An investigation into problem benzodiazepine use among individuals with a prescription

Miriam C. Fenton

Submitted in partial fulfillment of the
requirements for the degree of
Doctor of Philosophy
under the Executive Committee
of the Graduate School of Arts and Sciences

COLUMBIA UNIVERSITY
2015

ABSTRACT

An investigation into problem benzodiazepine use among individuals with a prescription

Miriam C. Fenton

In recent years, problem use of classified prescription drugs in the United States has become a critical public health concern garnering increased attention and resources[1-4]. Although the focus has primarily been on problem use of prescription drugs with the highest abuse potential, evidence of the increasing prevalence and growing burden of problem benzodiazepine use in the United States is mounting. Most epidemiological research on problem prescription drug use, including benzodiazepines, has focused on use among individuals without a prescription[5-9]. However, problem use also includes use with a prescription, but in ways, or for reasons, not recommended by a doctor[1,2]. Of particular importance are individuals with a benzodiazepine prescription who experience clinically significant impairment or distress as a result of using their prescription in problematic ways. Several prescription-related risk factors could increase the risk of problem benzodiazepine use among individuals prescribed benzodiazepines. These include characteristics of the benzodiazepines prescribed (including dosage and abuse liability of the prescribed benzodiazepine), the amount of benzodiazepine prescribed over time (including medication possession ratio [i.e. whether the benzodiazepine recipient has more medication than is medically necessary] and days supply of medication) and prescription contextual variables (including whether the prescription recipient also receives other controlled substances and utilizes psychotherapeutic services). In addition, characteristics of the benzodiazepine prescription recipient (including alcohol disorders, drug disorders, anxiety disorders and mood disorders) could also predict problem benzodiazepine use. This dissertation aims to consider the independent and joint roles of these factors in the risk of problem benzodiazepine use among individuals with a prescription. To this end, the current dissertation consists of three parts: a systematic literature review and two analytic research papers investigating risk factors for the development of problem benzodiazepine use, using prospective individual-level medical and pharmacy claims information in the 2003-2004 *Thompson Reuters MarketScan® Commercial Claims Databases*. Modifiable variables including prescription characteristics, the amount of benzodiazepine

prescribed over time and prescription contextual factors independently increased the risk of problem benzodiazepine use among individuals with a prescription. Psychiatric disorders, for which benzodiazepines are indicated (alcohol and anxiety disorders), or used off-label (drug and mood disorders), independently increased the risk of problem benzodiazepine use among individuals with a prescription. Further, psychotherapy and opioid prescriptions modified the increased risk of problem benzodiazepine use conferred by an anxiety disorder. This information can be used to develop specifically targeted prevention and treatment interventions, such as surveillance systems, to address the burden of problem benzodiazepine use in the U.S.

Table of Contents

List of figures and tables iii

Acknowledgements v

Dedication v

Chapter 1. Introduction 1

Chapter 2: Risk factors for clinically significant problem benzodiazepine use: a systematic review of the literature 5

ABSTRACT 5

INTRODUCTION 6

METHODS 8

Selection of articles 8

Measures 10

Analysis 11

RESULTS 12

Prescription-related factors 12

Mental health-related factors 14

DISCUSSION 19

Chapter 3. Prescription-related risk factors for problem benzodiazepine use among individuals prescribed benzodiazepine 43

ABSTRACT 43

INTRODUCTION 44

METHODS 46

Sample and procedures 46

Measures 48

Statistical analysis 52

Results 53

Sample characteristics (Table 3.1) 53
Benzodiazepine characteristics 53
The amount of benzodiazepine prescribed over time 54
Benzodiazepine prescription contextual variables 54
Discussion 55
TABLES 63
Chapter 4. Diagnostic risk factors for problem benzodiazepine use and their relationship to prescription-related risk factors, among individuals prescribed benzodiazepines 70
ABSTRACT 70
INTRODUCTION 71
METHODS 74
Sample and procedures 74
Measures 76
Statistical analysis 80
Results 82
Sample characteristics (Table 4.1) 82
The relationship between psychiatric disorders and problem benzodiazepine use (Tables 4.2 and 4.3) 82
Additive interaction results for psychiatric disorders and prescription related characteristics (Table 4.4) 83
Discussion 84
TABLES 91
Chapter 5. Conclusions 95
References 102
Appendices 112

List of figures and tables

Chapter	Figure number	Figure Title	Page
2	2.1	Flow of publications selected for review	26

Chapter	Table number	Table Title	Page
2	2.1	Description of studies included in the systematic literature review	27
	2.2	Psychometric assessment tools	28
	2.3	The relationship between a prescription and clinically significant problem benzodiazepine use	29
	2.4	The relationship between prescription dosage and clinically significant problem benzodiazepine use	30
	2.5	The relationship between provider type and clinically significant problem benzodiazepine use	31
	2.6	The relationship between provider type and clinically significant problem benzodiazepine use	32
	2.7	The relationship between alcohol disorders and clinically significant problem benzodiazepine use	33
	2.8	The relationship between drug disorders and clinically significant problem benzodiazepine use	34
	2.9	The relationship between anxiety and clinically significant problem benzodiazepine use	35
	2.10	The relationship between panic and clinically significant problem benzodiazepine use	36
	2.11	The relationship between lifetime specific phobia and clinically significant problem benzodiazepine use	37
	2.12	The relationship between social phobia and clinically significant problem benzodiazepine use	38
	2.13	The relationship between generalized anxiety and clinically significant problem benzodiazepine use	39
	2.14	The relationship between depression and clinically significant problem benzodiazepine use	40
	2.15	The relationship between mania and clinically significant problem benzodiazepine use	41

Chapter	Table number	Table Title	Page
3	3.1	Sample characteristics	62
	3.2	Benzodiazepine characteristics: frequencies	63
	3.3	Benzodiazepine characteristics: logistic regression results	64
	3.4	The amount of benzodiazepine prescribed: frequencies	65
	3.5	The amount of benzodiazepine prescribed: logistic regression results	66
	3.6	Benzodiazepine prescription contextual variables: frequencies	67
	3.7	Benzodiazepine prescription contextual variables: logistic regression results	68
4	4.1	Sample characteristics and their relationship to the outcome and predictors	92
	4.2	Frequencies for psychiatric disorders	93
	4.3	Logistic regression results for the relationship between psychiatric disorders and problem benzodiazepine use	94
	4.4	The amount of benzodiazepine prescribed: frequencies	95

Acknowledgements

First, I want to express my gratitude and appreciation for Sharon Schwartz, my academic advisor and dissertation sponsor, for her endless hours of help, support and guidance. This would not be possible without her. I am also extremely grateful to my reader, and unofficial co-sponsor, Mark Olfson who encouraged and helped me to shape my concept from inception to completion. I also want to thank the other members of my dissertation committee- Debbie Hasin for her valuable input as committee chair (and for her excellent training throughout the program!), and Silvia Martins and Melanie Wall for their very helpful feedback.

Next, I would like to thank Truven Health for providing me with access to the MarketScan data through the dissertation support program.

Lastly, I would like to thank Howard Chilcoat at Purdue Pharmaceuticals for his support and guidance with this project, and encouragement for future ideas and collaborations. Also in his team at Purdue Pharmaceuticals, I thank Aditi Kadakia and Venkatesh Harikrishnan, for their invaluable assistance with MarketScan and extreme patience answering my many questions. Without them I would probably still be writing my program!

Dedication

This dissertation is dedicated for my father for his unconditional love and support. I owe him everything.

Chapter 1. Introduction

Benzodiazepines have great clinical utility in the treatment of anxiety[10-12] and other disorders[12,13], and are widely prescribed in the United States[12,14]. Despite their accepted medical use, benzodiazepines are classified as Schedule IV controlled substances in The Controlled Substance Act of 1970[15,16]. This classification recognizes their modest, but clinically significant, abuse profile and risk of dependence[10,11,17].

In recent years, problem use of classified prescription drugs in the United States has become a critical public health concern garnering increased attention and resources[1-4]. Although the focus has primarily been on problem use of prescription drugs with the highest abuse potential, such as prescription opioids (Schedule II and III) and stimulants (Schedule II), evidence of the increasing prevalence and growing burden of problem benzodiazepine use in the United States is mounting. For example, there were over 400,000 emergency department visits in 2010 related to problem benzodiazepine use, which represents a 139% increase from 2004[10]. Further, approximately 60,000 substance use treatment admissions in 2008 were related to benzodiazepines- a 246% increase from 1998[18]. Such data is concerning, and establishes problem benzodiazepine use as an important public health problem warranting additional research attention[1-4].

Most epidemiological research on problem prescription drug use, including benzodiazepines, has focused on use among individuals without a prescription[5-9]. However, problem use also includes use with a prescription, but in ways, or for reasons, not recommended by a doctor[1,2]. Of particular importance are individuals with a benzodiazepine prescription who experience clinically significant impairment or distress as a result of using their prescription in problematic ways. In a clinical scenario, evidence of such problematic use could include a diagnosis of benzodiazepine abuse or dependence, or benzodiazepine-related poisoning. Accordingly, the present dissertation concerns clinically significant problem benzodiazepine use, including abuse, dependence or poisoning, among individuals prescribed benzodiazepines. Note that this definition focuses on harms related to benzodiazepines as drugs of

abuse, rather than other harms associated with medical use such as hip fractures, other falls and injuries and cognitive impairment.

Evidence that individuals with a prescription for benzodiazepines may have an increased risk of problem benzodiazepine use, comes from several sour\ces[3,19-23]. First, ecological studies suggest that increases in the prevalence and burden of problem benzodiazepine use over time correspond with increases in prescription rates[24,25]. Second, individual-level epidemiological surveys report that some problem benzodiazepine users obtain their medication from a legitimate prescription[21,26]. Third, there is considerable problem benzodiazepine use among individuals with a benzodiazepine prescription[27,28]. Fourth, benzodiazepine prescription and problem benzodiazepine use have been associated at an individual level[3,22,29]. Taken together, these studies suggest that individuals with a benzodiazepine prescription may be particularly vulnerable to problem benzodiazepine use.

An important reason to consider how a benzodiazepine prescription may be related to the development of problem benzodiazepine use is the modifiable nature of prescription practices. Clinicians can choose what is prescribed (e.g. the specific type of benzodiazepine), how it is prescribed (e.g. what other controlled medication the patient also receives) and to whom it is prescribed. These choices open up possibilities for interventions designed to reduce problem benzodiazepine use among individuals prescribed benzodiazepines. The modifiable nature of a prescription is particularly important since other risk factors that have been identified for problem benzodiazepine use, such as sex, race, age and psychiatric history[1,9], are non-modifiable. Given this, obtaining information on problem benzodiazepine use with a prescription could be an important step toward the development of effective targeted evidence-based prevention and treatment interventions.

Several prescription-related risk factors could increase the risk of problem benzodiazepine use among individuals prescribed benzodiazepines. These include characteristics of the benzodiazepines prescribed (including dosage and abuse liability as determined by the type, half-life, clinical onset and potency of the prescribed benzodiazepine), the amount of benzodiazepine prescribed over time (including medication

possession ratio [i.e. whether the benzodiazepine recipient has more medication than is medically necessary] and days' supply of medication) and prescription contextual variables (including whether the prescription recipient also receives other controlled substances and utilizes psychotherapeutic services). In addition, characteristics of the benzodiazepine prescription recipient (including alcohol disorders, drug disorders, anxiety disorders and mood disorders) could also predict problem benzodiazepine use. This dissertation aims to consider the independent and joint roles of these factors in the risk of problem benzodiazepine use among individuals with a prescription.

To this end, the current dissertation consists of three parts: a systematic literature review and two analytic research papers investigating risk factors for the development of problem benzodiazepine use. First, the systematic literature review was conducted to synthesize and systematically assess the published literature on the distribution and determinants of problem benzodiazepine use. Note that in this chapter, the outcome of interest, problem benzodiazepine use that causes clinically significant impairment as evidenced by abuse, dependence or poisoning, will specifically be referred to as "clinically significant problem use", which is in contrast to the rest of the dissertation in which the more simple term "problem use" will be employed. The purpose of this is to distinguish our clinically significant outcome of interest from broader definitions of problem use in the literature which might encompass non-clinically significant outcomes such as one-time recreational use with no serious consequences. Two analytic chapters will follow the systematic review. These were written to evaluate the independent and joint roles of risk factors relating to the benzodiazepine prescription and prescription recipient, in the development of problem benzodiazepine use. Using prospective individual-level medical and pharmacy claims information in the 2003-2004 *Thompson Reuters MarketScan® Commercial Claims Databases*, Chapter 3 considers whether the risk of problem benzodiazepine use among individuals with a prescription can be predicted by benzodiazepine characteristics, indicators of the amount of benzodiazepine prescribed over time, and prescription contextual factors, such as concurrent prescription of other controlled substances. In Chapter 4, we used these data to determine the independent role of prescription recipient characteristics in the development of problem benzodiazepine use, and to identify interactions between these prescription recipient characteristics and benzodiazepine-related risk factors identified in Chapter 3. Finally, an

integration and discussion of the findings is provided in Chapter 5. This dissertation aims to provide information on risk factors for problem benzodiazepine use among individuals with a prescription that can be utilized by individual clinicians or within the context of a public health intervention, to reduce the burden of problem benzodiazepine use.

Chapter 2: Risk factors for clinically significant problem benzodiazepine use: a systematic review of the literature

ABSTRACT

Background: Despite their great clinical utility and widespread medical use, benzodiazepines have come into the spotlight in recent years due to concerns regarding the increasing prevalence and growing burden of clinically significant problem use. The development of interventions designed to reduce problem benzodiazepine use requires information on modifiable risk factors for such problem use. *Purpose:* To this end, this paper systematically reviews and evaluates the literature on risk factors for clinically significant problem benzodiazepine use, specifically considering potentially modifiable risk factors including prescription and mental health-related variables. *Data Sources:* PubMed, Psychinfo and Scopus were searched for English-language publications between January 1993 and December 2003. Search terms included 45 combinations of 9 problem use-related keywords (problem use; nonmedical use; misuse; abuse; dependence; use disorders; addiction; overdose; poisoning) and 5 benzodiazepine-related keywords (benzodiazepine; tranquilizer; hypnotic; anxiety medication; anxiolytic). *Study selection:* Observational and experimental study designs that included a clinically significant problem benzodiazepine use-related outcome and tested the individual-level effects of at least one potential prescription or mental health-related risk factor were included in the review. *Data extraction:* All data extraction was conducted by the author. *Data synthesis:* Since insufficient data were available to conduct typical analyses for systematic reviews, such as metaanalysis, we employed a more narrative approach utilizing frequencies of study and test characteristics. *Results:* Ten publications were included in the review- 3 used large datasets of nationally representative US-based epidemiological surveillance data, 2 were conducted among patients prescribed benzodiazepines, 2 were conducted among patients with opioid disorders, 1 was conducted among patients with alcohol use disorders and 1 was conducted among patients with severe mental illness and comorbid substance use disorders[22]. We evaluated findings from these 10 studies for five modifiable prescription-related variables (having a prescription, half-life, dosage, length, provider type) and five mental health-related variables (alcohol disorders, drug disorders, anxiety disorders, mood disorders and mental health treatment). The characteristics most strongly and consistently associated problem benzodiazepine use were having a benzodiazepine

prescription, benzodiazepine dosage and prescription length, lifetime drug use, anxiety and mood disorders. Conclusions: The literature provides evidence to suggest a role of prescription and mental health-related risk factors in clinically significant problem benzodiazepine use. However, all of these studies are subject to methodological limitations that hinder interpretation. Most notably, temporality can only be established in one study, rendering reverse causation a possible explanation for most of the reported findings. Future work could address limitations of the included studies to consider, in a methodologically robust manner, the way in which the identified potential risk factors may influence the risk of clinically significant problem benzodiazepine use.

INTRODUCTION

The increasing prevalence and growing burden of problem use of controlled prescription drugs in the United States have raised concerns in recent years[1-4]. When used as prescribed, these prescription drugs can be highly effective clinical agents for the treatment of many medical problems[10-13]. However, problem use of these medications, (i.e. use without a prescription, or in ways or for reasons not recommended by a doctor) can cause serious, potentially fatal health consequences. Benzodiazepines represent one such class of abusable controlled prescription medication.

Benzodiazepines are effective anxiolytic and hypnotic medications which became widely available in the 1960s and have since been prescribed to hundreds of millions of people[30]. Benzodiazepines initially became a popular pharmacotherapeutic approach to the treatment of anxiety due to their rapid onset with low toxicity, desirable therapeutic actions and favorable side effect profile compared with older anxiolytic medications such as barbiturates[30]. Their continued widespread use as therapeutic agents, particularly in the treatment of acute anxiety, can be explained by similar efficacy but much faster onset of action than newer anxiolytics such as SSRIs[31]. Indeed, benzodiazepine prescriptions in the United States currently estimated to exceed 112 million annually[32].

Despite this widespread use, since their introduction there have been concerns that these compounds are overprescribed and have a potential for abuse and dependence. Following results from epidemiological

surveys indicating problematic use of benzodiazepines in the population, and laboratory studies demonstrating that regular, long-term use of therapeutic doses of benzodiazepines can produce physical dependence and withdrawal, legislation to regulate their prescribing was enacted[30]. At present, all benzodiazepines are included in the US Controlled Substances Act indicating the potential for, and danger of, problem use[16].

Of particular concern is the burden of clinically significant problem benzodiazepine use. That is, use that has a genuine noticeable impairing effect on an individuals' daily life. As mentioned in chapter 1, in a clinical scenario, evidence of such problematic use could include a diagnosis of benzodiazepine abuse or dependence, or benzodiazepine-related poisoning. Such clinically significant problem benzodiazepine use has been increasing at an alarming rate in recent years [1-4]. For example, data from the Drug Abuse Warning Network indicates that there were over 400,000 emergency department visits in 2010 resulting from the misuse of benzodiazepines- a 139% increase from 2004[10]. Further, the number of benzodiazepine unintentional drug overdose deaths in the US has increased in recent years from fewer than 300 in 1999 to 6,497 in 2010[33]. In addition, data from the Treatment Episodes Data Sets indicates that benzodiazepines were reported as a drug of abuse by approximately 60,000 treatment admissions in 2008- a 246% increase from 1998[18]. Note that these figures include benzodiazepine use in conjunction with other substances. Prevention and treatment of clinically significant problem benzodiazepine use in the population requires identification of high risk groups.

Individuals prescribed benzodiazepines may be at a particularly high risk of clinically significant problem benzodiazepine use. For example, in an examination of medical and surveillance records, between 46% and 80%- depending on the specific benzodiazepine- of individuals involved in fatal benzodiazepine-related overdoses had a prescription for that benzodiazepine[34]. The development of interventions designed to reduce problem benzodiazepine use among individuals with a prescription requires information on modifiable risk factors for clinically significant problem benzodiazepine use. This includes prescription-related characteristics (having a prescription and benzodiazepine characteristics such as

half-life, dosage and length, provider type) and mental health-related variables (prior or current alcohol disorders, drug disorders, anxiety disorders, mood disorders and mental health treatment).

To address the need for this type of information, this paper systematically reviews and evaluates the literature on risk factors for clinically significant problem benzodiazepine use. Specifically, we consider potentially modifiable risk factors including prescription and mental health-related variables. Of note, to ensure a thorough and comprehensive understanding of the potential role of these risk factors in clinically significant problem benzodiazepine use, when appropriate, our investigation will not be limited to individuals prescribed benzodiazepines. However, between-study sample differences will be accounted for, as will other methodological variations including measurement and analytic approaches.

METHODS

Selection of articles

Articles were identified through searches of three electronic databases for peer-reviewed published papers: PubMed, PsychInfo and Scopus. Search terms were selected based on two important terminological issues. First, problem use is nonspecific and lends itself to a broad range of interpretations including the use of prescription medication without a prescription, using one's own prescription in a way, or for a reason that is not intended by the prescriber, a diagnosis of a benzodiazepine use disorder (abuse/dependence) and overdose. The terms nonmedical use[1-3,9,35-38], misuse[8,37-40], abuse[37-40], dependence, benzodiazepine use disorder[3,22], problem use, addiction and overdose/poisoning, are used interchangeably and inconsistently in the literature to refer to any or all of these phenomena. Second, while some studies may consider benzodiazepines specifically[9,41], others may consider benzodiazepines in a composite variable described as "tranquilizer", "hypnotic", "anxiolytic" or "anxiety medication" [3,6,7,42]. To address these issues we searched the 45 combinations of 9 problem use-related keywords (problem use; nonmedical use; misuse; abuse; dependence; use disorders; addiction; overdose; poisoning) and 5 benzodiazepine-related keywords (benzodiazepine; tranquilizer; hypnotic; anxiety medication; anxiolytic).

Inclusion criteria: Inclusion criteria were: (1) original peer-reviewed research report (i.e. no case studies, review articles, letters or editorials); (2) written in the English language; (3) published in the last 20 years (i.e. from 1993-2013); (4) includes a clinically significant problem benzodiazepine use-related outcome (e.g. abuse, dependence, addiction, overdose or poisoning of benzodiazepines, tranquilizers, hypnotics, anxiety medication or anxiolytics); (5) tests the individual-level effects of at least one potential prescription (having a prescription and benzodiazepine characteristics such as half-life, dosage and length, provider type) or mental health-related risk factor (alcohol disorders, drug disorders, anxiety disorders, mood disorders and mental health treatment).

Article refinement *(Figure 2.1):* The process of article refinement for inclusion in the present systematic review is provided in figure 1.1. In brief, electronic database searches yielded 650 total and 556 unique results that were then screened for relevance. This resulted in an initial set of 86 articles. We then reviewed abstracts from these 86 articles and identified 29 articles that could meet inclusion criteria. The full text of these 29 articles was then reviewed for eligibility. Of these manuscripts, 19 were considered ineligible including 12 that did not consider clinically significant problem benzodiazepine use as an outcome[9,27,43-52], 6 that did not test for the effects of at least one potential prescription or mental health-related risk factor[28,41,53-56], and 1 that was not conducted at the individual-level[57]. Therefore the final number of papers included in the systematic review is 10. Information on study design, sample, and outcome and predictor measures for these 10 studies is provided in Table 2.1 below.

Sample description: Studies eligible for inclusion include those conducted in non-clinical (e.g. general population, community, college, adolescent) and clinical (e.g. treatment, health records) samples. All studies included in the review utilized an observational study design. The majority of studies were cross-sectional[1,3,56,58-62], rendering reverse causation a serious methodological threat. We also included one prospective study[22], but since the authors did not indicate whether individuals with the outcome at baseline were excluded, temporality cannot be established. In fact, only one of the studies included can establish temporality between the exposure and outcome- namely a matched case-control study that

considered the role of a prescription in fatal overdoses[29]. In this instance it would be impossible for the outcome to precede the predictor.

Measures

Clinically significant problem benzodiazepine use definition: Studies included in this review are limited to those that considered clinically significant problem use as an outcome. We defined this *a priori* as a measure indicating clinically significant problem use such as benzodiazepine abuse, dependence, poisoning or overdose. For more information on specific outcomes refer to Table 2.1. The majority of studies (N=8) measured a benzodiazepine use disorder according to established diagnostic criteria[1,3,22,56,58,59,61-63]. In addition, we included 1 study that measured fatal overdose[29] and one that measured benzodiazepine dependence based on the need for benzodiazepine detoxification[60], a reasonable indicator of clinically significant problematic use.

Of the eight studies that measured diagnoses of benzodiazepine abuse or dependence, six utilized a structured interview[1,3,22,58,59,63] while two utilized a semi-structured interview[61,62]. Detailed information on specific tools are provided in Table 2.2. For the purposes of creating standardized diagnostic measures, a structured interview is preferable to a semi-structured interview which relies more on clinical judgment which can create less psychometrically sound measures. This should be considered when interpreting results from De las Cuevas et al., [62] and Kan et al., [61] who both utilized semi-structured interviews. Indeed, in De las Cuevas et al., [62] the authors indicate that:

> "The SDS scale is not good enough in separating, differentiating, the "real" addiction (according to DSM IV criteria) (APA 1994) from the need of chronic treatment due to a chronic condition, like diabetes, or in this case anxiety[62]".

