PTSD, and ASPD between recent benzodiazepine users and non-users. Finally, independent correlates of past 30 day benzodiazepine use were determined using a step-wise multiple logistic regression with an adjusted odds ratio (AOR) and 95% confidence intervals (CI) reported for each variable. SPSS, version 20, was utilized for all analyses.

3. Results

503 participants were included in the study analysis. The majority of participants were male (57%, n=206), white (94%, n=473), and had at least a high school education (56%, n=284). The median age of participants was 33 years (interquartile range: 26 to 38 years). All participants reported a history of nonmedical prescription opioid use, and 98% (n=493) reported past 30 day use.

Table 1 displays the baseline characteristics among those who did (n=355) and did not (n=148) report any past 30 day use of alprazolam, clonazepam, or diazepam. Median and interquartile range (IQR) of age and years of education completed did not significantly differ (p=0.2, p=0.8,

respectively) between those who had used benzodiazepines and those who had not. However, benzodiazepine users did report a significantly greater (p=0.02) median of years of residence in Eastern Kentucky (n=30 years), than those who did not (n=27 years). Benzodiazepine users were significantly more likely to describe themselves as religious (p=0.01) and non-white (p=0.02) as compared to non-users. No significant differences in the socio-economic status were found among benzodiazepine users and non-users. However, subjects who reported their self-perceived health status as poor or fair had a 12.4% higher prevalence of benzodiazepine use (p=0.01). Contrary to the results of perceived health status, the presence of chronic health conditions was not significantly different among benzodiazepine users and non-users (p=0.1). Additionally, there was no significant difference in the type of health insurance (i.e.., Medicaid, Medicare, private) used in terms of benzodiazepine users and non-users.

Table 2 displays the univariate comparison of past 30 day substance use among benzodiazepine users and non-users. The benzodiazepine group reported significantly higher rates of past 30 day use of several substances when compared to non-users. Participants who reported past 30 day use of benzodiazepines were also 24% more likely to have illicitly used methadone ($p<0.001$), 23.1% more likely to use oxycodone ($p<0.001$), 18.8% more likely to use marijuana ($p<0.001$), and 12.7% more likely to use alcohol (p=0.01). The prevalence of reported past 30 day benzodiazepine use was very high with 71% (n=355) of participants reporting having used one or more benzodiazepines (i.e., alprazolam, clonazepam, or diazepam) at least once during the previous 30 day period. 88.5% (n=314) of participants who reported using benzodiazepines within the past 30 days reported using alprazolam. Clonazepam was the second most commonly used benzodiazepine with 190 subjects (54%) reporting using the prescription drug for nonmedical purposes. Diazepam, with 115 (32%) subjects reporting its use, was the least

commonly utilized benzodiazepine evaluated in this study. The majority of subjects reported using alprazolam only (n=119, 33.5%). 25.4% (n=90) subjects reported using both alprazolam and clonazepam, and 65 subjects (18.3%) reported using all three benzodiazepines (i.e., alprazolam, clonazepam, diazepam) evaluated in this study (Table 3). As shown in Table 4, the most common primary source of benzodiazepines was from friends or family members (n=211, 59%). The next most common source was from a dealer (n=60, 17%). Only 15% (n=53) of benzodiazepine users obtained their first prescription legitimately via a clinician such as a physician or dentist.

A strong relationship between the nonmedical use of benzodiazepines and DSM-IV psychiatric disorders was found in this study (Table 5). Participants that reported past 30 day use of alprazolam, clonazepam, and/or diazepam were found to have an 11.1% (p=0.01) higher prevalence of MDD versus benzodiazepine non-users. Additionally, the prevalence of GAD was 12.4% higher (p=0.005) in subjects who reported past 30 day benzodiazepine use. Although 6.6% more participants who reported recent benzodiazepine use met the criteria for a PTSD diagnosis, the relationship did not achieve statistical significance (p=0.053). Finally, the rates of ASPD were nearly identical between benzodiazepine users and non-users, 31.5% versus 31.1% respectively (p=0.9).

