The Association of Benzodiazepine Use with Smoking Cessation Among Hospitalized Smokers in a Clinical Trial

By

Austin T. Wilson

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Chairperson: Kimber P. Richter, Ph.D., M.P.H., M.A.

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Babalola Faseru, M.D., M.P.H.

_____

Taneisha S. Scheuermann, Ph.D.

Date Defended: May 20, 2016

The Thesis Committee for Austin Troy Wilson

certifies that this is the approved version of the following dissertation:

Effect of Benzodiazepines on Smoking Cessation

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Chairperson: Kimber P. Richter, Ph.D., M.P.H., M.A.

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Abstract

Objective: Benzodiazepines are an increasingly prescribed class of anxiolytic medications that target GABA-A receptors in the brain. Smoking also has indirect effects on GABA receptors. This secondary data analysis evaluates the effects of benzodiazepine use on smoking cessation rates among participants in a hospital-based cessation trial. To our knowledge, no other study has examined the effect of benzodiazepine use on smoking cessation rates.

Methods: Data from the Enhancing Quitline Utilization among In-Patients (EQUIP) study was analyzed as part of a secondary data analysis. Participants with a benzodiazepine prescription listed on their hospital discharge medication list were compared with those without a benzodiazepine prescription (total n=1054). Similar analyses were conducted between participants with either a long- or short-acting benzodiazepine prescription.

Results: A logistic regression modeling the odds of a participant quitting showed no statistical association with benzodiazepine prescription presence (Odds Ratio, OR, 0.93, 95% confidence interval 0.68, 1.28). Controlling for potential covariates maintained a negatively associated, non-significant OR of 0.88 (95% confidence interval 0.63, 1.22). Additionally, the logistic regression modeling produced non-significant odds ratios for both unadjusted and adjusted associations of long-acting versus short-acting benzodiazepine prescription presence on quit rates (adjusted O.R. 0.88, 95% confidence interval 0.49, 1.61).

Conclusions: In this sample of patients, the presence of a benzodiazepine prescription at discharge did not have a significant effect on 6-month biochemically verified quit rates. The odds of being quit based on the presence of a benzodiazepine prescription at discharge trended negatively across all unadjusted and adjusted analyses.

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Introduction

Smoking is the top preventable cause of death in the United States. Roughly forty percent of smokers attempt to quit each year[1]. Benzodiazepines are an increasingly prescribed class of anxiolytic medications that target GABA-A receptors[2]. Benzodiazepines could help or hinder smokers' ability to quit in several ways. Benzodiazepine use could hinder smokers' ability to quit because both chronic use of benzodiazepines[3] and smoking[4] can each independently affect GABA receptor function in the brain. Quitting either benzodiazepines or smoking leads to a decreased activation of GABA receptors. This lower activation has been linked to anxiety[5]. Anxious symptoms are a major barrier to staying quit[6]. Conversely, benzodiazepines could enhance smokers' likelihood of staying quit. As an anxiolytic, short-term use of benzodiazepines could reduce symptoms of anxiety that occur during quit attempts by binding to unbound GABA receptors previously affected by tobacco smoke.

The type of benzodiazepine taken could have a differential effect on smoking cessation. Benzodiazepines are categorized by duration of action. Symptomatic coverage differs between long (>24 hour half-life) and short (<24 hour half-life) acting benzodiazepines[7]. The difference in duration of action may lead to differential GABA receptor coverage, affecting receptor availability in the brain. Specifically, shorter-acting benzodiazepines could create peaks and troughs in receptor coverage; tobacco use could alleviate symptoms that emerge during trough levels. This relationship could maintain tobacco use and make it difficult to quit. To our knowledge, no study has examined the impact of benzodiazepine prescriptions on smoking cessation, nor the impact on smoking cessation of long- and short-acting benzodiazepines.

The objective of this secondary data analysis was to determine the effects of benzodiazepine use on smoking cessation rates among participants in a hospital-based cessation trial. A subgroup analysis was conducted to detect differences in smoking cessation rates between long- and short-acting benzodiazepine use.