Dealing with multiple outcomes: Three studies[3,29,61] included multiple outcome measures of clinically significant problem benzodiazepine use. Each of these outcomes is presented and evaluated separately.

Composite outcome variables: Although we excluded studies that only considered a composite prescription drug variable that could have included unrelated drug classes such as stimulants, we included 1 population-based study conducted in 2001-2[1] that considered a composite tranquilizer outcome and 4 studies (including 2 population-based studies conducted in 2001-2[3] and 2002-4 [58], a case-control electronic medical record study conducted in 2006-8[29] and 1 clinical study (date not available) [63]) that considered a composite tranquilizer/sedative outcome. An assumption that the study using a composite tranquilizer variable primarily measures benzodiazepines is reasonable, since respondents are asked about "*tranquilizers or anti-anxiety drugs, for example Valium, Librium, muscle relaxants or Xanax*". The three specific examples given (Valium, Librium and Xanax) are all benzodiazepines, and muscle-relaxants could also refer to benzodiazepines. However composite tranquilizer/sedative variables will be less specific since they will also include sedatives such as sleeping pills and barbiturates. This will be considered when interpreting results. Of note, data from a 1979 National Household survey indicated that benzodiazepines accounted for 84% of problem sedative/tranquilizer use in the U.S. population[64]. However, to the best of our knowledge, more recent data on this topic has not been published.

Risk factors: Five modifiable prescription-related variables (having a prescription, half-life, dosage, length, provider type, and five mental health-related variables (alcohol disorders, drug disorders, anxiety disorders, mood disorders and mental health treatment) were included. Detailed information on how these variables were measured is provided in Tables 2.2 to 2.14.

Analysis

The majority of studies[1,3,29,58,59,61,62] provided Odds Ratios (ORs) and corresponding 95% Confidence Intervals (95% CIs) for the association between predictors and a clinically significant problem benzodiazepine use binary outcome variable, obtained from logistic regression models adjusting for various sociodemographic and clinical variables. These results are considered the most reliable and will be the main focus of the present paper.

Three of the studies that considered prescription-related risk factors [22,29,62] and two studies that considered mental health-related risk factors[60,63] only provided information on bivariate associations for one or more risk factors. For consistency, Odds Ratios (ORs) were calculated from frequencies and are presented alongside p-values from chi-squared tests. However, since these studies did not provide any measure of the spread of the data (e.g. standard errors or standard deviations) alongside crude results, interpretation is limited. One exception is for a study that provides the crude OR and 95% CIs. In this and the aforementioned bivariate effect estimates, uncontrolled confounding could explain findings.

In two instances[59,62] the authors indicate that a risk factor had no significant effect without providing quantitative information (e.g. point estimate, confidence intervals, p values). These results will be mentioned in the text, but caution should be taken in their interpretation given the limited information provided.

RESULTS

Of the 10 studies included in the present paper, 3 used large datasets of nationally representative US-based epidemiological surveillance data[1,3,58], 2 were conducted among patients prescribed benzodiazepines[61,62], 2 were conducted among patients with opioid disorders[59,60], 1 was conducted among patients with alcohol use disorders[63] and 1 was conducted among patients with severe mental illness and comorbid substance use disorders[22]. We evaluated findings from these 10 studies for five modifiable prescription-related variables (having a prescription, half-life, dosage, length, provider type) and five mental health-related variables (alcohol disorders, drug disorders, anxiety disorders, mood disorders and mental health treatment).

Prescription-related factors

Prescription (Table 2.3): The role of a prescription was considered in 1 general population[3], 1 case-control electronic medical record study, and 1 clinical[22] study. Results are consistent– having a

prescription was a strong and significant predictor of clinically significant problem benzodiazepine use. In the general population study[3], the relationship appeared stronger for DSM-IV dependence than abuse.

Half-life: One study, conducted in a sample of individuals prescribed benzodiazepines,[61] reported a strong positive association between long benzodiazepine half-life and past year DSM-III benzodiazepine dependence (OR, 2.68; 95% CI, 1.41-5.10), which is contrary to their hypothesized association. In addition, another study conducted in a sample of individuals prescribed benzodiazepines[62] reported no significant association between half-life and DSM-IV benzodiazepine dependence, but did not provide any quantitative estimates or information regarding analytic procedure.

Dosage and prescription length: Results for dosage (Table 2.4) and prescription length (Table 2.5) are similar so are presented together. These variables were considered in two studies conducted in benzodiazepine treatment samples[61,62]. Both studies report a small but significant effect of dosage (ORs range from 1.02 to 1.04, see Table 2.14) and prescription length (ORs range from 1.00 to 1.01, see Table 2.15) on benzodiazepine dependence[61]. One of these studies[61] indicates that these "significant associations….were nevertheless too small (odds ratios approaching 1.0) to be clinically relevant.[61]". However, since the exposures are continuous variables the parameter represents the effect for each unit so the small ORs presented could in fact be indicative of larger effects. For example, in De Las Cuevas et al.[62], the OR presented for a 1mg increase in dosage is 1.04 (Table 2.4). This would mean that a difference of 10mg would be 1.48. With regards to prescription length, De Las Cuevas et al.[62], indicate that the OR for a 1 month increase is 1.01. This would mean that a difference of 18 months would be 1.20. Therefore it would seem that both dosage and prescription length may have a modest effect on benzodiazepine dependence.

Provider Type (Table 2.6): The two studies conducted in the benzodiazepine prescription samples[61,62] provided information on the relationship between provider type (psychiatrist vs. other) and benzodiazepine dependence. In one of these studies[61] the relationship was considered for DSM-III and ICD-10 dependence in a multivariable logistic regression model controlling for demographics, prescription

factors and psychiatric disorders. Results for both diagnostic approaches were similar. Effect estimates were small but above the null (1.45 and 1.57), but 95% CIs either crossed or included 1. In the other study[62] a strong and significant association was reported, however analyses were bivariate suggesting that findings could be explained by uncontrolled confounding.

Mental health-related factors

Alcohol disorders (Table 2.7): Two studies, both conducted in the adult U.S. general population, considered the role of DSM-IV alcohol abuse or dependence diagnoses in the risk of clinically significant problem benzodiazepine use[1,58]. Results are markedly different. Huang et al.,[1] found a very strong significant positive association while Becker et al.,[58] found an inverse, non-significant association.

It is unlikely that this difference is the result of Becker et al[58] controlling for psychiatric disorders, since the crude association (OR, 0.6; 95% CI, 0.3-1.3) in this study is almost identical to the adjusted association (OR, 0.6; 95% CI, 0.3-1.4). It is also unlikely to be explained by study date since both studies were conducted close to each other (2001-2[1] compared with 2002-3[58]). Becker et al[58] used a composite sedative/tranquilizer outcome variable, while Huang et al.,[1] used a composite tranquilizer variable. However, this is unlikely to explain the difference since Huang et al.,[1] found that the association between alcohol disorders and sedative abuse or dependence (OR, 13.4; 95% CI, 9.39-19.20) is similar to the association between alcohol disorders and tranquilizer abuse or /dependence (OR14.2; 95% CI, 9.56-21.08).

However there are some possible methodological explanations for discrepancies. First the timeframe of the exposure and outcome was lifetime for Huang et al.,[1] and past year for Becker et al.,[58]. Since Huang found an association and Becker did not, an association between lifetime alcohol and lifetime problem benzodiazepine use, but not between past year alcohol and past year problem alcohol use, is possible. Further, although both studies were conducted in representative U.S. samples, Huang et al.,[1] used the full sample while Becker et al.,[58] limited analyses to past year problem users of the outcome (i.e. problem sedative/tranquilizer users). That is, Becker et al., considered past year sedative/tranquilizer abuse and

dependence, among individuals who had engaged in any past year problem sedative/tranquilizer use. It is possible that the relationship between alcohol and problem use differs in these samples. Of note, it is interesting that although Becker et al.,[58] found an inverse relationship for alcohol disorders and sedative/tranquilizer abuse/dependence, they found a modest positive relationship for alcohol disorders and any problem sedative/tranquilizer use (OR, 1.6; 95% CI, 1.1-2.2).

Drug disorders (Table 2.8): One general population[1] and one clinical[59] study considered the relationship between lifetime drug disorders and lifetime clinically significant problem benzodiazepine use. Results are consistent with regard to direction and significance, but vary with magnitude. Specifically, Huang et al., [1] found extremely large effect estimates for other lifetime prescription drug disorders and lifetime illicit drug disorders (ORs 54.8 and 184), while Ross and Darke[59] found a strong, but less extreme association for number of lifetime drug dependencies (OR, 2.56). Huang et al., [1] do not speculate as to possible methodological explanations for such large ORs, but it is possible that estimates could be inflated by sparse cells and violation of model assumptions such as off-support inference (i.e. the regression line is created with gaps due to missing data points to support some of the association)[65].

Anxiety disorders: Table 2.9 provides information on anxiety disorders and clinically significant problem benzodiazepine use. In brief, an adult general population study[1] and two substance disorder samples[59,63] found a strong and significant association between a lifetime anxiety disorder and clinically significant problem benzodiazepine use. Conversely, a study conducted by Kan et al.,[61] in a sample of individuals with a benzodiazepine prescription found no association between current anxiety and benzodiazepine dependence. One possible explanation is the use of a current timeframe for the anxiety measure which is in contrast to the other studies that utilized lifetime anxiety measures. Perhaps the role of past year anxiety in clinically significant problem benzodiazepine use is different to the role of lifetime anxiety. However, it could also be due to the anxiety measure which consisted of a sum score for the anxiety scale from the SCL-90. This is in contrast to the other studies that considered binary diagnostic variables (e.g. diagnosis of an anxiety disorder vs no diagnosis of an anxiety disorder). Further, it is important to note that Kan et al.,[61] utilize a semi-structured diagnostic approach in contrast to the other studies that

considered anxiety which utilize a structured, psychometrically favorable, diagnostic tool (see Table 2.2. and corresponding text in the methods section). Therefore the null findings in the Kan[61] study could be an artifact of measurement error.

Further, it is possible that the results represent a true difference in the association between anxiety and benzodiazepine prescription for individuals prescribed benzodiazepines.

Of note, although Ross and Darke[59] found a significant crude relationship between lifetime anxiety disorders and benzodiazepine dependence, they found no association between the number of lifetime anxiety disorders, controlling for various demographic, benzodiazepine use and psychiatric characteristics. The authors do not provide quantitative information on the effect estimate so it is not possible to determine whether the lack of significance is a power issue. However another plausible explanation is that some of the variables that were controlled for (frequency of benzodiazepine use, benzodiazepine administration, age of initiation) could have been mediators rather than confounders. This is frequently an issue when temporality cannot be established.

In addition to these findings for anxiety disorders in general, some of the studies included in the systematic review also considered the association between specific anxiety disorders and clinically significant problem benzodiazepine use. This includes panic disorder (Table 2.10), specific phobia (Table 2.11), social phobia (Table 2.12) and generalized anxiety (Table 2.13). Results for all these disorders are similar and consistent with results reported for anxiety disorders in general. Namely that studies considering lifetime predictors report estimates above the null, while the study that considered past year predictors and outcome reported no effect of panic disorder (Table 1.10), social phobia symptoms (Table 2.12) or generalized anxiety (Table 2.13)[58]. This could indicate that the relationship between anxiety and clinically significant problem benzodiazepine use depends on the timeframe of these disorders.

Another possible methodological explanation is a sample-dependent association. Becker et al.,[58] only considered the relationships among past year problem sedative/tranquilizer users suggesting that the role

of these anxiety disorders in clinically significant problem benzodiazepine use may be different for problem benzodiazepine users, than for other samples. In support of this theory, Becker et al.,[58] did find a small but significant association between past year panic and any past year problem sedative/tranquilizer use in the full general population sample (OR, 1.3; 95% CI, 1.0-1.6). However, there was no effect of past year social phobia symptoms (OR, 1.2; 95% CI, 0.9-1.6) or generalized anxiety (OR, 1.1; 95% CI, 0.8-1.5) on any past year problem sedative/tranquilizer use in the full general population sample.

Becker et al.,[58] also differed from the other studies in their use of a combined sedative/tranquilizer variable. It is possible that the different results could be explained by of the inclusion of clinically significant problem sedative use in the outcome variable. However, this seems unlikely since Huang et al.,[1] found that the effect of lifetime panic, social phobia and generalized anxiety on lifetime sedative abuse/dependence, was similar to their effect on lifetime tranquilizer abuse/dependence. For example, for Huang et al.,[1] for panic with agoraphobia ORs were 4.2 (95% CI, 2.94-6.01) for sedatives and 3.8 (95% CI, 2.69-5.43) for tranquilizers. Of note, Becker et al.,[58] did find an association between past year agoraphobia symptoms and clinically significant problem use (OR, 2.0; 95% CI, 1.1-3.7). Since they do not indicate how agoraphobia was handled in their panic disorder variable[58], the meaning of the difference between effect estimates for panic and agoraphobia is unclear.

Mood disorders: Results for mood disorders are similar to results for anxiety disorders. That is there appears to be an effect of lifetime, but not past year, mood disorders on clinically significant problem benzodiazepine use.

Results for depression are presented in Table 2.14. Four studies[1,58-60], reported effect estimates above the null (adjusted ORs ranged from 1.7[58] to 3.4[1]). Only one of these four studies- an analysis of an adult general U.S. population sample by Becker et al.,[58]- failed to reach significance at the 0.05 level. In addition, the magnitude of the effect estimate was lower for this study than for the other studies. One possible explanation for this is that Becker et al.,[58] considered past year depression, while the other studies considered lifetime depression. It is possible that the association failed to reach significance due

to fewer people reporting past year depression, and it is also possible that there is a stronger association for lifetime depression than for past year depression. Another possible explanation is that this study considered a combined tranquilizer/sedative outcome, and it is possible that the relationship between mood disorders and clinically significant problem use may be specific to benzodiazepines. However, this seems an unlikely explanation since Huang et al., report similar results for the role of major depressive episode in sedative (OR, 2.4; 95% CI, 1.73-3.40) and tranquilizer (OR, 2.4; 95% CI, 1.69-3.28) abuse/dependence. Additionally, Becker et al.,[58] only considered the association among past year problem users, and it is possible that the role of depression in clinically significant problem benzodiazepine use may be different for these individuals. However, evidence against this theory is that Becker et al., [58] reported null findings for the relationship between past year major depressive episode and past year problem sedative/tranquilizer use in the full sample (OR, 1.2; 95% CI, 1.0-1.6).

Kan et al., conducted in a benzodiazepine prescription sample[61], found no association between past year benzodiazepine dependence and current depression score. This could be due to the depression measure which consisted of a sum score for the depression scale from the SCL-90. This is in contrast to the other studies[1,58-60] that considered binary diagnostic variables (e.g. diagnosis of major depression vs no diagnosis of major depression). Further, as was case with anxiety, the null finding reported by Kan,[61] could be an artifact of measurement error since this study utilized a semi-structured diagnostic interview, whereas the studies that found a depression-benzodiazepine association[1,58-60] utilized a structured diagnostic tool which provides more robust estimates.

It is also possible that the relationship between mood disorders and clinically significant benzodiazepine use differs for individuals prescribed benzodiazepines. Of note, similar to the case of anxiety disorders, Ross and Darke[59] found a significant crude relationship for lifetime major depression and dysthymia but no association between the number of lifetime depressive disorders, controlling for various demographic, benzodiazepine use and psychiatric characteristics. Again, no quantitative information is provided. Issues regarding power and possible control for mediators discussed in the anxiety disorder section also apply here.

With regards to mania (Table 2.15) Huang et al.,[1] found a strong and significant association for lifetime bipolar I and II, while Becker et al.,[58] found no association for past year mania. Explanations posited above (e.g. diagnostic timeframe, sample) could also apply here. As was the case with depression, Huang et al.,[1] present similar effect estimates for tranquilizers and sedatives, therefore the use of the combined sedative/tranquilizer variables in Becker et al.,[58] is unlikely to explain the different results in these two studies. For example, for Bipolar I, Huang et al.,[1] reports an OR of 5.9 (95% CI, 4.23-8.34) for sedatives and an OR of 5.5 (3.94-7.65) for tranquilizers.

In addition to results presented above, one other study considered mood disorders, but did not distinguish between depression and mania. Specifically, Ross et al.,[63] report that a lifetime mood disorder was not significantly associated with current DSM-III sedative/ tranquilizer abuse/dependence among patients with alcohol disorders without antisocial personality disorders in crude analyses (OR, 1.80; p>0.05).

Mental health treatment: One study[58] conducted in the general population considered mental health treatment. In this study, seeing a clinician for a mental health issue (OR, 2.1; 95% CI, 0.9-4.6) in the past year did not significantly predict past year clinically significant problem sedative/tranquilizer use among past year problem users, adjusting for demographic and psychiatric variables. Note that such wide confidence intervals reduce interpretability of the parameter.

DISCUSSION

To our knowledge, this is the first systematic review of the literature on modifiable risk factors for clinically significant problem benzodiazepine use. Despite concerns regarding the growing prevalence and burden of this problem benzodiazepine use in recent years[1-4], we found only a small number of peer reviewed papers in this area. Indeed, extensive literature searches across multiple electronic databases yielded only ten peer-reviewed studies that provide information on possible modifiable prescription and mental health-related risk factors for clinically significant problem benzodiazepine use. All of these studies are subject to methodological limitations that hinder interpretation. Most notably, temporality can only be established in one study[29], rendering reverse causation a possible explanation for most of the reported

findings. Nonetheless, the information provided in these studies point to potential risk factors for clinically significant problem benzodiazepine use that require further investigation using prospective data.

Results suggest that being prescribed benzodiazepines may play an important role in the development of clinically significant problem benzodiazepine use (as opposed to the acquisition of drugs through illicit sources only). This was true for general population, medical record and clinical samples, and for lifetime and current prescription and clinically significant problem benzodiazepine use. Although we found only three individual-level studies that directly tested this association, additional evidence that individuals with a prescription for benzodiazepines may have an increased risk of problem benzodiazepine use, and therefore warrant further research attention, comes from several sources[3,19-23]. First, there is some evidence from ecological-level studies to suggest that increases in the prevalence and burden of problem benzodiazepine use over time correspond to increases in prescription rates[24,25]. Second, individual-level epidemiological surveys report that some problem benzodiazepine users obtain their medication from a legitimate prescription[21,26]. Third, there is evidence of considerable problem benzodiazepine use among individuals with a benzodiazepine prescription[27,28]. Taken together, these studies imply that simply exposing an individual to benzodiazepines via a prescription may increase their risk of engaging in problem use and developing clinically significant problem use-related outcomes including abuse, dependence and fatal overdose. Given the benefits of these drugs when used as prescribed, identifying those at risk of problem use is of especially high importance.

An important reason to consider how a benzodiazepine prescription may be related to the development of problem benzodiazepine use is its modifiable nature. For example clinicians can choose what is prescribed and how it is prescribed. These choices open up possibilities for interventions designed to reduce problem benzodiazepine use among individuals with a prescription. Given this, we systematically reviewed the literature for modifiable prescription-related factors and found data on three factors relating to the prescription itself (half-life, dosage and prescription length) and one prescription contextual variable (provider type). It is important to note that this information is derived from only 2 studies[61,62]. However, findings are fairly consistent which increases confidence in results.

One unexpected finding from this review was that that long half-life predicted benzodiazepine dependence in multivariable analyses[62]. This is contrary to the hypothesized direction- we would expect characteristics that increase the abuse liability of a medication to predict clinically significant problem benzodiazepine use. For example, self-administration research consistently demonstrates that abuse liability is highest for benzodiazepines with a short-half life[62,66,67]. Therefore we would expect a short, not long, half-life to predict clinically significant problem use. One possible reason for the observed finding is that abuse liability is also determined by other pharmacological characteristics such as potency, rapidity of clinical onset, and therapeutic period[62,66,68]. The specific role of half-life may depend on these other characteristics, suggesting the need to consider multiple indicators of abuse liability when considering how abuse liability may be related to clinically significant problem benzodiazepine use. In addition, because long-acting benzodiazepines are used primarily for anxiety and mood disorders and short-acting agents are primarily used for insomnia, it is possible some aspects of anxiety or mood disorders that are not otherwise controlled in the models explain this association. Future work should take this into consideration.

Dosage could also predict problem benzodiazepine use. Prescription of a high benzodiazepine dosage increases the reinforcing effect of the medication[68] and could increase the likelihood of clinically significant problem benzodiazepine use symptoms (e.g. tolerance and withdrawal)[17]. Similarly, long-term use of benzodiazepines increases the risk of clinically significant problem benzodiazepine use symptoms such as tolerance and withdrawal[17,29,66,68], suggesting a role of prescription length. Consistent with this rationale, two small cross-sectional studies conducted in benzodiazepine treatment samples[61,62] report modest effects of dosage and prescription length. These results suggest that factors that are in the prescribing clinicians' control could be important determinants of problematic medication use. Such information could be critical to developing interventions designed to reduce the burden of problem benzodiazepine use in the population, and should be further investigated using robust methods.

Given concerns regarding the lack of addiction training in general, and prescription drug misuse in particular, among non-specialist clinicians[69-71], clinically significant problem benzodiazepine use may be

more prevalent in non-psychiatric settings. However, results from Kan et al.,[61] and De Las Cuevas et al.,[62] indicate a moderately increased risk of clinically significant problem benzodiazepine use among individuals prescribed benzodiazepines in psychiatric settings. This could represent a true association, however it be an artifact of methodological differences. For example, results could be explained by an increased vulnerability for problem benzodiazepine use among individuals prescribed medications in a psychiatric setting (e.g. by having a higher risk generally for substance use disorders by having a history of such disorders). It is also possible that the observed psychiatrist- clinically significant problem benzodiazepine use association could be explained by the cross-sectional nature of the studies and the severity of treatment samples. That is following the development of clinically significant problem use, individuals who previously received benzodiazepine prescriptions from non-specialists may have been referred to psychiatric specialists for continued medication management. In order to clarify this matter, it is important to study the role of provider type in the development of new problem benzodiazepine use in longitudinal study designs.

In addition to understanding specific factors relating to a benzodiazepine prescription that may increase the risk of problem use, underlying vulnerabilities for problem use should also be identified so that clinicians can make informed decisions when selecting benzodiazepine prescription recipients. For example, the risk of problem benzodiazepine use may be higher for individuals with alcohol use disorders than for individuals without alcohol use disorders. Specifically, individuals with alcohol use disorders have a greater sensitivity to the reinforcing and euphoric effects of benzodiazepines than individuals without alcohol use disorders[17,72-74], and benzodiazepine receptors are implicated in the etiology of alcohol dependence[75]. Given similarities in the etiology and processes of alcohol and drug disorders, drug disorders not related to benzodiazepines may also predict clinically significant problem benzodiazepine use. As such, we reviewed the literature for information on the role of alcohol and drug disorders in clinically significant problem benzodiazepine use.

The two studies that considered drug use disorders[1,59] were consistent in reporting a strong significant association. However, one of the studies[1] that considered alcohol disorders reported a strong significant

association, while the other[58] reported a non-significant inverse association. Unfortunately, interpretation of results is limited since both studies utilize cross-sectional designs and vary in terms of sample, measures and analysis. To clarify matters, the association between alcohol and problem benzodiazepine use should be addressed in a longitudinal manner in a sample of individuals with no problem benzodiazepine use at baseline.

Understanding this relationship is not only important to help clinicians assess baseline vulnerability to clinically significant problem use among candidates for benzodiazepines, but also important because benzodiazepines are approved by the FDA for use in alcohol withdrawal[12]. If in fact baseline alcohol disorders do predict new problem benzodiazepine use, harm-reduction interventions for this specific therapeutic use may be required. This may be particularly important for the widespread clinical use of benzodiazepines in alcohol detoxification[76]. For example, clinicians could choose to supervise benzodiazepine administration for acute alcohol-related problems.

Similar to alcohol disorders, since benzodiazepines are used to treat anxiety and mood disorders[12] it is also important to understand the relationship between mood and anxiety disorders and clinically significant problem benzodiazepine use. Accordingly, we considered these disorders in our systematic literature review.