A logistic regression model (Table 6) was developed to identify independent correlates of recent benzodiazepine use. After controlling for the possible confounding variables of age, sex, and race, the adjusted model revealed six variables associated with past 30 day benzodiazepine use. The strongest association was with illicit methadone use (AOR: 2.9, 95% CI: 1.9-4.6). Other benzodiazepine abuse factors included marijuana use (AOR: 2.6, 95% CI: 1.6-4.01) and oxycodone use (AOR: 2.5, 95% CI: 1.6-3.97). During the modeling process, substantial

collinearity between GAD and MDD was identified. Although both disorders were associated with benzodiazepine use, a diagnosis of GAD via the MINI was the more significant factor of benzodiazepine use (AOR: 1.7, 95% CI: 1.01-2.77) in the final model. A self-reported health status of poor or fair (AOR: 1.65, 95% CI: 1.05-2.6) as well as number of years a subject reported living in Appalachian, Kentucky (AOR: 1.03, 95% CI: 1.0-1.05) were also significant contributors to recent benzodiazepine use in the adjusted logistic model.

4. Discussion

The findings of this study are consistent with the hypothesis that nonmedical benzodiazepine use is strongly associated with major depressive disorder (MDD) and generalized anxiety disorder (GAD). While other reports have described the common co-occurrence of psychiatric and substance use disorders[11]; this is the first study to suggest that people who abuse benzodiazepines are significantly more likely to have specific psychiatric disorders. Therefore, future treatment and prevention programs must be developed to target both addiction and underlying psychiatric disorders. Overall, 26% of participants were found to have MDD without regard to benzodiazepine use. This rate is in agreement with recent literature that places the lifetime rate of developing a concurrent substance use disorder and MDD at 17.2%.[12] The results of this study raise the question of potential self-medication among opioid drug abusers. We found that those who met DSM-IV criteria for MDD or GAD were almost twice more likely to report nonmedical benzodiazepine use than those who did not. Considering benzodiazepines are indicated for the short term treatment of anxiety, benzodiazepine use was likely providing relief to an anxiety prone population of opioid drug abusers. This study did not find a significant relationship between benzodiazepine use and PTSD. While this result was plausibly due to the relatively small prevalence of PTSD among the study population; this finding was unexpected

due to a commonly held assumption regarding substance abuse as a coping mechanism utilized by individuals with PTSD.[13]

It is expected that the high prevalence of psychiatric conditions in this study contributed to subjects self-perceived health status. This study found poor health status was significantly associated with nonmedical use of benzodiazepines. However, whether poor health was a factor promoting benzodiazepine use or if benzodiazepine use led to decreased health cannot be determined. Of note, previous studies have found opioid users who co-abuse benzodiazepines experience higher substance dependence relapse rates and in general, poorer treatment outcomes.[14,15] Therefore, an investment in overcoming health disparities may be needed to stem the epidemic of drug abuse.

The large percentage of benzodiazepine users in this study is in accordance with existing literature which suggests that opioids and benzodiazepines are commonly abused in tandem for nonmedical purposes. Several studies have evaluated the drug use history of patients entering methadone clinics for treatment of opioid dependence. These studies found that anywhere between 18-54% of admitted patients required detoxification from benzodiazepines.[16,17,18] Alprazolam, which is the most commonly prescribed benzodiazepine nationally[19], was also the most prevalent benzodiazepine reportedly used in this study of opioid drug users.

The high prevalence of opioid and benzodiazepine co-use is concerning for several reasons. First, current practice guidelines do not support the long term use of benzodiazepines to treat anxiety. Also, benzodiazepines have been shown to be of little benefit for patients suffering from chronic pain.[20] Compounding these dangers, is the fact that many benzodiazepines increase opioid associated respiratory depression. Additionally, the effectiveness of the opioid antagonist

naloxone is decreased in the presence of benzodiazepines thus potentially hampering the treatment of acute overdoses. Statistics regarding acute overdose were not collected in this study, but opioids and benzodiazepines are reportedly the most common prescription drugs involved in these types of clinical scernarios.[21]