Methods

Study Design

The Enhancing Quitline Utilization among In-Patients (EQUIP) study is a two-arm randomized clinical trial designed to examine the impact of warm handoff on enrollment in quitline services and biochemically verified cessation at 6-months [8]. The purpose of EQUIP was to determine the relative effectiveness of warm handoff versus fax referral for transitioning inpatient smokers to post-discharge care. Participants in both study arms received the hospital's standard cessation brochure with information and resources for quitting smoking. Those in the fax referral group were provided the institution specific tobacco treatment service and were fax-referred to the quitline on the day they were discharged from the hospital. Those in the warm handoff group were personally connected with the quitline during their hospital stay. Follow-up was performed based on decisions made during this quitline counseling session. The study design and details are described in a prior publication [8]. We conducted a secondary data analysis of the study that examines the effects of benzodiazepine prescription at hospital discharge on biochemically verified cessation at 6-months.

Setting and Participants

Participants (n=1054) were smokers admitted into two large hospitals in Kansas with dedicated tobacco treatment interventionists on staff. Eligibility criteria included planning to stay

quit post-discharge, smoking any cigarettes within the past 30 days, being aged 18 or older, speaking English or Spanish, having access to a telephone post-discharge, having no other household member participating in the trial, not currently pregnant, and having no co-morbidity or health issue preventing full participation.

Measures

Demographics, highest level of education, tobacco use characteristics, Heaviness of Smoking Index (HSI)[9], Alcohol Use Disorder Identification Test (AUDIC-C)[10], and the Patient Health Questionnaire-2 (PHQ-2)[11] were obtained through the baseline survey. Discharge prescriptions, primary diagnoses, procedures, and length of stay were obtained from the electronic medical record (EMR). Psychiatric disorders and participants who had undergone cardiac or cerebrovascular surgery were identified using the Ninth Revision of the International Classification of Disease (ICD-9) and Diagnosis Related Group (DRG) codes.

Benzodiazepine medications were identified through discharge prescriptions abstracted from the EMR. Such medications were identified by drug name and categorized by active metabolite duration of action. Benzodiazepines with an average half-life exceeding 24 hours were categorized as long-acting agents (chlordiazepoxide, clonazepam, clorazepate, and diazepam). Benzodiazepines with an average half-life less than 24 hours were categorized as short-acting agents (alprazolam, lorazepam, and temazepam)[7].

As described in the design paper of EQUIP [8], abstinence was assessed with two measures. The first measure, self-reported abstinence at 1 and 6 months, was obtained by asking participants if they had smoked any cigarettes in the past 7 days. The second measure of abstinence was biochemically verified via salivary cotinine (<15ng/ml), carbon monoxide (<10

ppm), or proxy. Participants who failed to verify abstinence were counted as smokers in the final analysis.

Data Analyses

Because participants were not randomized by benzodiazepine prescription presence, we first determined baseline differences between groups. For all primary objective analyses, participants with a benzodiazepine prescription listed on their hospital discharge medication list were compared with those without a benzodiazepine prescription. These groups were compared with respect to demographics, tobacco use, hospital treatment, health behavior and psychosocial measures, and discharge medications. Similar analyses for the secondary objective were conducted between participants with either a long- or short-acting benzodiazepine prescription. Baseline measures were investigated using the Student's t-test and chi square test.

Next, a chi square test was used to determine unadjusted differences in quit rates between the investigated groups in the primary objective analysis (benzodiazepine/no benzodiazepine) and secondary objective analysis (long versus short-acting benzodiazepine). Logistic regression analyses of 6-month biochemically verified cessation rates were conducted. The logistic regression analyses modeled the odds of being quit at month six.

We also conducted regression analyses for each of the study objectives that adjusted for potential confounding variables. Adjustments included baseline differences between groups, variables associated with quitting in this sample, and variables predictive of quitting suggested by previous literature. Adjustments gleaned from cessation literature included gender, age, insurance status, HSI, and AUDIT-C [12].

Results

Primary Objective

Univariate Analysis

Comparisons of Demographics Measures. A total of 287 participants (27.2%) were prescribed a benzodiazepine at discharge (Table 1). There were no significant differences between groups on measures of age, Latino origin, education, or presence of other smokers. There were significant differences between the groups in gender, race, insurance status, primary diagnosis, surgery status, AUDIT-C, PHQ-2, and opiate prescription presence ($p < 0.05$).

Tobacco Use. There were no detectable differences between participants with benzodiazepine prescriptions and those without a benzodiazepine prescription in the number of cigarettes smoked per day, number of days smoked per month ($\geq$25 days/30 days), smoking upon awakening, HIS (>4), and confidence levels in staying quit.