In general, studies reported that anxiety (including panic, phobias and generalized anxiety) and mood (including depressive and manic) disorders predicted clinically significant problem benzodiazepine use in population-based and clinical samples. There were two primary exceptions to this- null findings for both anxiety and mood disorders were reported among past year problem users[58] and among individuals with a prescription[61]. In addition, a study conducted in a sample of patients with opioid disorders reported associations in crude, but not multivariable, analyses[59]. Since the risk of anxiety and mood disorders use is likely to be elevated in these populations, one possible explanation is that anxiety and mood disorders may not predict clinically significant problem use in populations with a higher prevalence of anxiety and mood disorders since there may be little variation on these factors. Evidence to support this theory comes

from a general population study that found anxiety (OR, 1.15; 95% CI, 0.87-1.53) and mood (OR, 1.16; 95% CI, 0.88-1.54) disorders did not predict problem sedative or tranquilizer use among individuals prescribed anxiety medication, controlling for sociodemographics, behavioral and psychiatric variables[3]. Thus, while anxiety and mood disorders may help identify individuals vulnerable to clinically significant problem benzodiazepine use in the general population and in some clinical samples, these disorders may not be as important in populations with higher prevalence of anxiety and mood disorders. However, in the absence of longitudinal information on these relationships, all posited explanations are speculative and require consideration using more robust methods.

In addition to understanding factors that may increase the risk of clinically significant problem benzodiazepine use, identifying possible protective factors is also important. One such factor may be mental health treatment. Psychological interventions may increase the probability of benzodiazepine cessation, compared with gradual dose reduction alone, among individuals prescribed these medications[77-79]. This suggests that individuals receiving psychotherapy may use benzodiazepines for a shorter period of time than individuals not receiving therapy, which may decrease their risk of developing tolerance and other symptoms associated with problem benzodiazepine use. Further, cognitive-behavioral and other evidence-based therapies are highly effective in the treatment of anxiety disorders[78]. Patients who receive such therapy, may be less likely to rely on their prescribed medication for reduction of anxiety symptoms, and may therefore be less likely to develop problem benzodiazepine use symptoms such as tolerance. In addition, several evidence-based therapies are effective treatments for substance-related problems[80-84]. Individuals at risk of engaging in problem benzodiazepine use may address this potential problem use in therapy and therefore be less likely to manifest this behavior. Therefore mental health treatment could reduce the risk of clinically significant problem benzodiazepine use. However, results from the one study that considered this variable were not in the hypothesized direction- seeing a clinician for a mental health issue appeared to increase the risk of clinically significant problem benzodiazepine use among past year problems users in the population[58]. This could be due to a lack of control for common causes of the exposure and outcome such as a general vulnerability to substance use disorders as indicated by a history of the other drug use disorders. It could also be a temporality

issue- the problem use may have initiated the clinician visit. Further work is required to determine the true association.

Methodological issues of the studies are noted. First and most notably, almost all of the studies are unable to establish temporality, not only between the exposure and outcome, but also between covariates. This raises the possibility of reverse causation, and control for mediators rather than confounders. To understand the true relationship of these predictors with the outcome and with each other, longitudinal investigation is required. Second, many studies did not report sufficient information to accurately assess the risk of bias. Further, our ability to synthesize the literature was, in several cases, hindered by insufficient reporting of results. To address this issue in future reviews, additional information could be obtained from authors of published studies. Third, utilization of different, or no, control covariates impeded our ability to identify potential influential factors that could explain results.

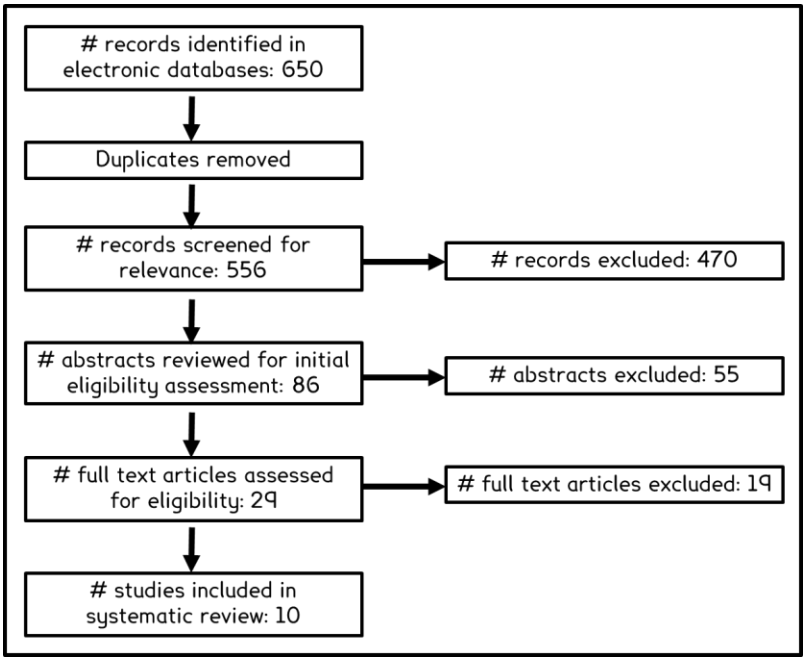
In addition, there are several limitations of the present review. First, between-study comparison is limited by variations in study design, sample characteristics, measurement and analytic procedure. Therefore all differences identified between studies could simply be methodological artifacts. However, this may increase our confidence in between-study consistencies such as the strong positive associations reported for having a prescription and for drug use disorders. Second, literature searches, data extraction and evaluation were only conducted by one individual (the study author), which increases the risk of random and systematic error at all stages. Finally, we were only able to find ten studies that met inclusion criteria. Indeed the number of studies considering each risk factor ranged from one to five. We may have been more confident in results had a greater number of high quality studies been available.

Despite these limitations the review has several strengths. It is the first attempt to utilize systematic methods to synthesize and evaluate the literature on modifiable prescription and mental-health risk factors for clinically significant benzodiazepine use. Potentially important risk factors have been identified, and possible effect modifiers (such as sample type) of their role in clinically significant problem benzodiazepine use have been suggested. Future work could address limitations of the included studies

to consider, in a methodologically robust manner, the way in which the identified potential risk factors may influence the risk of clinically significant problem benzodiazepine use.

FIGURES

Figure 2.1: Flow of publications selected for review



TABLES

Table 2.1. Description of studies included in the systematic literature review

Study	STUDY DESIGN/SAMPLE			OUTCOME:				PREDICTORS CONSIDERED	
	Sample type	N	study design	time frame	drug	type	%	Prescription characteristics	Mental health related characteristics
Huang et al., 2006[1]	U.S. population	43,093	cross-sectional	lifetime	tranquilizer	DSM-IV abuse/ dependence	1.00%	-----	alcohol, drug, anxiety, mood disorders
Becker at al., 2007[58]	U.S. population with past year problem sedative/ tranquilizer use	3,153	cross-sectional	past year	sedative/ tranquilizer	DSM-IV abuse/ dependence	9.80%	-----	alcohol, drug, anxiety, mood disorders; treatment
Fenton et al., 2010[3]	U.S. population	34,653	cross-sectional	lifetime	sedative/ tranquilizer	DSM-IV abuse DSM-IV dependence DSM-IV abuse/ dependence	1.30% 0.50% 1.90%	having a prescription	-----
Paulozzi et al., 2012[29]	Electronic medical records in New Mexico	6,293	Matched case-control	n/a	Sedative/ tranquilizer	Fatal overdose	n/a	having a prescription	-----
De las Cuevas et al., 2003[62]	clinical (benzodiazepine prescription) in Canary Islands	1,048	cross-sectional	current	benzodiazepine	DSM-IV dependence	47%	dosage, half-life, length, provider type	-----
Kan et al., 2004[61]	clinical (benzodiazepine prescription) in Netherlands	599	cross-sectional	past year	benzodiazepine	DSM-III dependence ICD-10 dependence	45.7% 56.6%	dosage, half-life, length, provider type	anxiety, depression
Ross 1993[63]	clinical (alcohol) in Toronto, Canada	427	cross-sectional	current	sedative/ tranquilizer	DSM-III abuse/dependence	20.37%	-----	anxiety and mood disorders
Rooney 1999[60]	clinical (opioid), location unknown	63	cross-sectional	current	benzodiazepine	dependence based on need for detoxification	53.97%	-----	depression
Ross & Darke 2000[59]	clinical (opioid) in Sydney, Australia	202	cross-sectional	lifetime	benzodiazepine	DSM-III-R dependence	25.74%	-----	drug, anxiety, mood disorders
Brunette et al., 2003[22]	clinical (comorbid) in New Hampshire	195	prospective	current	benzodiazepine	DSM-III abuse/dependence	10.26%	having a prescription	-----

---: study did not consider predictors in this category

Table 2.2. Psychometric assessment tools

STUDY	OUTCOME MEASURE	ASSESSMENT TOOL	TYPE OF ASSESSMENT
Ross 1993[63]	Current sedative/tranquilizer DSM-III abuse/dependence	Diagnostic Interview Schedule (DIS) version III	Structured
Ross & Darke 2000[59]	Lifetime DSM-III-R benzodiazepine dependence	Composite International Diagnostic Interview version 1.1. (CIDI)	Structured
Brunette et al., 2003[22]	Current DSM-III benzodiazepine abuse or dependence	Structured Clinical Interview for DSM-III-R	Structured
De las Cuevas et al., 2003[62]	Current DSM0IV benzodiazepine dependence	Severity of dependence Scale	Semi-structured
Kan et al., 2004[61]	Past year DSM-III or ICD-10 benzodiazepine dependence	Schedule for Clinical Assessments in Neuropsychiatry (SCAN)	Semi-structured
Huang et al., 2006[1]	Lifetime DSM-IV tranquilizer abuse or dependence	NIAAA Alcohol Use Disorder and Associated Disabilities Interview Schedule–IV (AUDADIS-IV)	Structured
Becker at al., 2007[58]	Past year sedative/tranquilizer DSM-IV abuse or dependence	NSDUH questions	Structured
Fenton et al., 2010[3]	Lifetime DSM-IV sedative or tranquilizer abuse or dependence	NIAAA Alcohol Use Disorder and Associated Disabilities Interview Schedule–IV (AUDADIS-IV): structured interview	Structured

Table 2.3. The relationship between a prescription and clinically significant problem benzodiazepine use

Study	Sample	Outcome			Predictor	Results		Control variables
		Timeframe	Drug	Type		OR	95% CIs or p value	
Fenton et al., 2010[3]	General Population	Lifetime	Sedative/ Tranquilizer	DSM-IV abuse	Ever prescribed anxiolytic medication	4.53	3.38-6.06	Sociodemographics
				DSM-IV dependence		8.66	5.62-13.34	Sociodemographics
				DSM-IV abuse/ dependence		5.42	4.33-6.97	Socio-demographics
Paulozzi et al., 2012[29]	Electronic medical records	n/a	Sedative/ Tranquilizer	Fatal overdose	1+ sedative/ hypnotic prescriptions	3.0	2.2-4.2	Sex and opioid prescription variables
					Overlapping sedative/ hypnotic prescriptions	11.0	8.2-14.7	None
Brunette et al., 2003[22]	Clinical	Current	Benzodiazepine	DSM-III dependence	Current benzodiazepine prescription	2.76	p<0.05	None

Table 2.4. The relationship between prescription dosage and clinically significant problem benzodiazepine use

Study	Sample	Outcome			Predictor	Results		Control variables
		Timeframe	Drug	Type		OR	95% CIs or p value	
De Las Cuevas et al., 2003[62]	Benzodiazepine prescription	During prescription (mean, 38.2 months; range 1-360 months)	Benzodiazepine	DSM-IV dependence	Average diazepam equivalent dosage	1.04	1.03-1.06	Duration, antidepressants
Kan et al., 2004[61]	Benzodiazepine prescription	Past year	Benzodiazepine	DSM-III dependence	Mean daily diazepam equivalent dosage	1.02	1.01-1.04	Demographics, prescription factors, mood and anxiety disorders
				ICD-10 dependence		1.03	1.01-1.05	

Table 2.5. The relationship between prescription length and clinically significant problem benzodiazepine use

Study	Sample	Outcome			Predictor	Results		Control variables
		Timeframe	Drug	Type		OR	95% CIs or p value	
De Las Cuevas et al., 2003[62]	Benzodiazepine prescription	During prescription (mean, 38.2 months; range 1-360 months)	Benzodiazepine	DSM-IV dependence	Length of treatment	1.01	1.01-1.02	Dose, duration, antidepressants
Kan et al., 2004[61]	Benzodiazepine prescription	Past year	Benzodiazepine	DSM-III dependence	Median duration of use	1.00	1.00-1.01	Demographics, prescription factors, anxiety and mood disorders
				ICD-10 dependence		1.01	1.00-1.01	

Table 2.6. The relationship between provider type and clinically significant problem benzodiazepine use

Study	Sample	Outcome			Predictor	Results		Control variables
		Timeframe	Drug	Type		OR	95% CIs or p value	
De Las Cuevas et al., 2003[62]	Benzodiazepine prescription	During prescription (mean, 38.2 months; range 1-360 months)	Benzodiazepine	DSM-IV dependence	Prescribed by psychiatrist	2.51	p<0.01	None (bivariate)
Kan et al., 2004[61]	Benzodiazepine prescription	Past year	Benzodiazepine	DSM-III dependence	Prescribed in psychiatric outpatient setting	1.45	0.92-2.31	Demographics, prescription factors, anxiety and mood disorders
				ICD-10 dependence		1.57	1.00-2.47	

Table 2.7. The relationship between alcohol disorders and clinically significant problem benzodiazepine use

Study	Sample	Outcome			Predictor	Results		Control variables
		Timeframe	Drug	Type		OR	95% CIs or p value	
Huang et al., 2006[1]	General population	Lifetime	Tranquilizer	DSM-IV abuse/ dependence	Lifetime alcohol disorder	14.2	9.56-21.08	Sociodemographics
Becker et al., 2007[58]	General population (past year problem sedative/ tranquilizer users)	Past year	Sedative/ Tranquilizer	DSM-IV abuse/ dependence	Past year alcohol disorder	0.6	0.3-1.4	Demographics and psychiatric disorders

Table 2.8. The relationship between drug disorders and clinically significant problem benzodiazepine use

Study	Sample	Outcome			Predictor	Results		Control variables
		Timeframe	Drug	Type		OR	95% CIs or p value	
Huang et al., 2006[1]	General population	Lifetime	Tranquilizer	DSM-IV abuse/ dependence	Other lifetime prescription drug disorder	184	130.3-259.8	Sociodemographics
					Lifetime illicit drug disorder	54.8	37.4-80.4	
Ross and Darke[59]	Clinical (opioid)	Lifetime	Benzodiazepine	DSM-III-R dependence	Number of lifetime drug dependencies	2.56	1.67-3.92	Demographics, drug use variables and psychiatric comorbidity

Table 2.9. The relationship between anxiety and clinically significant problem benzodiazepine use

Study	Sample	Outcome			Predictor	Results		Control variables
		Timeframe	Drug	Type		OR	95% CIs or p value	
Huang et al., 2006[1]	General population	Lifetime	Tranquilizer	DSM-IV abuse / dependence	Lifetime anxiety disorder	4.2	3.28-5.39	Sociodemographics
Kan et al., 2004[61]	Benzodiazepine prescription	Past year	Benzodiazepine	DSM-III dependence	Current anxiety score	1.02	0.98-1.07	Demographics, prescription factors, anxiety and mood disorders
				ICD-10 dependence		1.03	0.98-1.08	
Ross 1993[63]	Clinical (alcohol)	Current	Sedative/ tranquilizer	DSM-III abuse/ dependence	Lifetime anxiety disorder	5.62	p<0.05	None (bivariate)
Ross and Darke 2000[59]	Clinical (opioid)	Lifetime	Benzodiazepine	DSM-III-R dependence	Lifetime anxiety disorder	2.43	1.21-4.87	None

Table 2.10. The relationship between panic and clinically significant problem benzodiazepine use

Study	Sample	Outcome			Predictor	Results		Control variables
		Timeframe	Drug	Type		OR	95% CIs or p value	
Huang et al., 2006[1]	General population	Lifetime	Tranquilizer	DSM-IV abuse/ dependence	Lifetime panic with agoraphobia	7.9	4.56-13.64	Sociodemographics
					Lifetime panic without agoraphobia	3.8	2.69-5.43	
Becker et al., 2007[58]	General population (past year problem sedative/ tranquilizer users)	Past year	Sedative/ Tranquilizer	DSM-IV abuse/ dependence	Past year panic	1.1	0.6-1.9	Demographics and psychiatric disorders
Ross and Darke 2000[59]	Clinical (opioid)	Lifetime	Benzodiazepine	DSM-III-R dependence	Lifetime panic with agoraphobia	4.11	1.88-9.33	None

Table 2.11. The relationship between lifetime specific phobia and clinically significant problem benzodiazepine use

Study	Sample	Outcome			Results		Control variables
		Timeframe	Drug	Type	OR	95% CIs or p value	
Huang et al., 2006[1]	General population	Lifetime	Tranquilizer	DSM-IV abuse/ dependence	3.2	2.36-4.38	Sociodemographics
Ross and Darke 2000[59]	Clinical (opioid)	Lifetime	Benzodiazepine	DSM-III-R dependence	2.75	1.45-5.20	None

Table 2.12. The relationship between social phobia and clinically significant problem benzodiazepine use

Study	Sample	Outcome			Predictor	Results		Control variables
		Timeframe	Drug	Type		OR	95% CIs or p value	
Huang et al., 2006[1]	General population	Lifetime	Tranquilizer	DSM-IV abuse/ dependence	Lifetime social phobia	3.0	2.13-4.31	Sociodemographics
Becker et al., 2007[58]	General population (past year problem sedative/ tranquilizer users)	Past year	Sedative/ Tranquilizer	DSM-IV abuse/ dependence	Past year Social phobia symptoms	1.1	0.7-1.8	Demographics and psychiatric disorders
Ross and Darke 2000[59]	Clinical (opioid)	Lifetime	Benzodiazepine	DSM-III-R dependence	Lifetime simple phobias	1.79	0.95-3.35	None

Table 2.13. The relationship between generalized anxiety and clinically significant problem benzodiazepine use

Study	Sample	Outcome			Predictor	Results		Control variables
		Timeframe	Drug	Type		OR	95% CIs or p value	
Huang et al., 2006[1]	General population	Lifetime	Tranquilizer	DSM-IV abuse/ dependence	Lifetime generalized anxiety	4.3	3.07-6.13	Sociodemographics
Becker et al., 2007[58]	General population (past year problem sedative/ tranquilizer users)	Past year	Sedative/ Tranquilizer	DSM-IV abuse/ dependence	Past year generalized anxiety	0.8	0.3-1.9	Demographics and psychiatric disorders

Table 2.14. The relationship between depression and clinically significant problem benzodiazepine use

Study	Sample	Outcome			Predictor	Results		Control variables
		Timeframe	Drug	Type		OR	95% CIs or p value	
Huang et al., 2006[1]	General population	Lifetime	Tranquilizer	DSM-IV abuse or dependence	Lifetime major depressive disorder	2.4	1.69-3.28	Sociodemographics
					Lifetime dysthymia	3.4	2.37-4.82	
Becker et al., 2007[58]	General population (past year problem sedative/ tranquilizer users)	Past year	Sedative/ Tranquilizer	DSM-IV abuse/ dependence	Past year major depressive episode	1.7	0.9-3.5	Demographics and psychiatric disorders
Kan et al., 2004[61]	Benzodiazepine prescription	Past year	Benzodiazepine	DSM-III dependence	Current depression score	1.01	0.99-1.03	Demographics, prescription factors, anxiety and mood disorders
				ICD-10 dependence		1.01	0.98-1.03	
Rooney et al., 1999[60]	Clinical (opioid)	Current	Benzodiazepine	Dependence based on need for detoxification	History of depression	5.62	0.045	None
Ross and Darke 2000[59]	Clinical (opioid)	Lifetime	Benzodiazepine	DSM-III-R dependence	Lifetime major depression	3.14	1.66-5.97	None
					Lifetime dysthymia	2.93	1.44-5.95	

Table 2.15. The relationship between mania and clinically significant problem benzodiazepine use

Study	Sample	Outcome			Predictor	Results		Control variables
		Timeframe	Drug	Type		OR	95% CIs or p value	
Huang et al., 2006[1]	General population	Lifetime	Tranquilizer	DSM-IV abuse/ dependence	Lifetime bipolar I	5.5	3.94-7.65	Sociodemographics
					Lifetime bipolar II	4.2	2.44-7.32	
Becker et al., 2007[58]	General population (past year problem sedative/ tranquilizer users)	Past year	Sedative/ Tranquilizer	DSM-IV abuse/ dependence	Past year mania	1.0	0.5-2.0	Demographics and psychiatric disorders

Chapter 3. Prescription-related risk factors for problem benzodiazepine use among individuals prescribed benzodiazepine

ABSTRACT

Context: There is concern regarding the increasing prevalence and growing burden of problem benzodiazepine use in the United States. Individuals with a benzodiazepine prescription may be a particularly high risk group for problem use. Objective: We used health-claims data to determine whether the risk of problem benzodiazepine use among individuals with a prescription can be predicted by: 1) benzodiazepine characteristics; 2) indicators of the amount of benzodiazepine prescribed over time; 3) prescription contextual factors. Design, Setting and Participants: Medical and pharmacy claims of 231,267 individuals in the 2003 and 2004 *Thompson Reuters MarketScan® Commercial Claims Databases* who received a benzodiazepine prescription between July and December 2003. Main Outcome Measure: Problem benzodiazepine use, including benzodiazepine use disorder or overdose, during the follow-up period. Results: Dosage, potency, benzodiazepine type, Medication-Possession Ratio the number of days of benzodiazepine prescriptions received in the baseline, recent psychotherapy and prescription of other controlled substances predicted an increased risk of developing problem benzodiazepine use ($p<0.05$), controlling for demographics and any psychiatric disorder. Conclusion: Modifiable variables including prescription characteristics, the amount of benzodiazepine prescribed over time and prescription contextual factors independently increased the risk of problem benzodiazepine use among individuals with a prescription. This information can be used to develop specifically targeted prevention and treatment interventions, such as surveillance systems, to address the burden of problem benzodiazepine use in the U.S.

INTRODUCTION

Benzodiazepines have great clinical utility in the treatment of anxiety[10-12] and other disorders[12,13], and are widely prescribed in the United States[12,14]. However, benzodiazepines have an abuse potential[10,11,17], and in recent years there have been concerns about the increasing prevalence and growing burden of problem benzodiazepine use in the United States[1-4]. For example, there were 408,021 emergency department visits in 2010 resulting from the misuse of benzodiazepines, which represents a 139% increase from 2004[4]. Most epidemiological research on problem prescription drug use, including benzodiazepines, has focused on use among individuals without a prescription[5-9]. However, evidence of problem use among individuals prescribed the medication[9,16-20] points to the need for focused research attention on this vulnerable population. In particular, understanding individuals with a benzodiazepine prescription who experience clinically significant impairment or distress (e.g. diagnosis of abuse or dependence, or poisoning) as a result of their problematic benzodiazepine use among could be critical to reducing the public health burden association with problem benzodiazepine use.

Previous risk factors identified for problem benzodiazepine use, such as sex, race, age and psychiatric history[1,9] are important, but may be of limited value when designing interventions to reduce problem benzodiazepine use. Conversely, the modifiable nature of benzodiazepine prescription practices lends itself to various intervention opportunities. For example, providers can choose what is prescribed (i.e. benzodiazepine characteristics and the amount prescribed over time) and how it is prescribed (i.e. prescription context such as also being prescribed other controlled substances).