Benzodiazepines have been shown to increase the rewarding and reinforcing effects of opioids which potentiates further abuse and dependence.[22] Of note is the strong association between nonmedical use of benzodiazepines and illicit methadone and oxycodone use found in this study. This finding is consistent with literature that found drug users will augment the effects of oxycodone with benzodiazepines to increase their "high."[23] This observation is supported by pharmacokinetic studies that found that diazepam increased the concentration of methadone in the central nervous system.[24] Interestingly, this association was not noted in subjects reporting the use of Oxycontin®. Since Oxycontin® is a potent long acting formulation of oxycodone, this suggests opioid abusers may be utilizing benzodiazepines to intensify the effects of less potent narcotics.

Residents of Appalachia are often self-sufficient and distrustful of the healthcare system.[25,26] These traits give credence to the hypothesis of practicing self-medication to treat psychiatric disorders. This study found that the odds of using a benzodiazepine increase by 3% each additional year living in Eastern Kentucky, which suggests that as immersion in Appalachian culture increases, the likelihood of seeking professional treatment decreases. It is possible many participants were hesitant to seek professional assistance because of the stigma associated with psychiatric disorders. This study found that more than half of recent benzodiazepine users obtained their supply from friends or family members. These findings are consistent with a 2012 national study by McCabe et al. which reported that 55% of teenage subjects reporting

nonmedical use of opioids acquired them from friends or family.[27] Since the diversion of prescription pharmaceuticals is a contributing factor in over half of all fatal drug overdoses[28], an investment in campaigns that educate the public regarding the dangers of sharing prescription drugs appears to be warranted especially in this rural population.

The main limitation of this study is its cross-sectional design which does not allow for causality to be established. A further limitation of this study is that no measure of degree of benzodiazepine abuse or dependence was collected. Due to the constraint of using secondary data, only participants reporting the use of alprazolam, clonazepam, or diazepam were classified as benzodiazepine users. Therefore, it is possible a subject may have been mistakenly classified as a benzodiazepine non-user when in fact they used another agent of the class. However, since most participants reported using more than one benzodiazepine, this limitation likely had little impact on final results. Lastly, since the study population consisted of rural opioid users living in only one county of Kentucky, the results of this study may not be generalizable to all opioid users.

Despite these limitations, this study suggests nonmedical benzodiazepine use is associated with psychiatric disorders and reinforces the fact that nonmedical use of prescription drugs is a multi-faceted problem. The results of this study reinforce the need for intervention at both the individual and community level. High rates of MDD and GAD were found among this cohort of opioid drug abusers living in medically underserved region of Appalachian, Kentucky. The association of MDD and GAD with benzodiazepine use suggests subjects were possibly self-treating their conditions by escalating their degree of prescription drug abuse to include benzodiazepines. A lack of accessible mental healthcare providers may be a contributing factor to the high rates of nonmedical benzodiazepine use found in this study. An additional

contributing factor may be that people suffering from mood disorders fear exclusion in these typically clannish communities. If this is the case, further development of mental health outreach programs and access to healthcare services may reduce the abuse of benzodiazepines in Appalachian Kentucky. In 2012, the Kentucky legislature passed House Bill 1 in an attempt to improve prescription oversight of controlled substances. This legislation imposes regulations concerning pain clinics, improved guidelines for the prescribing of controlled substances, and requires the mandatory utilization of an electronic prescription drug monitoring program (e.g, KASPER [Kentucky All Schedule Prescription Electronic Reporting]). Longitudinal studies are needed to determine the effect of prescription drug monitoring programs (e.g., KASPER) on the accessibility of benzodiazepines. By limiting accessibility of these drugs, users may seek out the psychiatric treatment they require instead of attempting to self-medicate by using benzodiazepines and other drugs of abuse. However, due to the strong association of prescription drug abuse and psychiatric disorders, the provision of mental healthcare must be of utmost importance in order to stem the tide of drug abuse in Appalachian Kentucky.

References

1. Substance Abuse and Mental Health Services Administration, *Results from the 2011 National Survey on Drug Use and Health: Summary of National Findings*, NSDUH Series H-44, HHS Publication No. (SMA) 12-4713. Rockville, MD: Substance Abuse and Mental Health Services Administration, 2012.