Hospital Treatment. Comparisons between participants with a benzodiazepine prescription and those without a benzodiazepine prescription found no detectable differences in psychiatric comorbidities, emergency admissions, and length of stay. Participants had significantly different primary diagnoses and surgery occurrences.

Health Behavior and Psychosocial Measures. Participants with benzodiazepine prescriptions were less likely to report problematic alcohol use (AUDIT-C) and more likely to screen positive for possible depression (PHQ-2) versus those who were not prescribed a benzodiazepine.

Discharge Medication. Significantly more opiates were prescribed among those in the benzodiazepine prescription group versus those who were not prescribed a benzodiazepine ($p < 0.001$). Smoking cessation medications did not differ significantly between these groups.

Variables Associated With Quitting. Education (< High School), daily smoking (≥25 days/30 days), and hospital length of stay were found to be associated with quit rates among those who received a benzodiazepine prescription ($p < 0.05$) (Not shown).

Table 1. Baseline Characteristics by Benzodiazepine Prescription

Variable	**Total** (n= 1,054)	**Benzodiazepine Prescription** (n = 287)	**No Benzodiazepine Prescription** (n = 767)
Demographics			
Age, mean (SD)	49.89 (12.93)	49.01 (12.20)	50.22 (13.19)
Female, no. (%)*	581 (55.12%)	195 (67.94%)	386 (50.33%)
Race*			
White, no. (%)	719 (68.22%)	219 (76.31%)	500 (65.19%)
African American, no. (%)	262 (24.86%)	43 (14.98%)	219 (28.55%)
Other, no. (%)	73 (6.93%)	25 (8.71%)	48 (6.26%)
Latino, no. (%)	62 (5.91%)	19 (6.62%)	43 (5.61%)
Education < High School, no. (%)	231 (21.92%)	62 (21.60%)	169 (22.03%)
Lives with other smoker, no. (%)	523 (49.62%)	145 (50.52%)	378 (49.28%)
Primary Insurance*			
Medicaid, no. (%)	355 (33.68%)	103 (35.89%)	252 (32.86%)
Medicare, no. (%)	314 (29.79%)	103 (35.89%)	211 (37.51%)
Private, no. (%)	306 (29.03%)	69 (24.04%)	237 (30.90%)
VA, no. (%)	12 (1.14%)	3 (1.05%)	9 (1.17%)
Self-pay/none, no. (%)	67 (6.36%)	9 (3.14%)	58 (7.56%)
Tobacco Use			
CPD mean (SD)	15.97 (11.06)	16.14 (12.12)	15.62 (10.62)
Daily smoking (≥ 25/30 days), no. (%)	759 (72.01%)	200 (69.69%)	559 (72.88%)

Smoke within 30 mins of waking, no. (%)	753 (71.71%)	206 (71.78%)	547 (71.32%)
Heavy smoking index (HSI) $\geq$ 4 , no. (%)	347 (32.92%)	101 (35.19%)	246 (32.07%)
Confidence to quit/stay quit (possible range 1 – 5), mean (SD)	3.79 (1.12)	3.84 (1.10)	3.78 (1.12)
Hospital Treatment			
Reason for admission *			
Circulatory system, no. (%)	261 (24.76%)	44 (15.33%)	217 (28.29%)
Respiratory system, no. (%)	121 (11.48%)	36 (12.54%)	85 (11.08%)
Neoplasms, no. (%)	50 (4.74%)	17 (5.92%)	33 (4.30%)
Mental Disorders, no. (%)	22 (2.09%)	4 (1.39%)	18 (2.35%)
Other, no. (%)	600 (56.93%)	186 (64.81%)	414 (53.98%)
Psychiatric Co-morbidity, no. (%)	681 (64.6%)	188 (65.51%)	493 (64.28%)
Cardiac and cerebrovascular surgery, no. (%)*	121 (11.48%)	18 (6.27%)	103 (13.43%)
Emergency admissions, no. (%)	630 (59.8%)	159 (55.40%)	471 (61.41%)
Length of stay (hours), mean (SD)	134.88 (133.10)	146.76(137.10)	130.43(131.38)
Health Behavior and Psychosocial Measures			
Alcohol Use Disorder (AUDIT-C), no. (%)*	323 (30.65%)	53 (18.47%)	270 (35.20%)
Possible Depression (PHQ-2), no. (%)*	566 (53.80%)	185 (64.46%)	381 (49.67%)
Discharge Medication			
Opiate medication use, no. (%)*	677 (64.23%)	216 (75.26%)	461 (60.10%)
Smoking Cessation Medications			
Nicotine Replacement Therapy	258 (24.48%)	82 (28.57%)	176 (22.95%)
Varenicline	30 (2.85%)	11 (3.83%)	19 (2.48%)
Bupropion	52 (4.93%)	16 (5.57%)	36 (4.69%)

*p-value <0.05

Unadjusted Quit Rates by Benzodiazepine Use. No statistical difference was found in biochemically verified 6-month quit rates between those who received a benzodiazepine prescription and those who did not (p = 0.667) (Not shown).