Characteristics of the specific benzodiazepine prescribed could potentially predict problem use. For example, individuals prescribed benzodiazepines with a greater abuse liability, as determined by potency, duration of action and rapidity of clinical onset[66,68], could be at an increased risk of engaging in problem benzodiazepine use, compared with individuals prescribed benzodiazepines with a lower abuse liability. For example, alprazolam and lorazepam both have a high potency, short half-life and intermediate clinical onset, making their abuse liability greater than oxazepam and temazepam which have a low potency, short half-life and slow clinical onset. For more information on the abuse liability of some commonly

prescribed benzodiazepines please refer to appendix 2, table A2.1. Similarly, since dosage is positively related to the reinforcing effect of the medication[68], tolerance, withdrawal[17] and dependence[62], the risk of problem benzodiazepine use could be higher for individuals prescribed a higher benzodiazepine dosage than for individuals prescribed a lower dosage. For example, with regard to alprazolam, prescribing guidelines suggest a 1.5mg starting dose to be slowly titrated up to 4mg[85]. Caution is advised when prescribing more than 4mgs[85]. Alprazolam-equivalent doses for the most commonly prescribed benzodiazepines are provided in appendix 2, table A2.2. These issues appear to indicate the importance of considering the role of abuse liability and dosage in the development of problem benzodiazepine use among individuals with a prescription.

For individuals with existing prescriptions, the amount prescribed over time could be predictive of problem benzodiazepine use. For example, long-term use, which has been associated with tolerance, withdrawal and overdose[17,29,61,62,66,68], could predict problem benzodiazepine use. Problem use may also be related to the amount of medication that an individual possesses at any one time as measured by the Medication-Possession Ratio, which is the sum of the daily prescribed dosages the patient has during a defined period of time divided by the number of days during that prescription period. A positive Medication-Possession Ratio (e.g. from overlapping prescriptions or multiple provider episodes) would mean that an individual is in possession of more medication than is medically necessary, which could provide an opportunity to engage in problem benzodiazepine use. Given this, understanding the role of prescription length and Medication-Possession Ratio in the risk of problem benzodiazepine use could provide useful information to reduce this behavior among patients.

The context in which benzodiazepines are prescribed could also be related with the risk of problem use. For example, other controlled prescription medications, including opioids, sedatives and stimulants, can interact with benzodiazepines when taken concurrently[86-89]. Individuals with prescriptions for these other controlled medications could take them alongside benzodiazepines to augment their psychoactive properties, which would increase the risk of dependence, withdrawal and overdose. In addition, psychotherapeutic service utilization may reduce the risk of problem benzodiazepine use. Psychological

interventions may successfully treat anxiety disorders[78] so patients may be less likely to rely on their prescribed medication for the reduction of anxiety symptoms. Further, individuals at risk of engaging in problem benzodiazepine use may address this in therapy and therefore be less likely to manifest this behavior[80-84]. These individuals may also be at greatest risk of the problem outcomes due to their psychopathology, which may or may not be treated successfully in their therapy or pharmacologic treatment. Thus, there appears to be a need to assess how these contextual considerations may be related to the risk of problem benzodiazepine use among individuals with a prescription.

This paper intends to address the above hypotheses using a large prospective dataset of medical and pharmaceutical claims. Specifically, we intend to determine whether the risk of problem benzodiazepine use among individuals prescribed benzodiazepines can be predicted by:

1. Characteristics of the specific benzodiazepine prescribed including abuse liability and dosage.
2. Indicators of the amount of benzodiazepine prescribed over time including number of days and Medication Prescription Ratio
3. Prescription contextual factors including whether the prescription recipient utilizes psychotherapeutic services or receives other controlled substances

Please note that these analyses are limited to people who have filled prescriptions for benzodiazepines.

METHODS

Sample and procedures

This paper used longitudinal data from the January 1st 2003 to December 31st 2004 *MarketScan*® *Commercial Claims Databases*. The *MarketScan*® *Databases* provide comprehensive health-care data from enrollees of health care plans from large employers, and captures longitudinal person-specific information on medical services, expenditures, and enrollment across inpatient, outpatient, prescription drug and carve-out services (i.e. a program separate from the primary group health plan that is designed to provide a specialized type of care, such as a mental health carve-out). The databases are constructed from privately insured medical and prescription drug claims. The MarketScan Research Databases link

paid claims and encounter data to detailed patient information across sites and types of providers, and over time. Each patient is given a unique identifier which ensures patient confidentiality but allows for individual-level tracking of each patient over time and across medical, outpatient pharmaceutical, enrollment and benefit plan files.

The *Thompson Reuters MarketScan® Commercial Claims Databases* represents the medical experience of insured active employees, early (non-Medicare) retirees, Consolidated Omnibus Budget Reconciliation Act (COBRA) continues, and dependents insured by employer-sponsored plans (i.e. persons not eligible for Medicare). Collectively, the databases incorporate data from almost 100 payers including commercial insurance companies, Blue Cross and Blue Shield plans, and third-party administrators. Each employer database is constructed by collecting raw data from the appropriate payer(s). These raw data are service-level adjudicated paid claims and capitated encounters containing both inpatient and outpatient services. Clinical and demographic variables are standardized to common definitions, and benefit plan type, characteristics, enrollment, outpatient pharmaceutical claims and medical data are integrated. Clinical detail, such as major diagnostic categories, diagnosis-related groups and therapeutic class are added to claims.

Several measures are taken to ensure data accuracy. Checks on validity and reasonableness of the data include examining diagnosis codes, procedure codes, date(s) of service, sex and age, to compare recorded values to lists of possible valid values for those fields. For example, a diagnosis of prostate cancer in a woman would indicate an inaccuracy. Improper coding is flagged to recommend data quality improvement actions to the carrier or data processor. Diagnosis codes are compared with the procedure codes that were in effect at that time, and edited if necessary. Verification that both the experience and the denominator populations exist for all subsets of the data is made.

Since we were interested in individuals who develop problem use following a benzodiazepine prescription, the total study sample was limited to the 231,267 individuals in the 2003 and 2004 *Thompson Reuters MarketScan® Commercial Claims Databases* who were enrolled in their insurance

plan for at least 6 months preceding and 12 months following an index oral benzodiazepine prescription. The index prescription is the prescription whose effect we are examining. The 6 months preceding the index benzodiazepine prescription is referred to as the look-back period. The 12 months following the index prescription is referred to as the follow-up period. This study design allowed for a 12 month possible look-back period (January 2003-December 2003), an 18 month possible follow-up period (July 2003-December 2004), and a 6 month ascertainment period (July 2003-December 2003) within which to identify eligible index oral benzodiazepine prescriptions. Oral benzodiazepine prescriptions filled during the ascertainment period were considered ineligible if the days' supply was less than or equal to 0, or if the number of units dispensed, was less than 1. To calculate new, rather than prevalent, cases of problem benzodiazepine use during follow-up, we further excluded all individuals who were positive for problem benzodiazepine use during the 6 month-look back period. Additional points to note about the sample include: 1) for patients who filled multiple eligible index prescriptions, the first prescription filled was considered their index prescription (patients were entered into the cohort on the date that they first met eligibility criteria); 2) we utilized standard definitions of 6 months as 180 days and 12 months as 365 days; 3) analyses for indicators of the amount of benzodiazepine prescribed over time (days supply in baseline and Medication-Possession Ratio) were restricted to the 116,920 individuals in the total sample who received an oral benzodiazepine prescription during the 6 month look-back period in addition to their index prescription. Information on attrition is provided in Appendix 1.

Measures

Diagnoses and procedure codes in the *MarketScan® Commercial Claims Databases* use the International Classification of Disease, Ninth Revision, Clinical Modifications (ICD-9-CM) classification system[90]. Unless otherwise noted, variables were created for the total sample.

Outcome: Problem Benzodiazepine Use

Problem benzodiazepine use was defined as receiving a diagnosis corresponding to least one of the following codes in any field and in any setting during the 12 month follow-up period (July 2003-December 2004).

1. Diagnosis of benzodiazepine abuse or dependence (ICD-9 codes 305.4, 305.40, 305.41, 305.42, 305.43, or 304.1, 304.10, 304.11, 304.12, 304.13)
2. Poisoning involving benzodiazepine (accidental or non-accidental) (ICD-9 codes E853.2 or 969.4)

All other individuals were classified as negative for problem benzodiazepine use. Note that although all subjects are negative for problem benzodiazepine use during their 6 month look-back period, since we do not have information on problem benzodiazepine use prior to January 2003 this outcome measures new (at least within 6-month baseline period), rather than incident, cases of problem benzodiazepine use.

Note that a discussion of theoretical and data considerations in defining this variable, including sensitivity analyses, is provided in the discussion.

Hypothesized Risk Factors: Characteristics of the index benzodiazepine

Benzodiazepine Abuse Liability: To measure overall abuse liability of the benzodiazepine, each compound was given a value for its potency[68] (1=low potency, 2=high potency), half-life[68] (1=long half-life, 2=short half-life) and rapidity of clinical onset[91] (1=slow clinical onset, 2=intermediate clinical onset, 3=rapid clinical onset). These 3 values were then summed to create an overall abuse liability variable (continuous). Abuse liability values for each benzodiazepine are provided in appendix 2, table A2.1. The medications with the highest scores have the highest abuse liability, while the medications with the lowest scores have the lowest abuse liability.

Dosage: To measure the daily dosage of the index prescription, we divided the total alprazolam-equivalent milligrams dispensed by the number of days supplied and then created a three-level variable to reflect prescribing guidelines[85] which suggest a 1.5mg starting dose to be slowly titrated up to 4mg. Caution is advised when prescribing more than 4mgs. Therefore the levels of the categorical variable were less than or equal to 1.5mg (referent), between 1.5 mg and 4mg and more than 4mgs. This measurement of dose reflects the prescribed daily dose, but may not reflect the actual amount consumed.

Consistent with previous literature[55,56], we have used an “as-prescribed” approach for the daily dose variable. This assumes that patients take all prescribed benzodiazepines at the prescribed dose and on

the schedule recommended by their clinicians. However, it is important to note that this may not be an entirely valid assumption.

Note that comparative oral doses of benzodiazepines are provided in appendix 2, table A2.2.[91].

Hypothesized Risk Factors: Indicators of the amount of benzodiazepine prescribed over time

Indicators of the amount of benzodiazepine prescribed over time were only created for existing users.

Days' supply in baseline: We created a categorical variable to measure the number of days a patient was prescribed benzodiazepines during the look-back period (1: ≤30 days (referent); 2: 31-60 days; 3: 60-90 days; 4: 90-120 days; 5: 120-180 days; 6: >180 days). This categorization will allow us to determine the effect of long-term use which is usually defined as use for four months or more[17], identify a dose-response relationship and consider the role of overlapping prescriptions.

Medication-Possession Ratio: The Medication-Possession Ratio was measured by dividing the sum of the daily prescribed dosages the patient has during a defined period of time by the number of days during that prescription period. For example, if a patient filled 2 30-day prescriptions over a 60 day period then their MPR would be 30+30/60=1. This variable captures the MPR in the 6-month look-back period from the index prescription. A three level-categorical variable was then created to indicate whether a patient had an MPR less than or equal to 0.5 (referent), between 0.5 and 1, or greater than 1. Note that we created a three level variable due to heterogeneity of risk among those with an MPR of 1 or less.

Hypothesized Risk Factors: Prescription contextual factors

Utilization of psychotherapeutic services: A binary variable was created to indicate whether the patient utilized any psychotherapeutic service during their 6 month look-back period (1: psychotherapeutic service utilization; 0: no psychotherapeutic service utilization).

Prescription of other controlled substances: Three binary variables were created to identify individuals who received prescriptions for opioids (1: opioid prescription; 0: no opioid prescription), other

sedative/hypnotic including barbiturates (1: sedative prescription; 0: no sedative prescription) and stimulants (1: stimulant prescription; 0: no stimulant prescription) during the 6 month look-back period.

Hypothesized Confounders

Sociodemographics: Age at the time of the index prescription (continuous), geographic region (1:North East; 2:North Central; 3:South; 4:West; 5: unknown) and employment type (1=union; 2= non-union; 3: other/unknown) were included as possible confounders based on their theoretical relationship with the outcome in the literature [1,3,9].

Psychiatric disorders: A binary variable was created to determine whether an individual was diagnosed with any psychiatric disorder during the 6 month look-back period (1: any psychiatric disorder; 0: no psychiatric disorder). This includes all ICD-9 codes 290-319, including substance use and dependence (note that since all individuals with the outcome during the 6-month look back period were excluded, this variable does not measure benzodiazepine-related substance disorders).

Insomnia: Since benzodiazepines are often prescribed for initial insomnia, a binary variable was created to indicate whether an individual was diagnosed with any insomnia during the six month look-back period (1: any insomnia during the look-back period; 0: no insomnia during the look-back period). Note that specific ICD-9 codes are provided in appendix 3.

Benzodiazepine prescription history: A binary variable was created to indicate whether an individual received a benzodiazepine prescription during the 6 month look-back period. Individuals who did not receive a prescription during the look-back period are referred to as new prescriptions. Individuals who were prescribed benzodiazepines during the look-back period are referred to as existing prescription. (1: existing prescriptions; 0: new prescription)

Note that additional information on confounder selection is provided in the statistical analysis section.

Statistical analysis

Analyses were conducted in SAS 9.3. The outcome variable was problem benzodiazepine use during a 12 month follow-up period.

Confounder Selection: Confounders for all hypothesized predictors included age, geographic region, employment type (as a proxy for socioeconomic status) and any psychiatric disorder. These variables were selected *a priori* based on previous work in which they were found to be important predictors of problem benzodiazepine use[1,3,9] and met standard criteria for confounder selection including observed association with the exposures and outcome, and a change of 10% or more in the crude exposure-outcome association (beta). Note that gender was initially considered as a potential confounder based on past work associating it with problem benzodiazepine use and at least some of the predictors[1-3], however it was unrelated to the outcome in our dataset and was therefore not included as a confounder.

Additional potential confounders considered included insomnia since benzodiazepines are often prescribed for initial insomnia and benzodiazepine prescription history during the baseline period since medication effects may depend on history of medication use[92]. These variables both met the standard criteria for confounder selection provided in the above paragraph.

Main analyses: We generated a series of Logistic Regression models to examine the effect of each hypothesized risk factor on the outcome. We began by obtaining ORs and 95% CIs to assess (1) the crude relationship; (2) the relationship adjusting for sociodemographics and insomnia; (3) the relationship adjusting for sociodemographics, insomnia and psychiatric disorders; and (4) the relationship adjusting for sociodemographics, insomnia, psychiatric disorders and benzodiazepine prescription history. Note that analyses for the number of days prescribed and the Medication-Possession Ratio were only conducted among individuals with existing prescriptions, since they are not applicable to individuals not prescribed benzodiazepines during the look-back period. Therefore analysis of these risk factors was limited to models 1-3 described above. Differences between new and existing prescriptions are provided in appendices 3 and 5. Results from full models are provided in appendix 7.

RESULTS

Sample characteristics (Table 3.1)

The mean age of the total sample (N=231,267) was 48 years, approximately two thirds (69%) were female and a quarter (27%) had a union job. The majority filled prescriptions in the south (41%) and north central areas of the US (31%). Almost one quarter (22%) were diagnosed with a psychiatric disorder and approximately half (51%) received a benzodiazepine during the 6 month look-back period.

The outcome, problem benzodiazepine use during the 12 month follow-up period, was evident in 0.37% (N=852) of the sample, and was significantly ($p<0.05$) associated with younger age, having a union job, filling the prescription in the west, and being diagnosed with a psychiatric disorder or receiving a benzodiazepine prescription during the look-back period.

Note that crude relationships between sample characteristics and the predictors considered in this chapter are provided in appendix 5.

Benzodiazepine characteristics

The main analyses considered the role of dosage (reference group ≥1.5mgs) and abuse potential in the development of problem benzodiazepine use. Frequencies for benzodiazepine characteristics are provided in Table 3.2. Findings from logistic regression models assessing the relationship between benzodiazepine characteristics and problem benzodiazepine use are provided in Table 3.3.

As shown in Table 3.3, findings indicated a strong dose response relationship between the dosage of the index benzodiazepine prescription and the development of problem benzodiazepine use. This was attenuated somewhat by including confounders in the model, but remained evident in the fully adjusted model (ORs 2.20 and 3.70). With regard to abuse potential, significant associations observed in the crude model and when adjusting only for demographics and insomnia were lost when psychiatric disorders and benzodiazepine prescription history were added in the model.

Post-hoc analyses: To better understand the observed null relationship between abuse potential and problem benzodiazepine use we conducted post-hoc analyses to consider the role of components of the abuse potential score (half-life, clinical onset and potency) and also of the index benzodiazepine type. Frequencies for these variables are provided in Table 3.2 and results from logistic regression models are provided in Table 3.3. In brief, significant associations in the fully adjusted models (controlling for demographics, insomnia, psychiatric disorders and benzodiazepine prescription history) were only evident for the index benzodiazepine type (Table 3.3). Specifically, the risk of problem benzodiazepine use was higher for Alprazolam XR (OR, 2.07) and lower for lorazepam (OR, 0.86) than regular alprazolam.

The amount of benzodiazepine prescribed over time

Frequencies for the amount of benzodiazepine prescribed are provided in Table 3.4. Findings from logistic regression models assessing the relationship between amount and problem benzodiazepine use are provided in Table 3.5. Note that these variables were only considered among the 116,920 individuals who received a benzodiazepine prescription during the look-back period.

As shown in Table 3.5, both Medication-Possession Ratio (MPR) and number of days during the look-back period for which a benzodiazepine was prescribed predicted problem benzodiazepine use during the follow-up period in a strong dose response manner. For both of these variables, the inclusion of demographics and any psychiatric disorders did not substantially attenuate the observed associations.

Benzodiazepine prescription contextual variables

Frequencies for benzodiazepine prescription contextual variables are provided in Table 6. Findings from logistic regression models assessing the relationship between benzodiazepine characteristics and problem benzodiazepine use are provided in Table 7.

As shown in Table 3.7, when adjusting only for demographics and insomnia, all benzodiazepine prescription contextual factors were significant predictors of problem benzodiazepine use- magnitude of ORs ranged from 4.13 (psychotherapy) to 2.17 (stimulant prescription). When additionally controlling for any psychiatric disorder during baseline, the magnitude of the OR for psychotherapy dropped substantially from 4.13 to 1.45, but remained significant. Additionally adjusting for benzodiazepine prescription history did not substantially attenuate the observed finding. Note that the observed direction of effect for psychotherapy is contrary to our hypothesis that psychotherapy would reduce the risk of problem benzodiazepine use. With regard to prescription of other controlled substances during baseline, opioid and sedative prescriptions remained significant after adding psychiatric disorders and benzodiazepine prescription history into the model, however stimulant prescriptions lost significance.

DISCUSSION

Using a very large prospective dataset of medical and pharmacy health claims we found that, among patients prescribed benzodiazepines, the risk of using this medication in problematic ways could be predicted by modifiable prescription-related characteristics. Specifically, the risk of problem benzodiazepine use appears to depend on characteristics of the prescribed benzodiazepine (dosage and type of benzodiazepine prescribed), the amount of medication prescribed over time (Medication Possession Ratio and days supply) and prescription contextual factors (psychotherapy and recent prescriptions for controlled opioids or sedatives).

If verified, this information could be used to identify high risk patients at the time that the prescription is written or filled, which opens up excellent opportunities for effective targeted evidence-based prevention and treatment interventions. For example, real time prescription monitoring programs are used in many states and clinical settings to permit physicians and pharmacists to track all opioid prescriptions for a given patient, and identify high risk behaviors[93,94]. However there is a great deal of variability with regard to effectiveness in prescription drug monitoring programs[95]. It would appear that in order for these programs to be effective it is necessary to develop algorithms that can be easily utilized to guide medical decision-making and regulatory action based on timely and complete records of all relevant data[95,96]. The

findings presented in this paper could make an important contribution to building such an algorithm for benzodiazepines.

For example, dosage appears to have an important role in the development of new problem benzodiazepine use. Interestingly, a higher dose was related to a higher risk of problem use among all individuals prescribed benzodiazepines, and seemed to follow a dose-response pattern in line with prescription guidelines that recommend an initial dose of 1.5mg a day, to be titrated up to 4mg if necessary, and to use caution when exceeding 4mgs[85] . This information suggests the need to closely monitor patients prescribed higher doses, and underscores the value of prescribing within the recommended guidelines. It is important to note that higher doses are likely prescribed to patients with more severe psychopathology and therefore perhaps at greater risk for problematic use. Although observed associations did not change when controlling for indicators of severity (psychopathology and benzodiazepine prescription history), the potential threat of confounding by indication should be considered when interpreting results.

With regard to the abuse potential, findings are mixed. Given null findings for the combined effect of half-life, clinical onset and potency, we explored these factors individually and found that potency, but not half-life or clinical onset, predicted the risk of problem use, adjusting for demographics and psychiatric disorders. This would suggest that highly potent benzodiazepines, such as alprazolam and lorazepam, confer a higher risk of problem use than less potent benzodiazepines such as diazepam. Consistently, when we drilled down further and explored the effect of benzodiazepine type, we found a lower risk of problem use among those prescribed the less-potent diazepam compare to the more-potent alprazolam. However we also found a lower risk for lorazepam, which is a higher potency benzodiazepine. Adding additional confusion to the picture, Alprazolam-XR, which is specifically designed to have a longer therapeutic period and lower abuse-potential[97], increased the risk of problem use by more than 3 times among new prescriptions. Given the potential clinical importance of understanding how the type of benzodiazepine prescribed may affect the risk of problematic use, further research on this matter may be required.

The amount of benzodiazepine prescribed over time may be related to the development of problematic use among patients. In brief being prescribed more medication over a 6 month period increased the risk of developing problem use. We considered this in two different ways- by looking at the number of days supplied in the baseline and the medication possession ratio. Three interesting findings were apparent.

First, the risk of problem benzodiazepine use appeared to increase as the amount of medication increased. Specifically, with regard to number of days, there was a marked increase in risk at four months, which is consistent which previous research demonstrating that long-term use, usually defined as four months or more[17], has been associated with the development of benzodiazepine dependence and overdose [17,29,61,62,66,68]. This suggests that short-term prescribing of benzodiazepines may be safer than long-term prescribing.

Second is the effect of overlapping prescriptions. We found that being prescribed more than 180 days of prescriptions in a 180 day time period and having a Medication-Possession Ratio greater than 1, which indicates possession of more medication than is medically necessary (e.g. because of doctor-shopping), were both highly predictive of problem benzodiazepine use. This is consistent with our hypotheses and prior research[29]. Thus, identifying and intervening in individuals with overlapping prescriptions appears to be a potentially useful way to address the development of problem benzodiazepine use. Related to this issue is our finding that recent prescription of other controlled medication also predicts problem benzodiazepine use. Taken together, these results may suggest the importance of interventions which provide clinicians with knowledge of all prescriptions that their patients have recently received.

Third, results from the Medication-Possession Ratio analysis can also shed light on another issue- whether benzodiazepine prescription should be short or long-term. We found that the lowest risk of problem benzodiazepine use was for a Medication-Possession Ratio of less than 0.5. This means for example, that receiving three (or less) Tablets in a period of one week confers a lower risk of developing problem use than receiving four (or more) Tablets in a week. This could suggest that an “as-needed”

approach to prescribing benzodiazepines may carry a reduced risk of problem benzodiazepine use. However, an important clinical consideration is that taking a benzodiazepine, though providing prompt relief, can interfere with the patient from habituating to the anxiety provoking stimuli and relieve anxiety to such an extent that the patient may lose motivation to continue CBT or other treatments that seek to desensitize the patient. Further, although results held controlling for comorbid psychopathology and benzodiazepine prescription history, it is possible that findings could be explained by residual confounding from severity of psychopathology. That is, those with milder psychopathology may be prescribed benzodiazepines "as-needed" while those with more severe psychopathology could be prescribed a daily dose of benzodiazepines. These important issues should be considered in future research prior to clinical interpretation of our results.