2. Hansen RN, Oster G, Edelsberg J, Woody GE, Sullivan SD. Economic costs of nonmedical use of prescription opioids. Clin J Pain 2011;27:194–202.

3. Verispan LLC. Vector One National, Years 1998-2007, extracted July 2008 [cited by Belouin SJ, Reuter N, Borders-Hemphill V, Mehta H. Prescribing trends for opioids, benzodiazepines, amphetamines, and barbiturates from 1998-2007. Rockville, MD: Drug Testing Advisory Board, Substance Abuse and Mental Health Services Administration; August 2008. http://nac.samhsa.gov/dtab/presentations/aug08/seanbelouindtab0808_508.pdf. Accessed March 12, 2013.

4. U.S. Drug Enforcement Administration. Office of Diversion Control. Automation of Reports and Consolidated Orders System (ARCOS). Available at: http://www.deadiversion.usdoj.gov/arcos/retail_drug_summary/index.html. Accessed March 29, 2013

5. Zhang, Z., Infante, A. , Meit, M., & English, N. (2008). *An Analysis of Mental Health and Substance Abuse Disparities & Access to Treatment Services in the Appalachian Region*. Retrieved March, 2013 from the Appalachian Regional Commission Online Resource Center Web site: http://www.arc.gov/research/researchreportdetails.asp?REPORT_ID=71

6. Khantzian EJ: The self-medication hypothesis of addictive disorders: focus on heroin and cocaine dependence. *Am J Psychiatry* 1985, 142:1259-1264.

7. U.S. Census Bureau; American FactFinder Web site. http://factfinder2.census.gov. Accessed March 1, 2013.

8. Young AM, Havens JR, Leukefeld CG. 2012. A comparison of rural and urban nonmedical prescription opioid users' lifetime and recent drug use. Am J Drug Alcohol Abuse 38:220–227.

9. McLellan, A.T., Kushner, H., Metzger, D., Peters, R., Smith, I., Grissom, G., Pettinati, H., Argeriou, M., 1992. The fifth edition of the Addiction Severity Index. J. Subst. Abuse Treat. 9, 199–213.

10. Sheehan, D.V., Lecrubier, Y., Sheehan, K.H., Amorim, P., Janavs, J., Weiller, E., Hergueta, T., Baker, R., Dunbar, G.C., 1998. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J. Clin. Psychiatry 59 (Suppl.), 22–33.

11. Hasin DS, Goodwin RD, Stinson FS, Grant BF: Epidemiology of major depressive disorder: results from the National Epidemiologic Survey on Alcoholism and Related Conditions. Arch Gen Psychiatry 2005: 62:1097-116.

12. Kessler RC, Chiu WT, Demler O, Merikangas KR, Walters EE. Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. Arch Gen Psychiatry 2005; 62:617-627.

13. Waldrop AE, Back SE, Verduin ML, Brady KT. Triggers for cocaine and alcohol use in the presence and absence of posttraumatic stress disorder. Addict Behav. 2007;32:634–9.

14. Compton WM, Cottler LB, Abdallah AB, et al. Substance dependence and other psychiatric disorders among drug dependent subjects: race and gender correlates. Am J Addict 2000; 9:113-125.

15. Hasin D, Liu X, Nunes E, et al. Effects of major depression on remission and relapse of substance dependence. Arch Gen Psychiatry 2002; 59:375-380.

16. Gelkopf M, Bleich A, Hayward R, Bodner G, Adelson M. Characteristics of benzodiazepine abuse in methadone maintenance treatment patients: a 1 year prospective study in an Israeli clinic. Drug Alcohol Depnd. 1999; 55,63-68.

17. Rooney S, Kelly G, Bamford L, Sloan D, O'Connor JJ. Co-abuse of opiates and benzodiazepines. Irish J. Psychol. Med. 1999: 168:36-41.