Multivariate Analysis

A logistic regression modeling the odds of a participant quitting showed no statistical association with benzodiazepine prescription presence (OR 0.93, 95% confidence interval 0.68, 1.28) (Table 2). Addition of a priori predictors, baseline differences, and sample predictors of cessation maintained a negatively associated, non-significant OR of 0.88 (95% confidence interval 0.63, 1.22).

Table 2. Odds of Quitting in Presence of Benzodiazepine Prescription

Explanatory Variables	**Model 1**	**Model 2**	**Model 3**	**Model 4**
Benzodiazepine Prescription, O.R. (95% CI)	0.93 (0.68, 1.28)	0.90 (0.65, 1.25)	0.91 (0.65, 1.26)	0.88 (0.63, 1.22)
A Priori predictors	-	Yes	Yes	Yes
Baseline differences	-	-	Yes	Yes
Sample predictors of cessation	-	-	-	Yes

Secondary Objective

Univariate Analysis

Differences in Baseline Characteristics between Long- and Short-Acting Agents. More cerebrovascular and cardiac surgeries were conducted in those who received short-acting benzodiazepines versus participants who received long-acting benzodiazepines (p=0.043) (Not shown). In all other baseline measures no statistical differences were seen.

Variables associated with quitting. Hospital length of stay was found to be associated with quit rates among those who received a long-acting versus a short-acting benzodiazepine prescription (p = 0.026).

Unadjusted Quit Rates by Long- and Short-Acting Benzodiazepine Use. There was no detectable difference in quit rates between participants prescribed long-acting

benzodiazepines and participants prescribed short-acting benzodiazepines (p = 0.648) (Not Shown).

Multivariate Analysis

The logistic regression modeling produced non-significant odds ratios for both unadjusted and adjusted associations of long-acting versus short-acting benzodiazepine prescription presence on quit rates (adjusted OR 0.88, 95% confidence interval 0.49, 1.61).

Table 3. Odds of Quitting between Long- and Short-Acting Benzodiazepine Prescriptions

Explanatory Variables	**Model 1**	**Model 2**	**Model 3**	**Model 4**
Long-Acting Benzodiazepine, O.R. (95% CI)	0.87 (0.49, 1.55)	0.89 (0.50, 1.58)	0.87 (0.48, 1.57)	0.88 (0.49, 1.61)
A Priori Predictors	-	Yes	Yes	Yes
Baseline differences	-	-	Yes	Yes
Sample predictors of cessation	-	-	-	Yes

Discussion

In this sample of patients, the presence of a benzodiazepine prescription at discharge did not have a significant effect on 6-month biochemically verified quit rates. The odds of being quit based on the presence of a benzodiazepine prescription at discharge trended negatively across all unadjusted and adjusted analyses. To our knowledge, no other study has examined the effect of benzodiazepine use on smoking cessation rates.

There was no significant difference in quit rates between participants on long- versus short-acting benzodiazepines. Interestingly, quit rates were the same between participants with a short-acting benzodiazepine prescription and those who did not receive a benzodiazepine prescription.

Both tobacco smoke[4] and benzodiazepines[3] have an effect on GABA receptor function and availability. This interaction could affect smokers' ability to quit. Other studies have examined the effects of psychoactive medications on smoking cessation. Specifically, methadone has been studied for both pharmacokinetic and pharmacodynamic interactions with nicotine. These studies have found that pharmacodynamic interactions between opioids and nicotine may explain low smoking cessation rates. Biologically, this occurs through synergistic activation of endogenous opioid receptors[13].