Finally, contrary to our hypotheses, we found an increased risk of problem use among individuals who utilized psychotherapeutic services. This could be an issue of confounding by severity. Individuals who utilize psychotherapeutic services may have more severe psychiatric disorders which may make them more vulnerable to problem benzodiazepine use. However, controlling for two possible markers of severity- comorbid psychiatric disorders and benzodiazepine prescription history- did not substantially attenuate the magnitude of the effect estimate. In addition, we considered this issue with sensitivity analyses looking at the frequency of psychotherapeutic service utilization. Based on the distribution of the data, we created a 6 level variable to indicate whether an individual had filed claims for 0, 1, 2, 3, 4 or 5 or more visits during the baseline period. A significant association was only found for 2 visits compared to 0 visits, controlling for demographics, insomnia, psychiatric diagnoses and benzodiazepine prescription history (OR, 1.37; 95% CI, 1.03-1.84). Non-significant inverse associations were observed for 1 (OR, 0.82; 95% CI, 0.59-1.14) and 3 (OR, 0.95; 95% CI, 0.65-1.38) visits compared to 0 visits, controlling for demographics, insomnia, psychiatric diagnoses and benzodiazepine prescription history. Non-significant positive associations were observed for 4 (OR, 1.29; 95% CI, 0.75-1.69) and 5 (OR, 1.17; 95% CI, 0.93-1.46) visits compared to 0 visits, controlling for demographics, insomnia, psychiatric diagnoses and benzodiazepine prescription history. These results suggest a potentially complex relationship between psychotherapy and problem benzodiazepine use, that could be explored more fully in future research. In

particular, it would be appropriate to address this issue using a different type of data source (e.g. nationally representative population-based data) to determine whether our findings could be an artifact of measurement error associated with using claims data, or whether they may be indicative of a potential causal relationship.

Other potential measurement problems should also be considered. Our definition of problem benzodiazepine use will primarily measure individuals at the more severe end of the spectrum who receive clinical attention. However, utilizing a definition of problem use that captures individuals at the severe end of the spectrum may be a strength rather than a weakness. It could be argued that our definition focuses on the most important group- the problem users who represent a public health concern and contribute to the burden of problem use. Therefore findings for these more severe problem users may have a more substantial public health impact than findings for problem users at the lower end of the severity spectrum.

Another issue is that our compound outcome included some variables that were not specific to benzodiazepines- ICD-9 codes 305.4, 305.40, 305.41, 305.42, 305.43, or 304.1, 304.10, 304.11, 304.12 and 304.13 indicate an abuse or dependence diagnosis of any sedative or hypnotic. Conversely, ICD-9 codes E853.2 or 969.4 specifically indicate poisoning involving benzodiazepines. The decision to create this compound variable was based on theoretical and data considerations. With regard to theory, benzodiazepines are by far the most widely prescribed anxiolytic, particularly at the time of data collection (2003-4)[98]. Further, data from a 1979 National Household survey indicated that benzodiazepines accounted for 84% of problem sedative/tranquilizer use in the U.S. population[64] (to the best of our knowledge, more recent data on this topic has not been published). Therefore it seemed reasonable to assume that the vast majority of anxiolytic abuse/dependence cases involve benzodiazepines, particularly in our sample that only included individuals with a benzodiazepine prescription. With regard to data, we conducted sensitivity analyses in which we repeated analyses using an outcome that only included benzodiazepine-specific ICD-9 codes (i.e. ICD-9 codes E853.2 or 969.4, benzodiazepine poisoning) and again using an outcome that only included non-benzodiazepine specific ICD-9 codes (i.e. ICD-9 codes

305.4, 305.40, 305.41, 305.42, 305.43, or 304.1, 304.10, 304.11, 304.12 and 304.13). Results for primary analyses for the fully adjusted models are provided in appendix 6. Although small differences were observed (e.g. the dose-response effect of the index prescription dose was more marked for non-benzodiazepine specific outcome than for benzodiazepine-specific outcomes), there were no striking differences in the magnitude or significance of observed associations. Given these considerations, utilizing our compound variable seemed justified. Of note, to be as inclusive as possible, we included ICD-9 codes 305.43 and 304.13 (sedative, hypnotic or anxiolytic abuse or dependence in remission) in our compound outcome since all individuals with the outcome during the 6-month follow-up period were excluded, therefore a code for the outcome in remission could feasibly indicate someone who experienced the outcome at some point during the 12 month follow-up period. Only one individual was classified as having the outcome based solely on one of these criteria.

Sample-related limitations are also noted. First, an employee-based dataset may not generalize to other populations. Second are several time-frame issues. Since the data are limited to two years (2003 and 2004) we do not know about problem benzodiazepine use prior to 2003 and therefore cannot calculate incident problem benzodiazepine use. Instead, we have measured new instances of problem benzodiazepine use among individuals with no problem benzodiazepine use for six months. Future research should be conducted with data which spans a greater period of time to capture incident problem benzodiazepine use and incident prescriptions may also be helpful.

Also related to the time-frame is that the dataset are 10 years old. Although overall benzodiazepine prescription has not changed much during the past decade, and no new benzodiazepines have been approved by the FDA, there has been marked expansion in use of non-benzodiazepine hypnotics (e.g., zopidem, zoplicone, zaleplon)[99]. We considered this issue with sensitivity analyses in which results were replicated among individuals not prescribed anxiolytics other than benzodiazepines. Results for these analyses (fully adjusted models for primary analyses) are provided in appendix 7. Two differences were observed. First, although there was only a small decrease in the magnitude of the effect of psychotherapy, this association lost significance in the sensitivity analyses (OR: 1.25, 95% CI: 1.12-1.72

vs. OR: 1.39, 95% CI: 1.12-1.72). Conversely, the magnitude of the effect of stimulant prescription increased slightly and gained significance in the sensitivity analyses (OR: 1.46, 95% CI: 1.03-2.06 vs. OR: 1.28, 95% CI: 0.95-1.72). These results could suggest that psychotherapy and stimulant prescriptions have a different relationship to problem benzodiazepine use among individuals not prescribed other anxiolytics, and this could be explored in future work.

With the exception of analyses that involved the amount of benzodiazepine prescribed during the 6 month look-back period (i.e. Medication Possession Ratio and days supply), our study sample combined new (i.e. individuals without a benzodiazepine prescription during the 6-month look-back period) and existing (i.e. individuals with a benzodiazepine prescription during the 6-month look-back period) benzodiazepine users. By mixing incident and prevalent users, there is a risk of depletion of susceptibles – people who continue on benzodiazepines have different risks than new initiators for her outcomes partly because those who previously developed the outcome are presumably at much less risk of continuing prescriptions during her period of observation. As such, benzodiazepine prescription history was evaluated for, and met, empirical criteria for a confounder. However its addition to the models that adjusted for demographics, insomnia and psychiatric disorders did not lead to any marked differences in the magnitude or significance of observed associations. Benzodiazepine prescription history could also theoretically be acting as an effect modifier, we therefore conducted sensitivity analyses in which study results were repeated stratified by benzodiazepine prescription history, and then interaction terms were tested. Results for stratified analyses for the fully adjusted models are shown in appendix 6. Three differences were apparent. The effect of the highest index dose category (OR, 4.11; 95% CI 2.94-5.74 vs. OR, 2.19; 95% CI, 0.90-5.37), psychotherapy (OR, 1.42; 95% CI 1.11-1.83 vs. OR, 1.34; 95% CI, 0.89-2.00) and stimulant prescription (OR, 0.92; 95% CI 0.46-1.81 vs. OR, 1.41; 95% CI, 1.02-1.95) was significant for existing but not new benzodiazepine users. We therefore tested for interaction between benzodiazepine prescription history and all predictors, and found no significant interaction effects. Given this, combining new and existing prescriptions and controlling for benzodiazepine prescription history seemed a reasonable approach.

Finally, we are unable to consider whether benzodiazepine prescription predicts problem benzodiazepine use in the entire MarketScan population since there is a structural violation of the positivity assumption. That is, individuals prescribed benzodiazepines will be at an increased risk for problem use from factors other than the prescription which can't be controlled for. For example, individuals with psychiatric diagnoses that are indications for benzodiazepine prescriptions may have an increased risk of problem use, but we can't control for these diagnoses since they are required to obtain prescription. Therefore, this research is rooted in the assumption that individuals prescribed benzodiazepines are an important high risk group to consider for problem benzodiazepine use.

Nonetheless, the current paper has several notable strengths. It is the first attempt to obtain prospective information on risk factors for problem use of benzodiazepines among individuals with a benzodiazepine prescription. This includes risk factors which can be modified by the clinician to reduce the possibility of problem use among individuals with a prescription, including those who are most vulnerable. We have provided important information that can be used to determine which individuals will be at highest risk of problem use if they are prescribed benzodiazepines, and how to prescribe benzodiazepines in a way that minimizes the risk of problem use. Our definition of problem use represents an improvement over prior work which was limited to either abuse/dependence diagnoses[22,61,6261,63] or overdose[29,3424,100-102] (we combined these two indicators of problem use), or was subject to self-report bias[1-3,9,27,28,103]. Thus, the present findings contribute a significant advance in our understanding of the risk factors for problem benzodiazepine use among individuals with a prescription.

In summary, we have shown that modifiable variables including prescription characteristics, the amount of benzodiazepine prescribed over time and prescription contextual factors independently increased the risk of problem benzodiazepine use among individuals with a prescription. This information can be used to develop specifically targeted prevention and treatment interventions, such as surveillance systems, to address the burden of problem benzodiazepine use in the U.S.

TABLES

Table 3.1. Sample Characteristics: frequencies and relationship to the outcome

Sample characteristics		FREQUENCIES				Crude relationship to outcome		
		sample		proportion with outcome[a]				
		N or mean	%	N or mean	%	OR	lower 95% CI	upper 95% CI
age[b] (mean years)		48.48	n/a	48.48[e]	n/a	**0.97**	**0.96**	**0.97**
sex[b]	male	72,006	31.28	270	0.37		*REF*	
	female	158,195	68.72	542	0.34	0.91	0.79	1.06
employment type[b]	union	61,484	26.59	269	0.44		*REF*	
	not union	96,325	41.65	281	0.29	**0.67**	**0.56**	**0.79**
	other/unknown	73,458	31.76	302	0.41	0.94	0.80	1.11
region[c]	south	93,636	40.81	303	0.32		*REF*	
	northeast	17,440	7.60	60	0.34	1.06	0.81	1.40
	north central	70,171	30.68	260	0.37	1.15	0.97	1.35
	west	46,044	20.08	182	0.39	**1.22**	**1.02**	**1.47**
	unknown	2,098	0.91	7	0.33	1.03	0.49	2.18
Psychiatric diagnosis[d]	no	178,876	77.70	331	0.19		*REF*	
	yes	50,844	22.30	481	0.94	**5.10**	**4.44**	**5.87**
Insomnia[d]	No	226,703	98.48	785	0.35		*REF*	
	Yes	3,498	1.52	27	0.77	**2.24**	**1.52**	**3.30**
Benzodiazepine prescription history[d]	New	114,347	49.44	278	0.24		*REF*	
	Existing	116,920	50.56	574	0.49	**2.02**	**1.75**	**2.34**

[a] Outcome is problem benzodiazepine use during the follow-up period
[b] At the time of the index prescription
[c] Region in which the prescription was filled
[d] During the 6 month look-back period
[e] Mean age among individuals with the outcome. Note that mean age among individuals without the outcome is 56.47 years

Table 3.2. Benzodiazepine characteristics: frequencies

Benzodiazepine characteristics[a]		Sample		proportion with outcome[b]	
		N	*%*	*N*	*%*
Dose (alprazolam equivalent mgs)	≤1.5	185,632	80.27	524	0.28
	1.5-4.0	42,281	18.28	283	0.67
	>4.0	3,354	1.45	45	1.34
Index benzodiazepine type	Alprazolam	101,002	43.67	403	0.40
	Alprazolam-XR	982	0.42	13	1.32
	lorazepam	51,541	22.29	177	0.34
	temazepam	15,129	6.54	55	0.36
	chlordiazepoxide	2,196	0.95	12	0.55
	diazepam	44,746	19.35	118	0.26
	clorazepate	5,682	2.46	12	0.21
	other	9,989	4.32	62	0.62
Half-life	Short	174,233	75.69	648	0.37
	Long	55,968	24.31	164	0.29
Clinical onset	Short	17,592	7.64	56	0.32
	Intermediate	160,498	69.72	619	0.39
	Long	52,111	22.64	137	0.26
Potency	High	159,251	69.18	610	0.38
	Low	70,950	30.82	202	0.28

[a] Of the index benzodiazepine prescription
[b] Outcome is problem benzodiazepine use during the follow-up period

Table 3.3 Benzodiazepine characteristics: logistic regression results

Benzodiazepine characteristics[a]		LOGISTIC REGRESSION RESULTS											
		crude			adjusting for demographics and insomnia[b]			adjusting for demographics, insomnia and a psychiatric disorder			adjusting for demographics, insomnia, a psychiatric disorder and benzodiazepine prescription history		
		OR	*lower 95% CI*	*upper 95% CI*	*OR*	*lower 95% CI*	*upper 95% CI*	*OR*	*lower 95% CI*	*upper 95% CI*	*OR*	*lower 95% CI*	*upper 95% CI*
Main analyses:													
Dose (alprazolam equivalent mgs)	≤1.5		*REF*			*REF*			*REF*			*REF*	
	1.5-4.0	**2.38**	**2.06**	**2.75**	**2.54**	**2.19**	**2.94**	**2.35**	**2.02**	**2.72**	**2.20**	**1.90**	**2.55**
	>4.0	**4.80**	**3.54**	**6.53**	**5.04**	**3.71**	**6.87**	**4.14**	**3.04**	**5.64**	**3.70**	**2.71**	**5.06**
Abuse potential score (continuous)		**1.14**	**1.02**	**1.27**	**1.16**	**1.04**	**1.31**	1.07	0.95	1.19	1.02	0.91	1.14
Post-hoc analyses :													
Index benzodiazepine type	Alprazolam		*REF*			*REF*			*REF*			*REF*	
	Alprazolam-XR	**3.35**	**1.92**	**5.84**	**2.85**	**1.63**	**4.98**	1.71	0.98	2.99	**2.07**	**1.18**	**3.63**
	lorazepam	0.86	0.72	1.03	0.85	0.71	1.02	**0.82**	**0.68**	**0.98**	**0.86**	**0.72**	**1.03**
	temazepam	0.91	0.69	1.21	0.93	0.70	1.24	0.95	0.71	1.26	1.01	0.76	1.34
	chlordiazepoxide	1.37	0.77	2.44	1.57	0.88	2.80	1.47	0.83	2.62	1.60	0.89	2.84
	diazepam	**0.66**	**0.54**	**0.81**	**0.58**	**0.47**	**0.71**	**0.74**	**0.60**	**0.91**	0.83	0.67	1.02
	clorazepate	**0.53**	**0.30**	**0.94**	0.61	0.34	1.08	0.65	0.37	1.16	0.62	0.35	1.11
	other	**1.56**	**1.19**	**2.04**	**0.58**	**0.38**	**0.89**	0.65	0.42	1.00	0.70	0.45	1.08
Half-life	Short		*REF*			*REF*			*REF*			*REF*	
	Long	**0.79**	**0.66**	**0.94**	**0.73**	**0.61**	**0.86**	0.88	0.74	1.04	0.95	0.80	1.13
Clinical onset	Short		*REF*			*REF*			*REF*			*REF*	
	Intermediate	1.21	0.92	1.59	1.18	0.89	1.55	1.13	0.86	1.49	1.09	0.83	1.44
	Long	0.83	0.61	1.13	0.73	0.53	1.00	0.88	0.65	1.21	0.92	0.67	1.27
Potency	High		*REF*			*REF*			*REF*			*REF*	
	Low	**1.35**	**1.15**	**1.58**	**1.43**	**1.22**	**1.67**	**1.199**	**1.01**	**1.40**	1.11	0.95	1.31

[a] Of the index benzodiazepine prescription
[b] Demographic variables include age, geographic region and employment class

Table 3.4. The amount of benzodiazepine prescribed: frequencies among existing prescriptions

The amount of benzodiazepine prescribed[a]		Sample		Proportion with outcome[b]	
		N	*%*	*N*	*%*
Medication Possession Ratio	≤0.5	68,633	58.70	235	0.34
	0.5-1	41,783	35.74	253	0.61
	>1	6,504	5.56	86	1.32
Days supply in baseline	≤30 days	33,536	28.67	101	0.30
	30-60 days	17,942	15.35	70	0.39
	61-90 days	17,165	14.68	64	0.37
	91-120 days	12,415	10.62	59	0.48
	121-180 days	29,368	25.12	194	0.66
	>180 days	6,504	5.56	86	1.32

[a] During the 6 month look-back period
[b] Outcome is problem benzodiazepine use during the follow-up period

Table 3.5. The amount of benzodiazepine prescribed: logistic regression results among existing prescriptions

The amount of benzodiazepine prescribed[a]		LOGISTIC REGRESSION RESULTS								
		crude			adjusting for demographics and insomnia[b]			adjusting for demographics and a psychiatric disorder		
		OR	*lower 95% CI*	*upper 95% CI*	*OR*	*lower 95% CI*	*upper 95% CI*	*OR*	*lower 95% CI*	*upper 95% CI*
Medication Possession Ratio	≤0.5		*REF*			*REF*			*REF*	
	0.5-1	**1.77**	**1.48**	**2.12**	**2.01**	**1.68**	**2.41**	**1.83**	**1.53**	**2.20**
	>1	**3.90**	**3.04**	**5.00**	**4.23**	**3.30**	**5.44**	**3.46**	**2.70**	**4.46**
Days supply in baseline	≤30 days		*REF*			*REF*			*REF*	
	30-60 days	1. 30	0.96	1.76	**1.45**	**1.07**	**1.97**	1.36	1.00	1.85
	61-90 days	1.24	0.91	1.70	**1.55**	**1.13**	**2.13**	**1.44**	**1.05**	**1.98**
	91-120 days	**1.58**	**1.15**	**2. 18**	**1.87**	**1.35**	**2.58**	**1.65**	**1.19**	**2.28**
	121-180 days	**2.20**	**1.73**	**2.80**	**2.78**	**2.18**	**3.55**	**2.45**	**1.91**	**3.13**
	>180 days	**4.44**	**3.32**	**5.92**	**5.25**	**3.92**	**7.03**	**4.16**	**3.10**	**5.58**

[a] During the 6 month look-back period
[b] Demographic variables include age, geographic region and employment class period

Table 3.6. Benzodiazepine prescription contextual variables: frequencies

Benzodiazepine prescription contextual variables[a]		Sample		proportion with outcome[b]	
		N	*%*	*N*	*%*
Psychotherapy	yes	35,209	15.23	361	1.03
	no	195,051	84.73	451	0.23
Opioid prescription	yes	81,777	35.52	477	0.58
	no	148,424	64.48	335	0.23
Sedative prescription	yes	31,502	13.68	223	0.70
	no	198,699	86.32	591	0.30
Stimulant prescription	yes	5,763	2.50	49	0.85
	no	224,438	97.50	763	0.34

[a] During the 6 month lookback period
[b] Outcome is problem benzodiazepine use during the follow-up period

Table 3.7. Benzodiazepine prescription contextual variables: logistic regression results in the total sample

Benzodiazepine prescription contextual variables[a]	LOGISTIC REGRESSION RESULTS											
	crude			adjusting for demographics and insomnia[b]			adjusting for demographics, insomnia and a psychiatric disorder			adjusting for demographics, insomnia, psychiatric disorder and benzodiazepine prescription history		
	OR	*lower 95% CI*	*upper 95% CI*	*OR*	*lower 95% CI*	*upper 95% CI*	*OR*	*lower 95% CI*	*upper 95% CI*	*OR*	*lower 95% CI*	*upper 95% CI*
Psychotherapy[c]	**4.48**	**3.90**	**5.15**	**4.13**	**3.59**	**4.75**	**1.45**	**1.18**	**1.80**	**1.39**	**1.12**	**1.72**
Opioid prescription[c]	**2.60**	**2.26**	**2.98**	**2.78**	**2.41**	**3.20**	**2.67**	**2.32**	**3.08**	**2.45**	**2.12**	**2.83**
Sedative prescription[c]	**2.37**	**2.03**	**2.77**	**2.45**	**2.09**	**2.87**	**1.87**	**1.60**	**2.19**	**1.76**	**1.50**	**2.06**
Stimulant prescription[c]	**2.51**	**1.88**	**3.36**	**2.17**	**1.62**	**2.90**	1.32	0.98	1.78	1.28	0.95	1.72

[a] During the 6 month look-back period
[b] Demographic variables include age, geographic region and employment class

Chapter 4. Diagnostic risk factors for problem benzodiazepine use and their relationship to prescription-related risk factors, among individuals prescribed benzodiazepines

ABSTRACT

Context: There is concern regarding the increasing prevalence and growing burden of problem benzodiazepine use in the United States. Individuals with a benzodiazepine prescription who have psychiatric disorders that make them susceptible to problem benzodiazepine use may be a particularly high risk group requiring research attention. Objective: We used health-claims data to determine whether the risk of problem benzodiazepine use among individuals with a prescription can be predicted by alcohol, drug, anxiety and mood disorders, and whether the effects of these factors are modified by prescription-related characteristics. Design, Setting and Participants: Medical and pharmacy claims of 231,267 individuals in the 2003 and 2004 *Thompson Reuters MarketScan® Commercial Claims Databases* who received a benzodiazepine prescription between July and December 2003. Main Outcome Measure: Problem benzodiazepine use, including benzodiazepine use disorder or overdose, during the follow-up period. Results: Alcohol, drug and mood disorders were strong and robust significant predictors of problem benzodiazepine, controlling for demographics and any psychiatric disorder. A significant, but lower, effect of anxiety disorders was also observed. In addition, the relationship between anxiety disorders and opioid prescriptions was superadditive, while the relationship between anxiety disorders and psychotherapy was subadditive. Conclusion: Psychiatric disorders for which benzodiazepines are indicated (alcohol and anxiety disorders) or used off-label (drug and mood disorders) independently increased the risk of problem benzodiazepine use among individuals with a prescription. This suggests the need to carefully monitor individuals with these psychiatric disorders who are prescribed benzodiazepines. Psychotherapy and opioid prescriptions modify the increased risk of problem benzodiazepine use conferred by an anxiety disorder. This information could help to direct interventions specifically targeted to reducing problem benzodiazepine use among individuals with anxiety disorders who are prescribed benzodiazepines.

INTRODUCTION

Benzodiazepines are efficacious medications that are widely used in the medical management of anxiety[10-12] and other disorders[12,13] in the United States[12,14]. However, the abuse potential of these medications have created concerns due to recent increases in the prevalence and burden of problem use[1-4,10,11,17]. Of particular concern is the alarming rate at which clinically significant problem use, i.e. problem use associated with clinically significant impairment or distress, appears to be increasing. For example, the number of benzodiazepine-related substance abuse treatment admissions nearly tripled between 1998 and 2008, despite that fact that only an 11% increase was observed in overall treatment admissions[18]. Although most epidemiological research on problem prescription drug use, including benzodiazepines, has focused on use among individuals without a prescription[5-9], individuals with a prescription may be particularly vulnerable to problem use[9,16-20]. These individuals have access and exposure to the medication, and may also have underlying psychopathology that increases their risk of substance abuse problems. Understanding the role of such psychopathology in the development of problem benzodiazepine use among individuals prescribed the medication could provide important information that can be used to develop effective interventions to reduce the prevalence and burden of problem benzodiazepine use, targeted to the most high-risk groups. Four important groups that may be prescribed benzodiazepines include individuals with alcohol disorders, drug disorders, anxiety disorders and mood disorders.

Benzodiazepines are recommended as front-line medication for the management of acute alcohol withdrawal[68,104], however several pieces of evidence suggest a greater risk of problem benzodiazepine use for individuals with alcohol use disorders. Experimental benzodiazepine administration studies consistently report that individuals with alcohol use disorders have a greater sensitivity to the reinforcing and euphoric effects of benzodiazepines than individuals without alcohol use disorders[17,72-74]. This is further supported by recent evidence implicating benzodiazepine receptors in alcohol dependence[75]. In addition are the similar pharmacological properties of benzodiazepines and alcohol, namely their role as central nervous system depressants associated the GABA receptor complex[68]. A clinically useful effect of these pharmacologic similarities is that benzodiazepines can be used to reduce the symptoms of alcohol

detoxification[68]. However a potentially problematic effect is pharmacological synergy- co-administration of alcohol and benzodiazepines can produce an enhanced euphoric and reinforcing effect, resulting in a higher abuse potential[68]. Studies conducted in epidemiological and clinical populations are consistent with these basic science findings. Alcohol use disorders are associated with problem benzodiazepine use in population-based studies[1,3,9] and clinically significant problem benzodiazepine use often appears alongside clinically significant problem alcohol use [18]. Thus, individuals with alcohol problems may have a pre-existing vulnerability to problem benzodiazepine use, and exposing these individuals to benzodiazepines via a medical prescription might create the necessary circumstances for such use. If the risk of problem benzodiazepine use among those prescribed benzodiazepines is higher for individuals with alcohol disorders, then consideration of non-benzodiazepine based medication strategies could be required. A first step to determining whether this is necessary is to establish the risk of problem benzodiazepine use conferred by alcohol disorders among individuals with a benzodiazepine prescription.