18. Specka M, Bonnet U, Heilmann M, Schifano F, Scherbaum N. Longitudinal patterns of benzodiazepine consumption in a German cohort of methadone maintenance treatment patients. Hum. Psychopharmacol. 2011; 26:404-411.

19. Theodorou A, Johnson K, Slezak J, Szychowski J. Recent trends in utilization of antianxiety medication. Am J Pharm Benefits. 2009; 1: 225-229.

20. King SA, Strain JJ. Benzodiazepine use by chronic pain patients. Clin. J. Pain. 1990; 6:143-147.

21. Xiang Y, Zhao W, Xiang H, Smith GA. ED visits for drug-related poisoning in the United States, 2007. Am. J. Merg. Med. 2012; 30:293-301.

22. Walker, Bm, Ettenberg A. Benzodiazepine modulation of opiate reward. Exp. Clin. Psychopharmacol. 2001; 9:191-197.

23. Spiga R, Huang DB, Meisch RA, Graboski J. Human methadone self-administration: effects of diazepam pretreatment. Exp. Clin. Psychopharmacol. 2001; 9:40-46.

24. Shah NS, Patel VO, Donald AG. Effect of diazepam, desmethylimipramine, and SKF 525-A on the disposition of levo-methadone in mice after single or double injections. Drug Metab. Dispos. 1979; 7:241-242.

25. Smith, SL & Tessaro, IA. Cultural perspectives on diabetes in an Appalachian population. American Journal of Health Behavior. 2005; 29: 291-301.

26. Hatcher J, Dignan M, Schoenberg N. How do rural health care providers and patients view barriers to colorectal screening? Insights from Appalachian Kentucky. The Nursing Clinics of North America. 2011; 46:181-92.

27. Leftover Prescription Opioids and Nonmedical Use Among High School Seniors: A Multi-Cohort National Study.

28. Hall A. J., Logan J. E., Toblin R. L., Kaplan J. A., Kraner J. C., Bixler D. et al. Patterns of abuse among unintentional overdose fatalities. JAMA 2008; 300: 2613–20.

Table 1. Demographic data

Demographics	Benzo Use 30 d (n=355)		No Benzo Use 30 d (n=148)			Total (n=503)	
	n	%	n	%	*P*	n	%
Median age (IQR)	33 (26-38)		32 (25-36)		0.153	33 (26-38)	
Median years lived in Eastern Kentucky (IQR)	29 (24-35)		27 (22-33)		0.015	28 (23-25)	
Median years of education completed (IQR)	11 (10-12)		11 (10-12)		0.841	11(10-12)	
Male gender	194	54.6	92	62.2	0.121	286	56.9
Religious	112	31.5	29	19.6	0.007	141	28.0
Caucasian	329	92.7	145	98.0	0.020	474	94.2
Employment							
Full-time	114	32.1	59	39.9	0.095	173	34.4
Part-time	90	25.4	26	17.5	0.059	116	23.1
Disabled	48	13.5	19	12.8	0.837	67	13.3
Student/service/military	6	1.7	2	1.4	1.00	8	1.6
Controlled environment	2	1.4	6	1.7	.0096	8	1.6
Unemployed	95	26.8	36	24.3	0.57	131	26.0
Pension for physical disability	41	11.5	20	13.5	0.539	61	12.1
Someone contributes majority of support	143	40.3	47	31.8	0.072	190	37.8
Health insurance status							
Medicaid/Medicare	108	30.4	44	29.7	0.877	152	30.2
Private	14	3.9	4	2.7	0.606	18	3.6
Uninsured	233	65.6	100	67.6	0.676	333	66.2
Self-reported health status							
Poor/fair	178	50.2	56	37.8	0.012	234	46.5
Good	126	35.5	67	45.3	0.051	193	38.4
Very good/excellent	51	14.3	25	16.9	0.471	76	15.1
Chronic health condition(s)	131	36.9	44	29.7	0.124	175	34.8
Ever treated for drug abuse	177	49.9	79	53.4	0.472	256	50.9