Anxiety due to tobacco withdrawal has been associated with GABA receptor dysfunction [4]. It was proposed that GABA receptor binding could ameliorate anxiety associated with tobacco withdrawal, thus improving overall likeliness to quit among persons taking benzodiazepines. This, however, was not borne out by our primary objective analyses. Additionally, following the pharmacokinetic patterns of short-acting benzodiazepines, there are periods of the day where the GABA receptor may not be bound[7]. Windows of anxious symptoms may be more frequent due to this decreased binding; and thus, may lead to more relapse than seen with long-acting benzodiazepines. Our secondary objective analyses did not detect this effect.

This secondary data analysis was limited by several factors. Participants in the EQUIP trial were not randomized to either receive or not receive benzodiazepines. Although we adjusted for baseline differences, there may be other underlying differences between groups that obscured any independent effects on quitting that benzodiazepines might have. Also, participants may not be representative of average smokers wanting to quit. Non-hospitalized smokers wanting to quit may have different comorbidities and demographic characteristics. This study was not powered

to detect the effects of benzodiazepine use on smoking cessation rates. Moreover, presence of a benzodiazepine prescription at discharge may not accurately reflect participants' actual utilization of benzodiazepines. Also, we were unable to differentiate between acute and chronic benzodiazepine use. Anxiolytic tolerance to benzodiazepines is associated with extended duration of use[3]. More research is necessary to determine whether benzodiazepines effect smoking cessation.

While the number of benzodiazepine prescriptions is on the rise[2], little data is available on what role benzodiazepines might have in helping or hindering smoking cessation. Our preliminary data suggests that no difference in quit rates exists between those with a benzodiazepine prescription those without a benzodiazepine prescription. Basic studies should better explore the mechanisms through which tobacco smoke affects GABA receptors. Future studies should describe the patterns of tobacco use, benzodiazepine use, and psychiatric comorbidities, and pinpoint populations with high prevalence for targeted intervention.

References

1. U.S. Department of Health and Human Services. *The Health Consequences of Smoking—50 Years of Progress: A Report of the Surgeon General*. 2014 [cited 2016 May 6].
2. Bachhuber, M.A., et al., *Increasing Benzodiazepine Prescriptions and Overdose Mortality in the United States, 1996-2013.* Am J Public Health, 2016. **106**(4): p. 686-8.
3. Vinkers, C.H. and B. Olivier, *Mechanisms Underlying Tolerance after Long-Term Benzodiazepine Use: A Future for Subtype-Selective GABA(A) Receptor Modulators?* Adv Pharmacol Sci, 2012. **2012**: p. 416864.
4. Stokes, P.R., et al., *History of cigarette smoking is associated with higher limbic GABAA receptor availability.* Neuroimage, 2013. **69**: p. 70-7.
5. Atack, J.R., *GABAA receptor alpha2/alpha3 subtype-selective modulators as potential nonsedating anxiolytics.* Curr Top Behav Neurosci, 2010. **2**: p. 331-60.
6. Buczkowski, K., et al., *Motivations toward smoking cessation, reasons for relapse, and modes of quitting: results from a qualitative study among former and current smokers.* Patient Prefer Adherence, 2014. **8**: p. 1353-63.
7. Greenblatt, D.J., et al., *Benzodiazepines: a summary of pharmacokinetic properties.* Br J Clin Pharmacol, 1981. **11 Suppl 1**: p. 11s-16s.
8. Richter, K.P., et al., *Using "warm handoffs" to link hospitalized smokers with tobacco treatment after discharge: study protocol of a randomized controlled trial.* Trials, 2012. **13**: p. 127.
9. de Leon, J., et al., *Exploring brief measures of nicotine dependence for epidemiological surveys.* Addict Behav, 2003. **28**(8): p. 1481-6.
10. Bush, K., et al., *The AUDIT alcohol consumption questions (AUDIT-C): an effective brief screening test for problem drinking. Ambulatory Care Quality Improvement Project (ACQUIP). Alcohol Use Disorders Identification Test.* Arch Intern Med, 1998. **158**(16): p. 1789-95.
11. Kroenke, K., R.L. Spitzer, and J.B. Williams, *The Patient Health Questionnaire-2: validity of a two-item depression screener.* Med Care, 2003. **41**(11): p. 1284-92.
12. Hyland, A., et al., *Predictors of cessation in a cohort of current and former smokers followed over 13 years.* Nicotine Tob Res, 2004. **6 Suppl 3**: p. S363-9.
13. Zirakzadeh, A., et al., *Cigarette smoking in methadone maintained patients: an up-to-date review.* Curr Drug Abuse Rev, 2013. **6**(1): p. 77-84.