Benzodiazepines are also used in the treatment of detoxification from psychoactive drugs[68], such as opioids[105], to treat a range of symptoms such as insomnia, an anxiety or agitation[106]. As with alcohol, this medical approach is based on the pharmacological similarities between benzodiazepines and other psychoactive substances. For example, long-term opioid use can alter the GABA system, which is the primary system of action for benzodiazepines[106]. However, again as with alcohol, pharmacological similarities entail pharmacological synergy, which entails an elevated abuse potential profile of benzodiazepines. Accordingly, drug use disorders predict problem benzodiazepine use in population-based studies[1,3,9], and clinically significant problem benzodiazepine use cases are often accompanied by clinically significant problem of other drugs [18]. For example, 95% of all benzodiazepine-related treatment admissions in 2008 involved the abuse of another substance, and around 75% of these involved other psychoactive drugs (54.2% opioids, 11.4% marijuana, 9.6% other drugs)[18]. Therefore exposing individuals with other drug problems to benzodiazepines via a medical prescription could precipitate problem benzodiazepine use. Since this could have clinical implications on appropriate medication strategies for individuals with drug disorders, assessment of the role of drug use disorders in the development of problem benzodiazepine use among individuals with a prescription appears warranted.

Further, benzodiazepines are the FDA-approved pharmacotherapy of choice in the treatment of several anxiety disorders[11], and are widely used off-label in the treatment of mood disorders[13,68]. Cross-sectional epidemiological studies have demonstrated a specific association between anxiety and mood disorders and problem benzodiazepine use in the general population and among individuals with a prescription[3]. Therefore, individuals with these disorders who are prescribed benzodiazepines may require increased clinical attention to prevent the development of problem medication use, or perhaps alternative treatment options. To determine whether this may be necessary, it is important to establish the risk of problem benzodiazepine use conferred by anxiety and mood among individuals with a benzodiazepine.

Information on the specific role of alcohol, drug, anxiety and mood disorders in the development of problem benzodiazepine use among individuals with a prescription could help guide clinicians' decisions on which patients should be prescribed benzodiazepines. For example, clinicians could choose to prescribe other effective anxiety medications (e.g. selective serotonin reuptake inhibitors (SSRIs), venlafaxine, mirtazapine, hydroxyzine, buspirone[107]) to individuals who are at an increased risk of engaging in problem benzodiazepine use. However, there may be circumstances when a clinician thinks that benzodiazepines would be the most effective line of treatment even for an individual at increased risk (e.g. if other treatments have proven ineffective). In this event, it is important to understand ways to reduce this risk. One way to do this is to consider whether previously identified risk factors related to characteristics and the context of the benzodiazepine prescription (referred to as prescription-related characteristics) interact with psychiatric disorders to predict problem benzodiazepine use among individuals with a prescription.

Previously, we have shown that problem benzodiazepine use can be predicted by benzodiazepine dosage, the amount of time an individual is prescribed benzodiazepines (as measured by the number of days), the Medication-Possession Ratio (i.e. the amount of medication individual is in possession in relation to the medically necessary amount), prescription for controlled opioids and sedatives, and recent psychotherapy. If at least some individuals in the population require both psychiatric disorders (i.e.

alcohol, drug, anxiety or mood disorders) and prescription-related characteristics (i.e. dosage, number of days, Medication-Possession Ratio, prescription for opioids or sedatives, and psychotherapy) to develop problem benzodiazepine use, then the relationship between these two types of risk factors will be synergistic. That is, the risk of one will be exacerbated by the presence of the other. For these individuals, eliminating either the psychiatric disorder or the prescription-related characteristics would eliminate the risk of problem benzodiazepine use conferred by this causal pathway [108]. From a public health perspective, there could be great value in identifying easily-manipulable intervention-amenable prescription-related characteristics that could modify the pathway between psychiatric disorders and problem benzodiazepine use.

This paper intends to address the above issues using a large prospective dataset of medical and pharmaceutical claims. Specifically, we intend to determine whether:

1. The risk of problem benzodiazepine use among individuals prescribed benzodiazepines can be predicted by psychiatric disorders (alcohol use disorders, drug use disorders, anxiety disorders and mood disorders).
2. Previously identified prescription-related risk factors (including dosage, number of days supplied, Medication Possession Ratio, opioid prescription, sedative prescription, psychotherapy) modify the effect of the psychiatric disorders on the risk of problem benzodiazepine use, among individuals prescribed benzodiazepines.

METHODS

Sample and procedures

This paper used longitudinal data from the January 1st 2003 to December 31st 2004 *MarketScan*® *Commercial Claims Databases*. The *MarketScan*® *Databases* provide comprehensive health-care data from enrollees of health care plans from large employers, and captures longitudinal person-specific information on clinical utilization, expenditures, and enrollment across inpatient, outpatient, prescription drug and carve-out services (i.e. a program separate from the primary group health plan that is designed

to provide a specialized type of care, such as a mental health carve-out). The databases are constructed from privately insured medical and prescription drug claims. The MarketScan Research Databases link paid claims and encounter data to detailed patient information across sites and types of providers, and over time. Each patient is given a unique identifier which ensures patient confidentiality but allows for individual-level tracking of each patient over time and across medical, outpatient pharmaceutical, enrollment and benefit plan files.

The *Thompson Reuters MarketScan® Commercial Claims Databases* represents the medical experience of insured active employees, early (non-Medicare) retirees, Consolidated Omnibus Budget Reconciliation Act (COBRA) continues, and dependents insured by employer-sponsored plans (i.e. persons not eligible for Medicare). Collectively, the databases incorporate data from almost 100 payers including commercial insurance companies, Blue Cross and Blue Shield plans, and third-party administrators. Each employer database is constructed by collecting raw data from the appropriate payer(s). These raw data are service-level adjudicated paid claims and capitated encounters containing both inpatient and outpatient services. Clinical and demographic variables are standardized to common definitions, and benefit plan type, characteristics, enrollment, outpatient pharmaceutical claims and medical data are integrated. Clinical detail, such as major diagnostic categories, diagnosis-related groups and therapeutic class are added to claims.

Several measures are taken to ensure the robustness of the data. Edits on the reasonableness of data check the relationship between two or more fields to ensure that they are reasonable against norms. Examples of reasonableness checks include diagnosis against age or sex, and charge against payment. Validity checks are conducted for selected fields, including diagnosis codes, procedure codes, date(s) of service, sex and age, to compare recorded values to lists of possible valid values for those fields. Improper coding is flagged to recommend data quality improvement actions to the carrier or data processor. Diagnosis codes are compared with the procedure codes that were in effect at that time, and edited if necessary.

The total study sample was limited to the 231,267 individuals in the 2003 and 2004 *Thompson Reuters MarketScan® Commercial Claims Databases* who were enrolled in their insurance plan for at least 6 months (defined as 180 days) preceding and 12 months (defined as 365 days) following an index oral benzodiazepine prescription. The index prescription is the prescription whose effect we are examining. The 6 months preceding the index benzodiazepine prescription is referred to as the look-back period. The 12 months following the index prescription is referred to as the follow-up period. This study design allowed for a 12 month possible look-back period (January 2003-December 2003), an 18 month possible follow-up period (July 2003-December 2004), and a 6 month ascertainment period (July 2003-December 2003) within which to identify eligible index oral benzodiazepine prescriptions. Oral benzodiazepine prescriptions filled during the ascertainment period were considered ineligible if the days' supply was less than or equal to 0, or if the number of units dispensed, was less than 1. To calculate new, rather than prevalent, cases of problem benzodiazepine use during follow-up, we further excluded all individuals who were positive for problem benzodiazepine use during the 6 month-look back period. Note that for patients who filled multiple eligible index prescriptions, the first prescription filled was considered their index prescription. Information on attrition is provided in Appendix 1.

Measures

Diagnoses and procedure codes in the *MarketScan® Commercial Claims Databases* use the International Classification of Disease, Ninth Revision, Clinical Modifications (ICD-9-CM) classification system[90]. Unless otherwise noted, variables were created for the total sample.

Outcome: Problem Benzodiazepine Use

Problem benzodiazepine use was defined as receiving a diagnosis corresponding to least one of the following codes in any field and in any setting during the 12 month follow-up period (July 2003-December 2004).

3. Diagnosis of benzodiazepine abuse or dependence (ICD-9 codes 305.4, 305.40, 305.41, 305.42, 305.43, or 304.1, 304.10, 304.11, 304.12, 304.13)
4. Poisoning involving benzodiazepine (accidental or non-accidental) (ICD-9 codes E853.2 or 969.4)

All other individuals were classified as negative for problem benzodiazepine use. Note that although all subjects are negative for problem benzodiazepine use during their 6 month look-back period, since we do not have information on problem benzodiazepine use prior to January 2003 this outcome measures new, rather than incident, cases of problem benzodiazepine use.

Hypothesized Risk Factors: Psychiatric Disorders

The time-frame for all psychiatric disorders is the six month look-back period. Psychiatric disorder measures only capture individuals who filed a claim related to the psychiatric disorder during the 6 month look-back period. Please note that more detailed information on the ICD-9 codes used to create these variables is provided in appendix 2.

Alcohol Use Disorders: A binary alcohol use disorder variable will be created. Alcohol disorders will be classified as positive if the subject received a diagnosis of any alcohol-related disorder (ICD9 codes: 303, 303.0, 303.00, 303.01, 303.02, 303.03, 303.9, 303.90, 303.91, 303.92, 303.93, 305, 305.0, 291, 291.0, 291.1, 291.2, 291.3, 291.4, 291.5, 291.8, 291.81, 291.82, 291.8, 9291.9, 977.3, 980, 980.0, E8601) in any field and in any setting (1:any alcohol use disorder; 0:no alcohol use disorder).

Drug Use Disorders: A binary drug use disorder variable will be classified as positive if the subject received a diagnosis of any drug-related disorder (ICD9 codes: 292, 292.0, 292.1, 292.11, 292.12, 292.2, 292.8, 292.81, 292.82, 292.83, 292.84, 292.85, 292.89, 292.9, 304, 304.0, 304.00, 304.01, 304.02, 304.03, 304.2, 304.20, 304.22', 304.23, 304.3, 304.30, 304.31, 304.32, 304.33, 304.4, 304.40, 304.41, 304.42, 304.43, 304.5, 304.50, 304.51, 304.52, 304.53, 304.6, 304.60, 304.61, 304.62, 304.63, 304.7, 304.70, 304.71, 304.72, 304.73, 304.8, 304.81, 304.82, 304.83, 304.9, 304.90, 304.91, 304.92, 304.93, 305, 305.0, 305.00, 305.01, 305.02, 305.03, 305.1, 305.10, 305.2, 305.20, 305.21, 305.22, 305.23, 305.3, 305.30, 305.32, 305.33, 305.5, 305.50, 305.51, 305.52, 305.53, 305.6, 305.60, 305.62, 305.63, 305.7, 305.70, 305.71, 305.73, 305.8, 305.83, 305.90, 305.91, 305.92, 305.93, E850.0, E850.1, E850.2, E851, E852) in any field and in any setting (1:any drug use disorder; 0:no drug use disorder).

Anxiety Disorders: A binary anxiety disorder variable will be classified as positive if the subject received a diagnosis of any anxiety disorder (ICD-9 codes: 293.84, 293.89, 300, 300.0, 300.00, 300.01, 300.02, 300.09, 300.2, 300.20, 300.21, 300.22, 300.23, 300.29, 308.3) in any field and in any setting (1:any anxiety disorder; 0:no anxiety disorder).

Mood Disorders: A binary mood disorder variable will be classified as positive if the subject received a diagnosis of any mood disorder (ICD-9 codes: 296, 296.0, 296.01, 296.02, 296.03, 296.04, 296.05, 296.06, 296.1, 296.10, 296.11, 296.12, 296.13, 296.14, 296.15, 296.16, 296.2, 296.20, 296.21, 296.22, 29623, 29624, 296.25, 296.26, 296.3, 296.30, 296.31, 29.632, 296.33, 296.34, 296.35, 296.36, 296.4, 296.40, 296.41, 296.42, 296.43, 296.44, 296.45, 296.46, 296.5, 296.50, 296.51, 296.52, 296.53, 296.54, 296.55, 296.56, 296.6, 296.60, 296.61, 296.62, 296.63, 296.64, 296.65, 296.66, 296.7, 296.80, 296.81, 296.82, 296.89, 296.9, 296.90, 296.99, 298.0, 300.4, 301.13, 311, 311.0) in any field and in any setting (1:any mood disorder; 0:no mood disorder).

Hypothesized Effect Modifiers: Prescription-Related Characteristics

Dosage: To measure the daily dosage of the index prescription, we divided the total alprazolam-equivalent milligrams dispensed by the number of days supplied and then created a three-level variable to reflect prescribing guidelines[85] which suggest a 1.5mg starting dose to be slowly titrated up to 4mg. Caution is advised when prescribing more than 4mgs. Therefore the levels of the categorical variable were less than or equal to 1.5mg (referent), between 1.5 mg and 4mg and more than 4mgs. This measurement of dose reflects the prescribed daily dose, but may not reflect the actual amount consumed.

Days' supply in baseline: We created a categorical variable to measure the number of days a patient was prescribed benzodiazepines during the look-back period (1: ≤30 days (referent); 2: 31-60 days; 3: 60-90 days; 4: 90-120 days; 5: 120-180 days; 6: >180 days). This categorization will allow us to determine the effect of long-term use which is usually defined as use for four months or more[17], identify a dose-response relationship and consider the role of overlapping prescriptions. Note that this variable was only created for individuals who received a benzodiazepine prescription during the look-back period.

Medication-Possession Ratio: The Medication-Possession Ratio was measured was measured by dividing the sum of the daily prescribed dosages the patient has during a defined period of time by the number of days during that prescription period. For example, if a patient filled 2 30-day prescriptions over a 60 day period then their MPR would be 30+30/60=1. A three level-categorical variable was then created to indicate whether a patient had an MPR less than or equal to 0.5 (referent), between 0.5 and 1, or greater than 1. Note that this variable was only created for individuals who received a benzodiazepine prescription during the look-back period.

Utilization of psychotherapeutic services: A binary variable was created to indicate whether the patient utilized any psychotherapeutic service during their 6 month look-back period (1: psychotherapeutic service utilization; 0: no psychotherapeutic service utilization).

Prescription of other controlled substances: Three binary variables were created to identify individuals who received prescriptions for opioids (1: opioid prescription; 0: no opioid prescription), other sedative/hypnotic including barbiturates (1: sedative prescription; 0: no sedative prescription) and stimulants (1: stimulant prescription; 0: no stimulant prescription) during the 6 month look-back period.

Hypothesized Confounders

Sociodemographics: Age at the time of the index prescription (continuous), sex (1:male; 2:female), geographic region (1:North East; 2:North Central; 3:South; 4:West; 5: unknown) and employment type (1:union; 2:non-union; 3:other/unknown) were included as possible confounders based on relationships between related variables and the exposures and outcomes in the literature[1,3,9], and observed relationships and in the dataset.

Insomnia: Since benzodiazepines are often prescribed for initial insomnia, a binary variable was created to indicate whether an individual was diagnosed with any insomnia during the six month look-back period

(1: any insomnia during the look-back period; 0: no insomnia during the look-back period). Note that specific ICD-9 codes are provided in appendix 2.

Benzodiazepine prescription history: A binary variable was created to indicate whether an individual received a benzodiazepine prescription during the 6 month look-back period (1: existing prescriptions; 0: new prescription).

Note that additional information on confounder selection is provided in the statistical analysis section.

Statistical analysis

Analyses were conducted in SAS 9.3. The outcome variable was problem benzodiazepine use during a 12 month follow-up period.

Confounders: Confounders for all hypothesized predictors included age, geographic region, employment type and comorbid alcohol, drug, mood or anxiety disorders. These variables were selected a priori based on previous work in which they were found to be important predictors of problem benzodiazepine use[1,3,9] and met standard criteria for confounder inclusion including observed association with the exposures and outcome ($p<0.05$), and a change of 10% or more in the crude exposure-outcome association (beta). Note that gender was initially considered as a potential confounder based on past work associating it with problem benzodiazepine use and at least some of the predictors[1-3], however it was unrelated to the outcome in our dataset and was therefore not included as a confounder. Also note that comorbidity was considered as a binary variable (1: any other disorder present, 0: no other disorder present) in interaction analyses.

In addition, we also considered benzodiazepine prescription history during the baseline period as a potential confounder given research suggesting that covariates for medication users at study entry can be affected by the medication itself which could introduce confounding in the causal pathway[92], and this variable met the standard criteria for confounder selection provided in the above paragraph. Since

benzodiazepines are used to treat insomnia, we evaluated insomnia as a confounder, and included it in analyses involving drug, anxiety and mood disorders (it was not related to alcohol disorders).

Analyses: To address aim 1 and determine whether the risk of problem benzodiazepine use among individuals prescribed benzodiazepines can be predicted by psychiatric disorders (alcohol use disorders, drug use disorders, anxiety disorders and mood disorders), we generated a series of Logistic Regression models to examine the effect of each hypothesized risk factor on the outcome. We began by estimating crude and sociodemographic-adjusted ORs and 95% CIs first in four separate models for each of the psychiatric disorders. Next, we generated one logistic regression model that included all four psychiatric disorders and the sociodemographic characteristics. Following, we added benzodiazepine prescription history into the model that contained the four psychiatric disorders and the sociodemographic characteristics.

To address aim 2 and determine whether these psychiatric disorders interact with previously identified prescription-related risk factors to predict the risk of problem benzodiazepine use, among individuals prescribed benzodiazepines we estimated attributable proportions due to synergy (APs) [108,109] and 95% CIs for problem benzodiazepine use utilizing the method of Andersson et al., [110], which has been used extensively in previous analyses of additive interactions with binary outcomes, e.g., [111,112]. Full models for aim 2 are provided in appendix 6.

For each psychiatric disorder, and each previously identified prescription-related risk factors (including dosage, days supply, medication-possession ratio, opioid prescription, sedative prescription, psychotherapy) APs were calculated using the formula (OR_{11} - OR_{10} - OR_{01} + 1) / OR_{11} [108,113] which tests whether the joint effect of the psychiatric disorder and the prescription-related characteristic (OR_{11}) differs from the sum of the effect of the psychiatric disorder in the absence of the prescription-related characteristic (OR_{10}) and the effect of the prescription-related characteristic in the absence of the psychiatric disorder (OR_{01}). An AP of 0 indicates no synergy (i.e. that $OR_{11} = OR_{10} + OR_{01}$), while an AP greater than 0 indicates synergy (i.e. that $OR_{11} > OR_{10} + OR_{01}$). Analyses for all psychiatric disorders

adjusted for sociodemographics, comorbid disorder and benzodiazepine prescription history. Analyses for all drug, anxiety and mood disorders additionally controlled for insomnia.

Note that analyses that included the prescription-related characteristics number of days prescribed and the Medication-Possession Ratio were only conducted among individuals with existing prescriptions, since they are not applicable to individuals not prescribed benzodiazepines during the look-back period.

RESULTS

Sample characteristics (Table 4.1)

The mean age of the total sample was 48 years, approximately two thirds (68.8%) were female and a quarter (27%) had a union job. The majority filled prescriptions in the south (41%) and north central (31%) areas of the US. Almost one quarter (22%) were diagnosed with any psychiatric disorder and approximately half (51%) received a benzodiazepine during the 6 month look-back period.

The outcome, problem benzodiazepine use during the 12 month follow-up period was rare (0.37%, N=855), and was significantly ($p<0.05$) associated with younger age, having a union job, filling the prescription in the west and receiving a benzodiazepine prescription during the look-back period.

The relationship between psychiatric disorders and problem benzodiazepine use (Tables 4.2 and 4.3)

Frequencies for psychiatric disorders are provided in Table 4.2. In order of prevalence, during the 6-month look-back period, 13.03% of the sample received a diagnosis of a mood disorder, 6.74% received an anxiety disorder diagnosis, 1.71% were diagnosed with a drug use disorder and 0.52% received an alcohol use disorder diagnosis.

Logistic regression results for the relationship between psychiatric disorders and problem benzodiazepine use are provided in Table 4.3. All four psychiatric disorders were significant predictors of problem benzodiazepine use in all considered models. Adjustment for demographics and insomnia did not

substantially change the magnitude or significance of effect estimates, however notable decreases in the magnitude of effect estimates occurred after controlling for comorbid disorders. This was most evident for alcohol use disorders, which decreased from 10.35 to 3.61. Results were not substantially changed by additionally controlling for benzodiazepine prescription history- the largest change in magnitude of the OR was for mood disorders which decreased from 4.02 to 3.54. The magnitude of the effect of alcohol (OR, 3.76), drug (3.27) and mood (OR, 3.54) were markedly higher than the effect of anxiety disorders (OR, 1.59), in the final model that adjusted for demographics, insomnia, psychiatric disorders and benzodiazepine use history.

Additive interaction results for psychiatric disorders and prescription related characteristics (Table 4.4).

Table 4.4 provides information on the individual and joint effects of the psychiatric disorders and prescription-related characteristics, and the results of the tests for additive interaction. Significant departures from additivity in the odds for problem benzodiazepine use were found in the relationship of anxiety disorders and opioid prescriptions, and of anxiety disorders and psychotherapy, adjusting for demographics, comorbid disorders and benzodiazepine prescription history. Among individuals with anxiety disorders and the prescription-related characteristic, the proportion of problem benzodiazepine use attributable to the interaction between the anxiety disorder and prescription-related characteristics was 0.157 (95% CI, 0.022-0.292) for opioid prescription, and -0.315 (95% CI, -0.539- -0.090) for psychotherapy. The odds ratios for these associations are shown in Table 4.

The relationship between anxiety disorders and opioid prescriptions was superadditive. That is, the joint effect of having an anxiety disorder and opioid prescription was greater than the sum of the individual effects of these risk factors. The relationship between anxiety disorders and psychotherapy was subadditive. That is, the joint effect of having an anxiety disorder and psychotherapy was less than the sum of the individual effects of these risk factors.

DISCUSSION

Using a very large prospective dataset of medical and pharmacy health claims, we found that among patients prescribed benzodiazepines, the risk of using this medication in problematic ways is higher among individuals recently diagnosed with alcohol, drug, anxiety and mood disorders. The role of anxiety disorders was modified by opioid prescriptions and psychotherapy. Such information could be used to identify high risk patients at the time that the prescription is written or filled and intervene with targeted evidence-based prevention and treatment interventions.

Alcohol and drug disorders each conferred over a three-fold risk of clinically significant problem benzodiazepine use among individuals prescribed benzodiazepines, independent of demographic characteristics, insomnia, comorbid psychiatric disorders and benzodiazepine prescription history. This is consistent with basic science, epidemiological and clinical research suggesting an association between alcohol and drug disorders and problem benzodiazepine use[1,3,9 18,68,75,105,106]. The clinical importance of our finding that alcohol and drug disorders predict clinically significant problem benzodiazepine use among individuals prescribed benzodiazepine lies in the widespread use of benzodiazepines in the treatment of detoxification from alcohol and other psychoactive drugs. These results may suggest a need for harm-reduction strategies when using benzodiazepines among alcohol and drug disorder patients. For example, when used in the management of substance use detoxification, the risk of developing problem benzodiazepine use may be minimized if, at least during the initial phases of treatment, benzodiazepine administration is supervised, and take-home medications are limited in the following stages of treatment. Further, when addressing other medical problems that benzodiazepines may be efficacious for (e.g. insomnia and anxiety) among patients with existing alcohol and drug disorders, clinicians may wish to consider non-benzodiazepine alternatives such as SSRIs[107]. The efficacy of such approaches could be considered.