Table 2. Prevalence of psychiatric disorders and substance abuse

Psychiatric disorders	Benzo Use 30 d (n=355)		No Benzo Use 30 d (n=148)			Total (n=503)	
	n	%	n	%	*P*	n	%
MDD	104	29.3	27	18.2	0.01	131	26.0
GAD	116	32.7	30	20.3	0.005	146	29.0
PTSD	57	16.1	14	9.5	0.053	71	14.1
ASPD	112	31.5	46	31.1	0.918	158	31.4
Substance use (30 day)							
Any opioid	352	99.2	141	95.3	0.009	493	98.0
Alcohol	208	58.6	68	45.9	0.009	276	54.9
Heroin	14	3.9	8	5.4	0.465	22	4.4
Illicit methadone	241	67.9	65	43.9	0.000	306	60.8
Licit methadone	12	3.4	2	1.4	0.207	14	2.8
Oxycodone ER	252	71.0	99	66.9	0.362	351	69.8
Oxycodone	281	79.2	83	56.1	0.000	364	72.4
Crack	45	12.7	12	8.1	0.141	57	11.3
Cocaine	88	24.8	25	16.9	0.053	113	22.5
Methamphetamine	14	3.9	3	2.0	0.278	17	3.4
Marijuana	237	66.8	71	48	0.000	285	56.7

Table 3. Detailed analysis of benzodiazepine use (n=355)

Self-reported benzodiazepine use		
	n	%
Alprazolam alone	119	33.5
Clonazepam and alprazolam	90	25.4
Alprazolam, clonazepam, diazepam	65	18.3
Diazepam and alprazolam	40	11.3
Clonazepam alone	31	8.7
Diazepam alone	6	1.7
Clonazepam and diazepam	4	1.1
Total	355	100

Table 4. Sources of benzodiazepines

Source first time used benzodiazepine		
	n	%
Spouse	16	4.5
Family	57	16.1
Friends	138	38.9
Physician/Dentist	52	14.6
Dealer	60	16.9
Stolen	17	4.8
Multiple sources	1	0.3
No response	14	3.9
Total	355	100

Table 5. Association between benzodiazepine use and psychiatric disorders

Association between benzodiazepine use and psychiatric disorders									
	MDD			GAD			PTSD		
	Odds Ratio	*95% CI*	*P*	Odds Ratio	95% CI	*P*	Odds Ratio	95% CI	*P*
Alprazolam alone	1.250	0.791-1.974	0.338	0.871	0.550-1.381	0.557	0.845	0.459-1.556	0.588
Clonazepam alone	0.528	0.198-1.405	0.194	0.569	0228-1.418	0.221	0.403	0.094-1.727	0.289
Diazepam alone	5.827	1.05-32.194	0.042	0.486	0.056-4.192	0.677	1.220	0.140-10.598	0.601
Clonazepam and diazepam	8.695	0.896-84.340	0.056	0.814	0.084-7.888	1.000	2.043	0.210-19.917	0.457
Clonazepam and alprazolam	1.192	0.718-1.978	0.497	1.537	0.951-2.484	0.078	1.151	0.610-2.171	0.665
Diazepam and alprazolam	0.942	0.447-1.985	0.875	1.350	0.684-2.666	0.386	2.548	1.209-5.367	0.011
Alprazolam, clonazepam, diazepam	1.423	0.811-2.499	0.218	2.210	1.297-3.766	0.003	1.638	0.840-3.193	0.144
Total	1.857	1.154-2.988	0.010	1.909	1.208-3.018	0.005	1.831	0.986-3.400	0.053

Table 6. Independent factors of past 30 day benzodiazepine use

Factors of benzodiazepine use in opioid drug abusers			
	Odds Ratio	Adjusted Odds Ratio*	95% CI
Illicit methadone	2.755	2.944	1.902-4.557
Marijuana	2.264	2.565	1.640-4.013
Oxycodone	2.463	2.521	1.602-3.968
GAD	1.736	1.669	1.005-2.770
Poor/Fair health	1.751	1.652	1.049-2.600
Time lived in eastern KY	1.027	1.028	1.004-1.052