Another potentially clinically important finding is that mood disorders also increased the risk of problem benzodiazepine use among individuals with a prescription. The magnitude of this association was comparable to the magnitude of associations observed for alcohol and drug disorders. This is particularly

important since mood disorders were by far the most prevalent psychiatric disorder among our sample of individuals prescribed benzodiazepines (13% compared to 6.7% anxiety disorders, 1.7% drug use disorders and 0.5% mood disorders). Although mood disorders are not an FDA-approved indication for benzodiazepines, clinical evidence suggests widespread off-label use[13,68]. Our finding may suggest the need for research to carefully consider the clinical benefits of benzodiazepines in the treatment of mood disorders, in relation to the potential risk of developing problem benzodiazepine use. It may also indicate the need to consider evidence-based non-benzodiazepine alternatives such as SSRIs[107] as a first line treatment for mood disorders.

Benzodiazepines are the pharmacotherapy of choice in the treatment of several anxiety disorders[11], and although anxiety disorders were associated with problem benzodiazepine use, the magnitude of this association was substantially lower than the association observed for alcohol, drug and mood disorders (OR 1.59, compared to 3.76, 3.27 and 3.54 respectively). The lower magnitude of this association may suggest that it is particularly amenable to intervention. Positively, we have identified two effect modifiers that could be used to mitigate the risk of problem use conferred by an anxiety disorder.

First is opioid prescription. We found a synergistic relationship between baseline anxiety disorders and prescription for controlled opioids. This suggests that there are at least some individuals in the population that require both an anxiety disorder and an opioid prescription in order to develop problem benzodiazepine use if they are prescribed benzodiazepines. This suggests that clinicians may wish to carefully consider the use of benzodiazepines in patients with an anxiety disorder who have recently received an opioid prescription. However, this is a very complex issue potentially intertwined with treatment for pain conditions, or with seeking opioids but taking whatever medications a particular physician was willing to prescribe. Such issues should be considered more fully prior to clinical translation of findings. Results could also provide evidence to support the argument for a universal prescription monitoring program, so that clinicians can obtain information on other prescriptions their patients may have been prescribed. However, again it is important to note that we did not find any evidence that opioid prescription modified the effect of alcohol, drug or mood disorders on the risk of problem benzodiazepine

use. Further, we found no interaction between sedative prescriptions and any of the psychiatric disorders. This suggests that the effect is specific to anxiety disorders and opioid prescriptions, a matter which could be considered further in future work.

Second is psychotherapy. We found an antagonistic relationship between baseline anxiety disorders and recent psychotherapy in the risk for problem benzodiazepine use. In other words, the risk of problem benzodiazepine use conferred by an anxiety disorder appears to be mitigated by psychotherapy. This suggests that inclusion of a psychotherapeutic component in the utilization of benzodiazepines for anxiety disorder could help to prevent the risk of problem benzodiazepine use. However, it is possible that this finding could be explained by systematic or random error. Additional research to clarify this issue would be helpful.

Study limitations are noted. First are measurement issues. Our definition of problem benzodiazepine use will primarily measure individuals at the more severe end of the spectrum who receive clinical attention. However, utilizing a definition of problem use which captures individuals at the severe end of the spectrum may be a strength rather than a weakness. It could be argued that our definition focuses on the most important group- the problem users who represent a public health concern and contribute to the burden of problem use. Therefore findings for these more severe problem users may have a more substantial public health impact than findings for problem users at the lower end of the severity spectrum. In addition, our definition of problem use represents an improvement over prior work which was limited to abuse/dependence diagnoses[22,61,6261,63] or overdose[29,3424,100-102], or was subject to self-report bias[1-3,9,27,28,103].

Another issue is that our compound outcome included some variables that were not specific to benzodiazepines- ICD-9 codes 305.4, 305.40, 305.41, 305.42, 305.43, or 304.1, 304.10, 304.11, 304.12 and 304.13 indicate an abuse or dependence diagnosis of any sedative or hypnotic. Conversely, ICD-9 codes E853.2 or 969.4 specifically indicate poisoning involving benzodiazepines. The decision to create this compound variable was based on theoretical considerations which are outlined in the discussion

section of chapter 2. However, to determine the effect of this decision, we conducted sensitivity analyses in which we repeated analyses using an outcome that only included benzodiazepine-specific ICD-9 codes (i.e. ICD-9 codes E853.2 or 969.4, benzodiazepine poisoning) and again using an outcome that only included non-benzodiazepine specific ICD-9 codes (i.e. ICD-9 codes 305.4, 305.40, 305.41, 305.42, 305.43, or 304.1, 304.10, 304.11, 304.12 and 304.13). Results for primary analyses for the fully adjusted models are provided in appendix 5. Although the direction of effect remained the same, some changes in magnitude of association were observed. The odds ratio for the benzodiazepine-specific outcome, non-benzodiazepine specific outcome and compound outcome used in the primary analyses was 2.92 and 3.33 and 3.76 respectively for alcohol disorders, 2.29, 4.69 and 3.27 respectively for drug disorders, 1.02, 1.48 and 1.59 respectively for anxiety disorders and 2.50, 1.66 and 3.54 respectively for mood disorders. Further, the anxiety disorder association was not significant for the benzodiazepine-specific outcome ($p<0.05$). It is not clear whether these differences in results can be explained by specificity of association to anxiolytic type, or if they are due to some other differences e.g. abuse dependence diagnoses versus poisoning. Thus, while alcohol, drug and mood disorders, and to some extent anxiety disorders, appear to be important predictors of problem anxiolytic use, these sensitivity analyses suggest the need to drill down further to understand what is driving the observed association.

Our measures of psychiatric disorders are also subject to misclassification since they will only capture individuals who filed claims relating to a diagnosis of the psychiatric disorder during the six month baseline period. Factors that might affect whether a claim is filed to reimburse treatment for a psychiatric disorder include issues such as severity, practitioner type and treatment-seeking behaviors. Another issue with these variables is that they represent clinical diagnoses which introduce confounding by specialty mental health treatment seeking. Many patients with depression, for example, do not seek treatment for their symptoms and among those who seek treatment, those who are treated by mental health specialists are far more likely to receive a depression diagnosis than those who see a generalist. Most antidepressants prescribed by generalists, for example, have no associated depression or anxiety disorder diagnoses. Similar confounding exists regarding the outcome measure itself. The outcome may be incidentally diagnosed by the same clinician who is diagnosing the other psychiatric

disorders for which care was primarily sought. Due to methodological limitations, we were unable to address these issues, however it is important for future research to consider how factors such as physician specialty may confound associations.

Since the data are limited to two years (2003 and 2004) we do not know about problem benzodiazepine use prior to 2003 and therefore cannot calculate incident problem benzodiazepine use. Instead, we have measured new instances of problem benzodiazepine use among individuals with no problem benzodiazepine use for six months. Future research should be conducted with data which spans a greater period of time to capture incident problem benzodiazepine use and incident prescriptions may also be helpful.

Also related to the time-frame is that the dataset are 10 years old. Although overall benzodiazepine prescription has not changed much during the past decade, and no new benzodiazepines have been approved by the FDA, there has been marked expansion in use of non-benzodiazepine hypnotics (e.g., zopidem, zoplicone, zaleplon)[99]. We considered this issue with sensitivity analyses in which results were replicated among individuals not prescribed other anxiolytics. Differences in magnitude only were observed for alcohol and mood disorders which dropped from 3.76 and 3.54 to 2.89 and 1.81 respectively. Reduced magnitude (1.59 to 1.09) and loss of significance ($p<0.05$) was observed for anxiety disorders. No differences were observed for drug disorders. These results could suggest that alcohol, anxiety and mood disorders have a different relationship to problem benzodiazepine use among individuals not prescribed other anxiolytics, and this could be explored in future work. It is also important to consider these relationships in more recent data- an analysis that we intend to conduct.

Sample-related limitations are also noted. First, an employee-based dataset may not generalize to other populations. Second, in order to maximize power, our study sample combined new (i.e. individuals without a benzodiazepine prescription during the 6-month look-back period) and existing (i.e. individuals with a benzodiazepine prescription during the 6-month look-back period) benzodiazepine users. By mixing incident and prevalent users, there is a risk of depletion of susceptibles – people who continue on

benzodiazepines have different risks than new initiators for her outcomes partly because those who previously developed the outcome are presumably at much less risk of continuing prescriptions during her period of observation. As such, benzodiazepine prescription history was evaluated for, and met, empirical criteria for a confounder. Its addition to the models that adjusted for demographics, insomnia and psychiatric disorders did not lead to any marked differences in the magnitude or significance of observed associations. However, to address the possibility that prescription history was acting as an effect modifier, we also conducted sensitivity analyses which involved stratifying results by benzodiazepine prescription history and also testing for interaction between predictors and prescription history. Results for primary analyses for the fully adjusted stratified models are shown in appendix 5. The most apparent difference is that the effect estimate for alcohol disorders was higher for new than existing prescriptions (OR 4.13 and 2.88 respectively). However, we found no significant interaction effects between any of the psychiatric disorders and benzodiazepine prescription history. As such, combining new and existing prescription in the main analyses seemed reasonable.

Caution should be taken in interpretation of interaction analyses. We considered several interaction analyses and only found two significant interactions, and although these assessments were rooted in Bayesian priors, this is not much beyond expectations due to chance. Further, these interactions could be the result of residual confounding or measurement error. Finally, we are unable to consider whether benzodiazepine prescription predicts problem benzodiazepine use in the entire MarketScan population since there is a structural violation of the positivity assumption. That is, individuals prescribed benzodiazepines will be at an increased risk for problem use from factors other than the prescription which can't be controlled for. For example, individuals with psychiatric diagnoses that are indications for benzodiazepine prescriptions may have an increased risk of problem use, but we can't control for these diagnoses since they are required to obtain prescription. Therefore, this research is rooted in the assumption that individuals prescribed benzodiazepines are an important high risk group to consider for problem benzodiazepine use.

In summary, we have shown that, among individuals with a benzodiazepine prescription, the risk of problem benzodiazepine use is significantly increased by the presence of alcohol, drug, anxiety and mood disorders, independent of demographics, comorbid psychiatric disorders, and benzodiazepine treatment history. This suggests the need to carefully monitor individuals with these psychiatric disorders who are prescribed benzodiazepines. Further, we have found that psychotherapy and opioid prescriptions modify the increased risk of problem benzodiazepine use conferred by an anxiety disorder. This information could help to direct interventions specifically targeted to reducing problem benzodiazepine use among individuals with anxiety disorders who are prescribed benzodiazepines.

TABLES

Table 4.1. Sample Characteristics and their relationship to the outcome and predictors

Sample characteristics		FREQUENCIES: sample N or mean	sample %	proportion with outcome[a] N or mean	proportion with outcome[a] %	Crude relationship to: Problem benzodiazepine use OR	Problem benzodiazepine use 95% CI	Alcohol use disorder OR	Alcohol use disorder 95% CI	Drug use disorder OR	Drug use disorder 95% CI	Anxiety disorder OR	Anxiety disorder 95% CI	Mood disorder OR	Mood disorder 95% CI
age[b] (mean years)		48.48	n/a	48.48[e]	n/a	**0.97**	**0.96-0.97**	**0.99**	**0.99-1.00**	**0.99**	**0.99-0.99**	**0.98**	**0.98-0.98**	**0.99**	**0.99-0.99**
sex[b]	male	72,006	31.28	270	0.37	*REF*		*REF*		*REF*		*REF*		*REF*	
	female	158,195	68.72	542	0.34	0.91	0.79-1.06	**0.28**	**0.25-0.32**	**0.66**	**0.62-0.70**	1.03	0.97-1.04	**1.30**	**1.26-1.33**
employment type[b]	union	61,484	26.59	269	0.44	*REF*		*REF*		*REF*		*REF*		*REF*	
	not union	96,325	41.65	281	0.29	**0.67**	**0.56-0.79**	**0.44**	**0.38-0.50**	**0.51**	**0.47-0.56**	**1.06**	**1.02-1.10**	**0.72**	**0.69-0.74**
	other/ unknown	73,458	31.76	302	0.41	0.94	0.80-1.11	**0.67**	**0.58-0.77**	0.99	0.92-1.07	**1.23**	**1.18-1.28**	**0.2**	**0.89-0.95**
region[c]	south	93,636	40.81	303	0.32	*REF*		*REF*		*REF*		*REF*		*REF*	
	northeast	17,440	7.60	60	0.34	1.06	0.81-1.41	**1.65**	**1.30-2.09**	0.81	0.69-0.94	**1.50**	**1.42-1.59**	**1.17**	**1.10-1.21**
	north central	70,171	30.68	260	0.37	1.15	0.97-1.35	**2.27**	**1.97-2.63**	1.47	1.36-1.59	**1.16**	**1.11-1.21**	**1.38**	**1.34-1.42**
	west	46,044	20.08	182	0.39	**1.22**	**1.02-1.47**	**2.17**	**1.85-2.55**	**1.60**	**1.47-1.74**	**1.33**	**1.27-1.39**	**1.28**	**1.24-1.32**
	unknown	2,098	0.91	7	0.33	1.03	0.49-2.18	1.07	0.51-2.28	1.11	0.78-1.58	**1.24**	**1.05-1.47**	**1.15**	**1.01-1.31**
Insomnia[d]	No	226,703	98.48	785	0.35	*REF*		*REF*		*REF*		*REF*		*REF*	
	Yes	3,498	1.52	27	0.77	**2.24**	**1.52-3.30**	1.34	0.89-2.00	**1.58**	**1.29-1.95**	**1.88**	**1.69-2.08**	**1.62**	**1.49-1.76**
Benzodiazepine Prescription history[d]	New	114,202	49.38	279	0.24	*REF*		*REF*		*REF*		*REF*		*REF*	
	Existing	117,065	50.62	576	0.49	**2.02**	**1.75-2.34**	**1.10**	**1.10-1.22**	**1.20**	**1.12-1.27**	**1.91**	**1.85-1.97**	**1.88**	**1.84-1.93**

[a] Outcome is problem benzodiazepine use during the follow-up period
[b] At the time of the index prescription
[c] Region in which the prescription was filled
[d] During the 6 month look-back period
[e] Mean age among individuals with the outcome. Note that mean age among individuals without the outcome is 56.47 years

Table 4.2. Frequencies for psychiatric disorders

Psychiatric disorder[a]		TOTAL SAMPLE (N=231,267)			
		Sample		proportion with outcome[b]	
		N	*%*	*N*	*%*
Alcohol use disorder	Yes	1,191	0.52	42	3.53
	No	229,010	99.48	770	0.34
Drug use disorder	Yes	3,935	1.71	87	2.21
	No	226,266	98.29	725	0.32
Anxiety disorder	Yes	15,514	6.74	129	0.83
	No	214,687	93.26	683	0.32
Mood disorder	Yes	29,996	13.03	364	1.15
	No	200,202	86.97	466	0.23

[a] During the 6 month follow-up period
[b] Outcome is problem benzodiazepine use during the follow-up period

Table 4.3. Logistic regression results for the relationship between psychiatric disorders and problem benzodiazepine use

Psychiatric Disorders[a]	LOGISTIC REGRESSION RESULTS											
	crude			adjusting for demographics and insomnia[b]			adjusting for demographics, insomnia and psychiatric disorders[c]			adjusting for demographics, insomnia, psychiatric disorders and benzodiazepine prescription history[d]		
	OR	*lower 95% CI*	*upper 95% CI*	*OR*	*lower 95% CI*	*upper 95% CI*	*OR*	*lower 95% CI*	*upper 95% CI*	*OR*	*lower 95% CI*	*upper 95% CI*
Alcohol use disorder	**10.84**	**7.90**	**14.87**	**10.35**	**7.53**	**14.22**	**3.61**	**2.52**	**5.18**	**3.76**	**2.62**	**5.40**
Drug use disorder	**7.03**	**5.62**	**8.81**	**6.42**	**5.12**	**8.06**	**3.32**	**2.57**	**4.29**	**3.27**	**2.53**	**4.23**
Anxiety disorder	**2.63**	**2.18**	**3.17**	**2.36**	**1.95**	**2.86**	**1.79**	**1.47**	**2.17**	**1.59**	**1.31**	**1.94**
Mood disorder	**5.00**	**4.35**	**5.75**	**4.71**	**4.10**	**5.42**	**4.02**	**3.48**	**4.64**	**3.54**	**3.06**	**4.10**

[a] During the 6 month follow-up period

[b] Results obtained from four separate models adjusting for demographic variables including age, geographic region and employment class**.** Insomnia was included as a covariate in the drug, anxiety and mood disorder models only since it was not associated with alcohol use disorders in crude analyses (See table 4.2).

[c] Results obtained from one model that includes demographic variables (age, geographic region and employment class) and the four psychiatric disorders (alcohol use disorder, drug use disorder, anxiety disorder, mood disorder)

[c] Results obtained from one model that includes demographic variables (age, geographic region and employment class), the four psychiatric disorders (alcohol use disorder, drug use disorder, anxiety disorder, mood disorder) and history of a benzodiazepine prescription during the baseline period.

Table 4.4. Results for additive interaction analyses between psychiatric disorders and prescription-related characteristics

Psychiatric Disorder *Prescription-related Characteristic*	**Individual and Joint Effect of Psychiatric Disorders and Prescription-related characteristics on Problem Benzodiazepine Use**									**Test for Additive interaction**		
	Individual effect of psychiatric disorder			**Individual effect of prescription-related characteristic**			**Joint effect of psychiatric disorder and prescription-related characteristic**					
	OR	**Lower 95% CI**	**Upper 95% CI**	**OR**	**Lower 95% CI**	**Upper 95% CI**	**OR**	**Lower 95% CI**	**Upper 95% CI**	**AP**	**Lower 95% CI**	**Upper 95% CI**
Alcohol Disorder:												
Dosage	2.50	2.13	2.95	1.74	1.49	2.03	2.09	0.77	5.653	-0.555	-2.116	1.007
Days supply	2.91	2.19	3.86	1.33	1.21	1.46	2.70	2.01	3.61	-0.202	-0.649	0.244
MPR	2.45	1.99	3.03	1.65	1.47	1.86	2.60	1.25	5.26	-0.209	-1.098	0.679
Opioid Prescription	2.80	2.22	3.53	1.55	1.44	1.67	3.31	2.64	4.14	-0.013	-0.304	0.279
Sedative Prescription	2.34	1.91	2.87	1.32	1.21	1.43	3.38	2.60	4.40	0.215	-0.031	0.461
Psychotherapy	2.68	2.05	3.50	1.22	1.10	1.35	2.80	2.27	3.50	-0.034	-0.354	0.287
Drug Disorder :												
Dosage	2.09	1.86	2.35	1.77	1.51	2.08	2.32	1.40	3.84	-0.235	-0.875	0.405
Days supply	2.58	2.07	3.21	1.35	1.23	1.49	2.53	2.10	3.05	-0.158	-0.440	0.125
MPR	2.17	1.88	2.51	1.70	1.50	1.92	1.94	1.29	2.93	-0.475	-1.104	0.153
Opioid Prescription	2.16	1.75	2.66	1.53	1.42	1.65	2.71	2.35	3.12	0.010	-0.196	0.216
Sedative Prescription	2.05	1.78	2.37	1.31	1.20	1.43	2.54	2.11	3.07	0.071	-0.134	0.275
Psychotherapy	2.17	1.83	2.58	1.27	1.14	1.40	2.51	2.12	2.97	0.028	-0.173	0.229
Anxiety Disorder:												
Dosage	1.28	1.16	1.42	1.70	1.43	2.01	2.11	1.48	3.02	0.063	-0.300	0.426
Days supply	1.32	1.08	1.62	1.29	1.17	1.43	1.75	1.52	2.03	0.078	-0.109	0.265
MPR	1.21	1.07	1.37	1.60	1.38	1.79	2.06	1.64	2.60	0.136	-0.090	0.362
Opioid Prescription	1.21	1.04	1.41	1.50	1.37	1.60	2.01	1.77	2.28	**0.157***	**0.022**	**0.292**
Sedative Prescription	1.28	1.14	1.44	1.30	1.19	1.42	1.59	1.35	1.87	0.003	-0.183	0.190
Psychotherapy	1.53	1.33	1.76	1.25	1.12	1.39	1.35	1.18	1.55	**-0.315***	**-0.539**	**-0.090**
Mood Disorder:												
Dosage	2.07	1.92	2.22	2.03	1.67	2.48	3.19	2.51	4.06	0.028	-0.234	0.289
Days supply	1.95	1.67	2.27	1.331	1.16	1.48	2.51	2.22	2.84	0.101	-0.022	0.225
MPR	1.93	1.76	2.11	`	1.57	2.15	2.65	2.24	3.14	-0.040	-0.239	0.160
Opioid Prescription	2.26	2.03	2.52	1.73	1.57	1.90	2.88	2.59	3.20	-0.038	-0.145	0.068
Sedative Prescription	1.87	1.72	2.04	1.30	1.16	1.45	2.40	2.16	2.66	0.097	-0.014	0.209
Psychotherapy	1.74	1.51	2.01	1.22	1.06	1.40	2.05	1.90	2.22	0.047	-0.102	0.196

Abbreviations: OR, Odds Ratio; 95% CI, 95% Confidence Intervals; AP, Attributable Proportion; MPR, Medication Possession Ratio

* Attributable Proportion due to interaction is significant (p<0.05)

Chapter 5. Conclusions

The problematic use, and associated burden, of abusable controlled prescription medication has been increasing at an alarming rate in recent years[1-4]. A growing body of literature has developed around this "hot topic". Epidemiological studies have focused on use among individuals without a prescription[5-9]. Problem users with a prescription have been largely overlooked, but appear to be an important high risk group. This dissertation focused on problem users with a prescription, and honed in on benzodiazepines since this is an abusable medication whose problematic use has not been as widely investigated as other psychoactive medications.

Indeed, despite concerns regarding the growing prevalence and burden of clinically significant problem benzodiazepine use in recent years[1-4], extensive literature searches across multiple electronic databases yielded only ten peer-reviewed studies that provide information on possible modifiable prescription and mental health-related risk factors for severe problem benzodiazepine use. Further, the interpretability of these studies is substantially hindered by methodological limitations, particularly a failure to establish temporality[29]. Nonetheless, they provide information on potential risk factors for severe problem benzodiazepine use that require further investigation. The purpose of this dissertation was to consider these and other related risk factors in a methodologically robust manner, using prospective data.

Specifically, utilizing two years of prospective health claims data, we considered risk factors for the development of new cases of problematic benzodiazepine use in the 12 months following receipt of a benzodiazepine prescription. Several risk factors were identified. With regard to benzodiazepine characteristics, a strong dose-response relationship was identified for the dosage of the index benzodiazepine prescription; however there was no impact of abuse liability. With regard to the amount of benzodiazepine prescribed over time, both the Medication-Possession Ratio and the number of days that the medication was supplied predicted the development of problem benzodiazepine use in a dose response manner. For the prescription contextual factors, psychotherapy and prescription for opioids and sedatives (but not stimulants) predicted problematic use. It is important to note that the direction of effect for psychotherapy was opposite to the hypothesized direction- we thought that psychotherapy would

reduce the risk of problematic use, but in fact it increased the risk of problem use. All of the prescription recipient characteristics that we considered were significant risk factors, although the magnitude of effect was markedly lower for anxiety disorders, than it was for alcohol, drug and mood disorders. The effect of all of these risk factors was independent of demographics, comorbid psychiatric disorders and history of benzodiazepine prescription.

We also considered the joint roles of risk factors. The objective was to identify modifiable benzodiazepine-prescription related factors (including benzodiazepine characteristics, the amount prescribed over time and prescription contextual variables) that may interact with the prescription recipient characteristics (including alcohol, drug, anxiety and mood disorder). In additive interaction analyses between the six benzodiazepine-related risk factors that were significant independent predictors of problem use (dosage, number of days supplied, Medication Possession Ratio, opioid prescription, sedative prescription, psychotherapy) and the four prescription recipient characteristics (alcohol, drug, anxiety and mood disorders), we identified two significant additive interaction relationships.