*controlling for age, sex, race

Figure 1. Self-reported benzodiazepine use

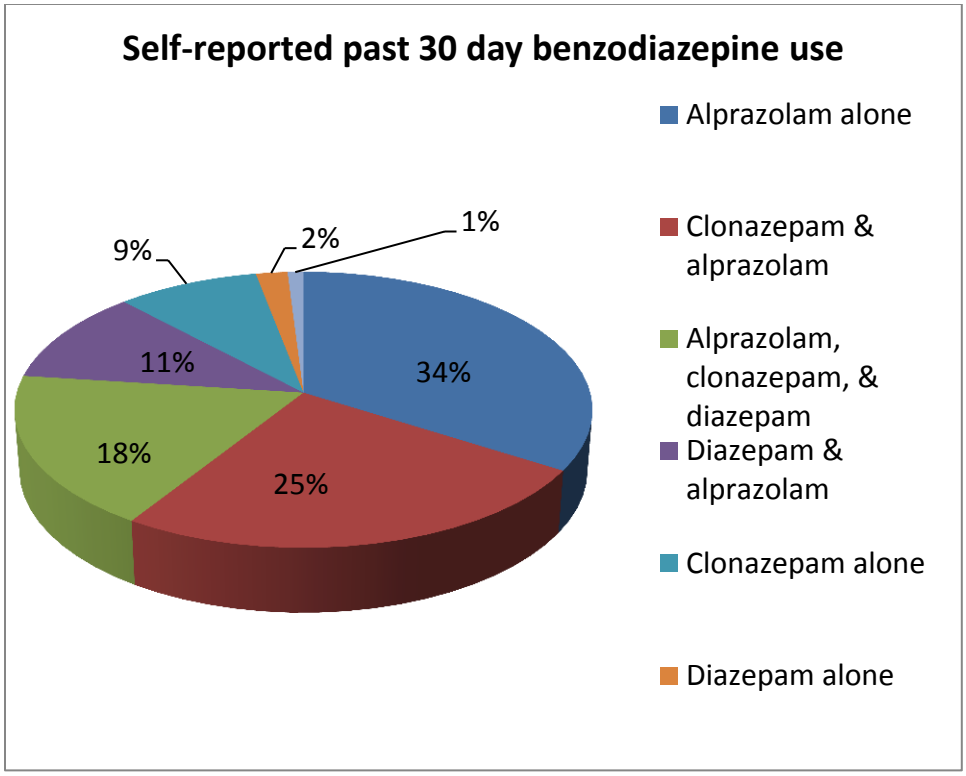

Figure 2. Association of benzodiazepine use with psychiatric disorders

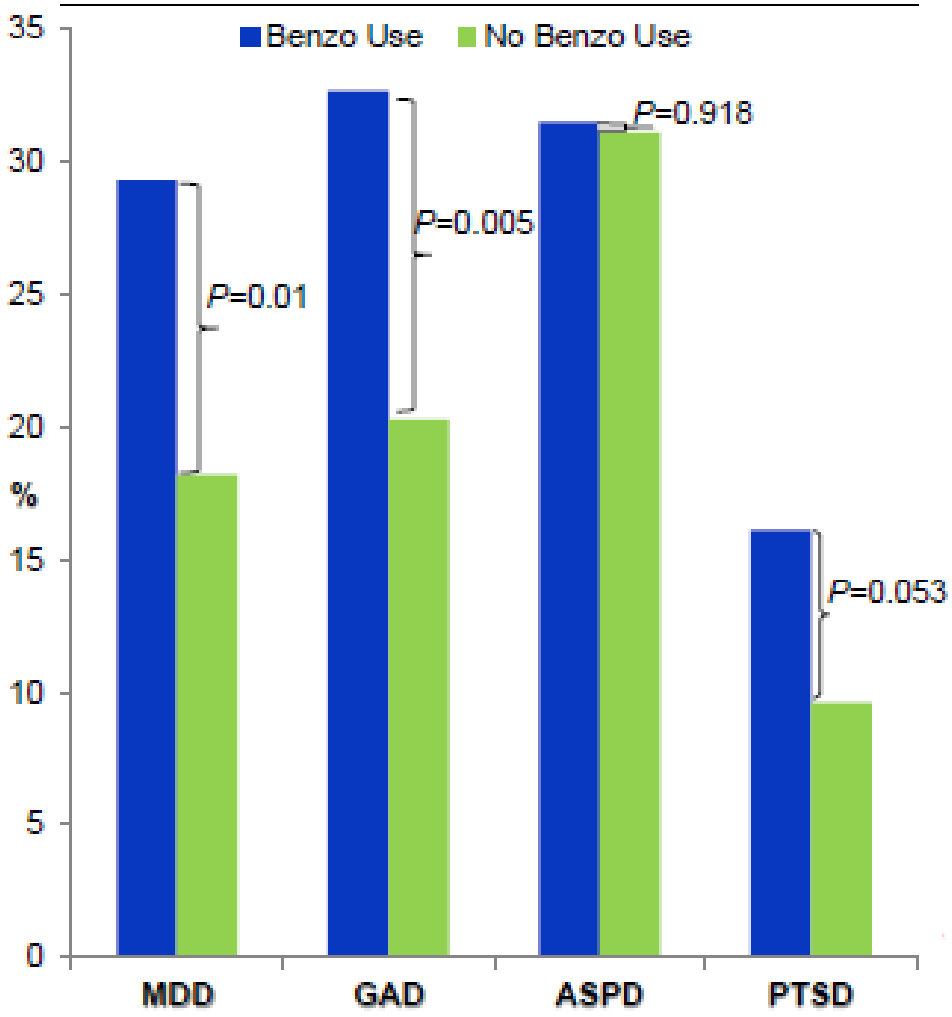

Figure 3. Forest plot of factors of benzodiazepine use

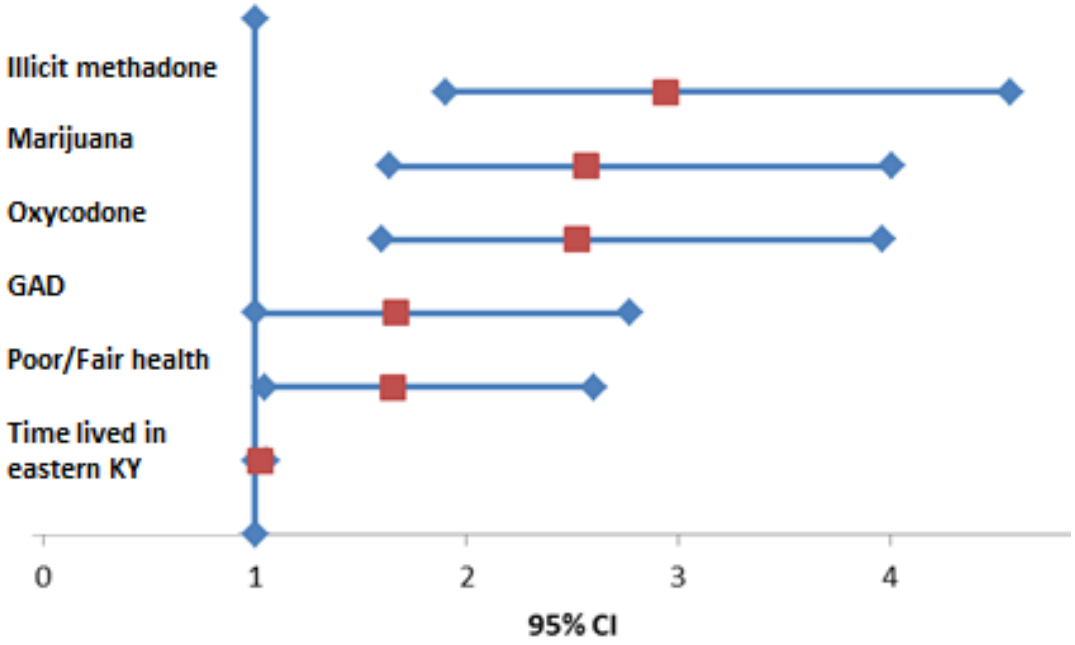

Figure 4. Sources of benzodiazepines