There was a synergistic relationship between baseline anxiety disorders and prescription for controlled opioids. This suggests that there are at least some individuals in the population who do not develop problem use unless they have both an anxiety disorder and opioid prescription if they are prescribed benzodiazepines (assuming the absence of other causal pathways to the outcome). Therefore clinicians may wish to proceed with caution when considering benzodiazepine treatment in patients with an anxiety disorder who have recently received an opioid prescription. Alternative treatment strategies may be more appropriate for these patients. We also found interaction between baseline anxiety disorders and recent psychotherapy in the risk for problem benzodiazepine use. This might indicate potential value of inclusion of a psychotherapeutic component in when managing anxiety disorders with benzodiazepines. However, the direction of the main effect of psychotherapy was contrary to our hypotheses (it increased rather than decreased the risk of problem use), and could plausibly be explained by random or systematic error. This is particularly true since we conducted several interaction analyses and only found two significant relationships, which is not much more than would be expected by chance. Therefore caution in

interpreting this finding is warranted. Indeed the only way to really know this for sure would be random assignment of psychotherapy or not, since there are many things potentially influencing this result that make interpretation complex. Nonetheless, information on these relationships could prove important in the development of interventions specifically targeted at reducing problem benzodiazepine use among individuals with anxiety disorders who are prescribed benzodiazepines. This is especially pertinent since benzodiazepines are indicated, and widely used, in the pharmacotherapeutic management of anxiety disorders[10-12]. Further work could be conducted to consider this issue.

Although this study addresses weaknesses evident in the existing literature, such as an inability to establish temporality, and provides clinically-relevant novel information, several limitations should be considered when interpreting results. This study is limited to two years of claims data. Therefore we cannot calculate incident problem benzodiazepine use since we do not have information on this event prior to 2003. In addition, the data are already a decade old which could reduce the applicability to current findings. However, the effect of this may be minimal since overall benzodiazepine prescriptions have not changed much during the past decade, and no new benzodiazepines have been approved by the FDA. However, many issues have changed in 10 years, including the rise of non-benzodiazepine hypnotics. We addressed this with sensitivity analyses that excluded individuals prescribed other anxiolytics (See appendix 5) and found some differences that warrant further exploration. Of note, we intend to replicate analyses using more recent data prior to publishing results. In addition, we used an employee-based dataset- it is possible that findings may not generalize to other populations. Similar analyses could be conducted in Medicare and Medicaid claims datasets, and in more recent datasets, to determine applicability of our findings to other populations and time-periods.

Another problem with this dataset, a problem that is true of all health claims datasets, is that the diagnostic variables will only capture individuals at the more severe end of the spectrum who receive clinical attention. With regards to measurement of the outcome (problem benzodiazepine use), this may be a strength rather than a weakness. It could be argued that our definition focuses on the most important group- the problem users who represent a public health concern and contribute to the burden of problem

use. Therefore findings for these more severe problem users may have a more substantial public health impact than findings for problem users at the lower end of the severity spectrum. In addition, it is possible that risk factors for problem benzodiazepine use are similar for various levels of severity. If this is true, then our findings have application for a much larger group of individuals. This could be addressed in future research. Nonetheless, it is important to acknowledge that this dissertation concerns a rare outcome that was only present in 0.37% of the sample. Given this, we cannot conclude that prescription users are at high risk of problem use.

One potential issue with our compound variable is that we combined benzodiazepine specific and non-specific diagnostic codes. We attempted to parcel out the difference between these in sensitivity analyses in which we considered results for benzodiazepine-specific codes (poisoning) and general anxiolytic codes (abuse dependence). Some differences in results were evidence for the psychiatric disorders, but it is unclear whether this represents a benzodiazepine vs anxiolytic difference or a poisoning vs abuse/dependence difference. This is an important issue that should be addressed in future work.

With regards to risk factors, there were several variables that we had originally intended to consider but were unable to because of limitations in the data. For example, we had hoped to address the role of the type of clinician (psychiatrist vs. other) who prescribed the index benzodiazepine prescription. This was not possible since we did not have any information on the prescribing clinician. We could have roughly estimated the effect by creating a variable to indicate whether an individual visited a psychiatrist within a one month window of the index prescription, but the potential for misclassification would be high. Further, we would have been measuring the risk factor in the follow-up period rendering reverse causation a good contender for explaining any observed effect. For these reasons, we chose not to consider this variable. Future research could address this risk factor using data that does provider provider-specific information.

Two other risk factors that we had hoped to consider among individuals who received benzodiazepine prescriptions during the baseline period were the number of prescribers for benzodiazepine prescriptions and the number of pharmacies that benzodiazepine prescriptions were filled at. We did not have provider-

specific or pharmacy-specific information, however had originally thought that we could estimate the effect of these variables by simply considering the number of physicians an individual visited and the number of pharmacies an individual filled prescriptions at, during the baseline period. Unfortunately, around 50% of the information was missing for both of these variables. When this was considered alongside the potential misclassification that our original approach would have entailed, we decided that in the face of these methodological limitations, inclusion of these variables would be inappropriate. We think that these are important potential risk factors and hope that they are considered in future research using more appropriate data.

The number of null interaction relationships was surprising, particularly for alcohol use disorders. The rationale for these hypotheses was strong. Individuals with alcohol use disorders have a greater sensitivity to the reinforcing and euphoric effects of benzodiazepines than individuals without alcohol use disorders[17,72-74], and benzodiazepine receptors have been implicated in the etiology alcohol dependence[75]. Our hypothesis that exposing individuals with alcohol disorders to benzodiazepines via a medical prescription might create the necessary circumstances for problematic benzodiazepine use, was supported by the strong and robust association between alcohol use disorders and problem benzodiazepine use. However, there was no interaction between alcohol use disorders and factors which affect the risk of abuse such as dosage (which can increase the reinforcing nature) and amount of benzodiazepine prescribed (which can increase the risk of tolerance and withdrawal). Since benzodiazepines are indicated for alcohol dependence, it may be clinically important for further research to try to identify other prescription-related factors that modify the risk of problem benzodiazepine use conferred by an alcohol use disorder. One such factor might involve supervision of benzodiazepine administration during the initial phases of treatment and limited take-home medication in the following stages.

Despite these methodological limitations, the current project has several notable strengths. It provides novel prospective information on risk factors for problem use of benzodiazepines among individuals with a benzodiazepine prescription. This includes risk factors which can be modified by the clinician to reduce

the possibility of problem use among individuals with a prescription, including those who are most vulnerable. Thus, the present findings contribute a significant advance in our understanding of the risk factors for problem benzodiazepine use among individuals with a prescription.

In addition to the potential clinical application of the specific information gleaned from our analyses, this dissertation constitutes an important contribution to the problem prescription drug use literature in general. It highlights a previously overlooked high-risk group- individuals with a prescription. Furthermore, it provides a novel robust methodology that can be used to study problem prescription drug among this group using existing data. Our definition of problem use represents an improvement over prior work which was limited to abuse/dependence diagnoses[22,61,6261,63] or overdose[29,3424,100-102], or was subject to self-report bias[1-3,9,27,28,103]. Further, we were able to investigate problem benzodiazepine use in a prospective manner, and therefore were able to distinguish between prevalent and new cases of problem benzodiazepine use, could establish temporality between the risk factors and outcome. Our approach can be easily modified to address related research questions e.g. problem opioid use among individuals with an opioid prescription, or problem stimulant use among individuals with a stimulant prescription. It can also provide a template for investigating these research questions in other populations e.g. with Medicare or Medicaid data.

In conclusion, this dissertation has identified several important characteristics relating to the benzodiazepine prescription, the prescription context and the prescription recipient, that increase the risk of problem benzodiazepine use among individuals prescribed benzodiazepines. Specifically, important predictors of problem benzodiazepine use among individuals with a prescription include dosage, number of days supplied, Medication Possession Ratio, opioid prescription, sedative prescription, psychotherapy, and alcohol, drug, anxiety and mood disorders. This information could be utilized to reduce the burden of problem benzodiazepine use by individual clinicians or within the context of a public health intervention. Evidence that psychotherapy and opioid prescriptions modify the role of anxiety disorders on problem benzodiazepine use could be useful to specifically prevent the development of problem benzodiazepine

use among individuals with anxiety disorders. Future research could consider other factors that may modify the effect of alcohol, drug and mood disorders on problem benzodiazepine use.

References

1. Huang B, Dawson DA, Stinson FS, Hasin DS, Ruan WJ, Saha TD, Smith SM, Goldstein RB, Grant BF. Prevalence, correlates, and comorbidity of nonmedical prescription drug use and drug use disorders in the United States: Results of the National Epidemiologic Survey on Alcohol and Related Conditions. *J Clin Psychiatry.* 2006;67(7):1062-1073.

2. Blanco C, Alderson D, Ogburn E, Grant BF, Nunes EV, Hatzenbuehler ML, Hasin DS. Changes in the prevalence of non-medical prescription drug use and drug use disorders in the United States: 1991-1992 and 2001-2002. *Drug Alcohol Depend.* 2007;90(2-3):252-260.

3. Fenton MC, Keyes KM, Martins SS, Hasin DS. The role of a prescription in anxiety medication use, abuse, and dependence. *Am J Psychiatry.* 2010;167(10):1247-1253.

4. Substance Abuse and Mental Health Services Administration Center for Behavioral Health Statistics and Quality. *Highlights of the 2010 Drug Abuse Warning Network (DAWN) Findings on Drug-Related Emergency Department Visits.* Rockville, MD 2012.

5. McCabe SE. Screening for drug abuse among medical and nonmedical users of prescription drugs in a probability sample of college students. *Arch Pediatr Adolesc Med.* 2008;162(3):225-231.

6. Opaleye ES, Noto AR, Sanchez ZM, Amato TC, Locatelli DP, Gossop M, Ferri CP. Nonprescribed use of tranquilizers or sedatives by adolescents: a Brazilian national survey. *BMC Public Health.* 2013;13:499.

7. Kokkevi A, Fotiou A, Arapaki A, Richardson C. Prevalence, patterns, and correlates of tranquilizer and sedative use among European adolescents. *J Adolesc Health.* 2008;43(6):584-592.

8. Hall MT, Howard MO, McCabe SE. Subtypes of adolescent sedative/anxiolytic misusers: A latent profile analysis. *Addict Behav.* 2010;35(10):882-889.

9. McCabe SE. Correlates of nonmedical use of prescription benzodiazepine anxiolytics: results from a national survey of U.S. college students. *Drug Alcohol Depend.* 2005;79(1):53-62.

10. Hoffman EJ, Mathew SJ. Anxiety disorders: a comprehensive review of pharmacotherapies. *Mt Sinai J Med.* 2008;75(3):248-262.

11. O'Brien C P. Benzodiazepine use, abuse, and dependence. *J Clin Psychiatry.* 2005;66 Suppl 2:28-33.

12. Brunton L, Blumenthal D, Buxton I, Parker K. *Goodman and Gilman's manual of pharmacology and therapeutics*: McGraw-Hill Professional; 2007.

13. Demyttenaere K, Bonnewyn A, Bruffaerts R, De Girolamo G, Gasquet I, Kovess V, Haro JM, Alonso J. Clinical factors influencing the prescription of antidepressants and benzodiazepines: results from the European study of the epidemiology of mental disorders (ESEMeD). *J Affect Disord.* 2008;110(1-2):84-93.

14. Raofi S, Schappert, SM. *Medication therapy in ambulatory medical care: United States, 2003–04.*: Medication therapy in ambulatory medical care: United States, 2003–04.; 2006

15. Code US. Title 21 United States Code (USC) Controlled Substances Act, CHAPTER 13 - DRUG ABUSE PREVENTION AND CONTROL. In: Office USGP, ed. *21*. U.S. Government Printing Office; 2012 Edition

16. Drug Enforcement Administration Office of Diversion Control Drug and Chemical Evaluation Section. *Benzodiazepines*: Drug Enforcement Administration 2013.

17. Griffiths RR, Weerts EM. Benzodiazepine self-administration in humans and laboratory animals--implications for problems of long-term use and abuse. *Psychopharmacology (Berl).* 1997;134(1):1-37.

18. Substance Abuse and Mental Health Services Administration Center for Behavioral Health Statistics and Quality. *The TEDS Report: Substance Abuse Treatment Admissions for Abuse of Benzodiazepines.* Rockville, MD 2011.

19. Johnston LD, O'Malley, P. M., Bachman, J. G., Schulenberg, J. E. . *Monitoring the Future national survey results on drug use, 1975-2007. Volume I: Secondary school students.* Bethesda, MD: National Institute on Drug Abuse; 2008.

20. Johnston LD, O'Malley, P. M., Bachman, J. G., & Schulenberg, J. E. . Marijuana use continues to rise among U.S. teens, while alcohol use hits historic lows. Ann Arbor, MI: University of Michigan News Service 2011: http://www.monitoringthefuture.org. Accessed October 8th 2012.

21. Substance Abuse and Mental Health Services Administration (SAMHSA). National Survey on Drug Use and Health, 2006 and 2007.

http://www.samhsa.gov/data/NSDUH/2k7NSDUH/tabs/Sect7peTabs1to58.htm#Tab7.52A. Accessed October 8th 2012.

22. Brunette MF, Noordsy DL, Xie H, Drake RE. Benzodiazepine use and abuse among patients with severe mental illness and co-occurring substance use disorders. *Psychiatr Serv.* 2003;54(10):1395-1401.

23. Busto U, Simpkins J, Sellers EM, Sisson B, Segal R. Objective determination of benzodiazepine use and abuse in alcoholics. *Br J Addict.* 1983;78(4):429-435.

24. Cai R, Crane E, Poneleit K, Paulozzi L. Emergency department visits involving nonmedical use of selected prescription drugs in the United States, 2004-2008. *J Pain Palliat Care Pharmacother.* 2010;24(3):293-297.

25. Ekedahl A, Lidbeck J, Lithman T, Noreen D, Melander A. Benzodiazepine prescribing patterns in a high-prescribing Scandinavian community. *Eur J Clin Pharmacol.* 1993;44(2):141-146.

26. study MtF. Source of Prescription Drugs among Those Who Used in Last Year, Grade 12, 2007–2011. In: Michigan TUo, ed. Vol 2013; 2011.

27. McLarnon ME, Monaghan TL, Stewart SH, Barrett SP. Drug misuse and diversion in adults prescribed anxiolytics and sedatives. *Pharmacotherapy.* 2011;31(3):262-272.

28. Iguchi MY, Handelsman L, Bickel WK, Griffiths RR. Benzodiazepine and sedative use/abuse by methadone maintenance clients. *Drug Alcohol Depend.* 1993;32(3):257-266.

29. Paulozzi LJ, Kilbourne EM, Shah NG, Nolte KB, Desai HA, Landen MG, Harvey W, Loring LD. A history of being prescribed controlled substances and risk of drug overdose death. *Pain Med.* 2012;13(1):87-95.

30. Rosenbaum JF. Attitudes toward benzodiazepines over the years. *J Clin Psychiatry.* 2005;66 Suppl 2:4-8.

31. Offidani E, Guidi J, Tomba E, Fava GA. Efficacy and tolerability of benzodiazepines versus antidepressants in anxiety disorders: a systematic review and meta-analysis. *Psychother Psychosom.* 2013;82(6):355-362.

32. Cascade E, Kalali AH. Use of benzodiazepines in the treatment of anxiety. *Psychiatry (Edgmont).* 2008;5(9):21-22.

33. Jones CM, Mack KA, Paulozzi LJ. Pharmaceutical overdose deaths, United States, 2010. *JAMA.* 2013;309(7):657-659.

34. Hall AJ, Logan JE, Toblin RL, Kaplan JA, Kraner JC, Bixler D, Crosby AE, Paulozzi LJ. Patterns of abuse among unintentional pharmaceutical overdose fatalities. *JAMA.* 2008;300(22):2613-2620.

35. Boyd CJ, Esteban McCabe S, Teter CJ. Medical and nonmedical use of prescription pain medication by youth in a Detroit-area public school district. *Drug Alcohol Depend.* 2006;81(1):37-45.

36. Goldstein S. Report from the National Survey on Drug Use and Health: nonmedical stimulant use, other drug use, delinquent behaviors, and depression among adolescents. *J Atten Disord.* 2008;12(1):3.

37. Hernandez SH, Nelson LS. Prescription drug abuse: insight into the epidemic. *Clin Pharmacol Ther.* 2010;88(3):307-317.

38. Boyd CJ, McCabe SE. Coming to terms with the nonmedical use of prescription medications. *Subst Abuse Treat Prev Policy.* 2008;3:22.

39. RADARS. RADARS® System Releases U.S. Data on Prescription Drug Abuse, Misuse and Diversion. *Denver Health News* [http://www.radars.org/Portals/1/RADARS%20release_05-22-2007_Complete%20Document_8.pdf, 2009

40. Logan J, Liu Y, Paulozzi L, Zhang K, Jones C. Opioid Prescribing in Emergency Departments: The Prevalence of Potentially Inappropriate Prescribing and Misuse. *Med Care.* 2013.

41. Bleich A, Gelkopf M, Schmidt V, Hayward R, Bodner G, Adelson M. Correlates of benzodiazepine abuse in methadone maintenance treatment. A 1 year prospective study in an Israeli clinic. *Addiction.* 1999;94(10):1533-1540.

42. Ladewig D. [Abuse of benzodiazepine tranquilizers. Results of a Switzerland survey of practicing physicians]. *Med Welt.* 1982;33(38):1306-1309.

43. Yacoubian GS, Jr. Correlates of benzodiazepine use among a sample of arrestees surveyed through the Arrestee Drug Abuse Monitoring (ADAM) Program. *Subst Use Misuse.* 2003;38(1):127-139.

44. Assanangkornchai S, Sam-Angsri N, Rerngpongpan S, Edwards JG. Anxiolytic and hypnotic drug misuse in Thailand: findings from a national household survey. *Drug Alcohol Rev.* 2010;29(1):101-111.

45. Lin SC, Chen CC, Chen YH, Chung KS, Lin CH. Benzodiazepine prescription among patients with severe mental illness and co-occurring alcohol abuse/dependence in Taiwan. *Hum Psychopharmacol.* 2011;26(3):201-207.

46. Martinez-Cano H, de Iceta Ibanez de Gauna M, Vela-Bueno A, Wittchen HU. DSM-III-R co-morbidity in benzodiazepine dependence. *Addiction.* 1999;94(1):97-107.

47. Ciraulo DA, Sarid-Segal O, Knapp C, Ciraulo AM, Greenblatt DJ, Shader RI. Liability to alprazolam abuse in daughters of alcoholics. *Am J Psychiatry.* 1996;153(7):956-958.

48. Meltzer EC, Rybin D, Meshesha LZ, Saitz R, Samet JH, Rubens SL, Liebschutz JM. Aberrant drug-related behaviors: unsystematic documentation does not identify prescription drug use disorder. *Pain Med.* 2012;13(11):1436-1443.

49. McCabe SE, Boyd CJ, Young A. Medical and nonmedical use of prescription drugs among secondary school students. *J Adolesc Health.* 2007;40(1):76-83.

50. Simoni-Wastila L, Ritter G, Strickler G. Gender and other factors associated with the nonmedical use of abusable prescription drugs. *Subst Use Misuse.* 2004;39(1):1-23.

51. Bleich A, Gelkopf M, Weizman T, Adelson M. Benzodiazepine abuse in a methadone maintenance treatment clinic in Israel: characteristics and a pharmacotherapeutic approach. *Isr J Psychiatry Relat Sci.* 2002;39(2):104-112.

52. Schuman-Olivier Z, Hoeppner BB, Weiss RD, Borodovsky J, Shaffer HJ, Albanese MJ. Benzodiazepine use during buprenorphine treatment for opioid dependence: Clinical and safety outcomes. *Drug Alcohol Depend.* 2013;132(3):580-586.

53. Kurtz SP, Surratt HL, Levi-Minzi MA, Mooss A. Benzodiazepine dependence among multidrug users in the club scene. *Drug Alcohol Depend.* 2011;119(1-2):99-105.

54. 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 Depend.* 1999;55(1-2):63-68.

55. Kan CC, Breteler MH, van der Ven AH, Timmermans MA, Zitman FG. Assessment of benzodiazepine dependence in alcohol and drug dependent outpatients: a research report. *Subst Use Misuse.* 2001;36(8):1085-1109.

56. Naja WJ, Pelissolo A, Haddad RS, Baddoura R, Baddoura C. A general population survey on patterns of benzodiazepine use and dependence in Lebanon. *Acta Psychiatr Scand.* 2000;102(6):429-431.

57. Melander A, Henricson K, Stenberg P, Lowenhielm P, Malmvik J, Sternebring B, Kaij L, Bergdahl U. Anxiolytic-hypnotic drugs: relationships between prescribing, abuse and suicide. *Eur J Clin Pharmacol.* 1991;41(6):525-529.

58. Becker WC, Fiellin DA, Desai RA. Non-medical use, abuse and dependence on sedatives and tranquilizers among U.S. adults: psychiatric and socio-demographic correlates. *Drug Alcohol Depend.* 2007;90(2-3):280-287.

59. Ross J, Darke S. The nature of benzodiazepine dependence among heroin users in Sydney, Australia. *Addiction.* 2000;95(12):1785-1793.

60. Rooney S, Kelly G, Bamford L, Sloan D, O'Connor JJ. Co-abuse of opiates and benzodiazepines. *Ir J Med Sci.* 1999;168(1):36-41.

61. Kan CC, Hilberink SR, Breteler MH. Determination of the main risk factors for benzodiazepine dependence using a multivariate and multidimensional approach. *Compr Psychiatry.* 2004;45(2):88-94.

62. De Las Cuevas C, Sanz E, de la Fuente J. Benzodiazepines: more "behavioural" addiction than dependence. *Psychopharmacology (Berl).* 2003;167(3):297-303.

63. Ross HE. Benzodiazepine use and anxiolytic abuse and dependence in treated alcoholics. *Addiction.* 1993;88(2):209-218.

64. Mellinger GD, Balter MB, Uhlenhuth EH. Prevalence and correlates of the long-term regular use of anxiolytics. *JAMA.* 1984;251(3):375-379.

65. Oakes JM. Commentary: advancing neighbourhood-effects research--selection, inferential support, and structural confounding. *Int J Epidemiol.* 2006;35(3):643-647.

66. Cloos J. Benzodiazepines and Addiction:Myths and Realities (Part 1). *Psychiatric Times.* 2010;XXVII(7):4.

67. Roache JD, Meisch RA. Findings from self-administration research on the addiction potential of benzodiazepines. *Psychiatric Annals.* 1995;25(3):5.

68. Longo LP, Johnson B. Addiction: Part I. Benzodiazepines--side effects, abuse risk and alternatives. *Am Fam Physician.* 2000;61(7):2121-2128.

69. Kothari D, Gourevitch MN, Lee JD, Grossman E, Truncali A, Ark TK, Kalet AL. Undergraduate medical education in substance abuse: a review of the quality of the literature. *Acad Med.* 2011;86(1):98-112.

70. CASA NCoAaSAaCU. *Under the Counter: The Diversion and Abuse of Controlled Prescription Drugs in the U.S.* 2005.

71. CASA NCoAaSAaCU. *Missed Opportunity: National Survey of Primary Care Physicians and Patients on Substance Abuse* 2000.

72. de Wit H, Doty P. Preference for ethanol and diazepam in light and moderate social drinkers: a within-subjects study. *Psychopharmacology (Berl).* 1994;115(4):529-538.

73. deWit H, Pierri J, Johanson CE. Reinforcing and subjective effects of diazepam in nondrug-abusing volunteers. *Pharmacol Biochem Behav.* 1989;33(1):205-213.

74. Ciraulo DA, Barnhill JG, Greenblatt DJ, Shader RI, Ciraulo AM, Tarmey MF, Molloy MA, Foti ME. Abuse liability and clinical pharmacokinetics of alprazolam in alcoholic men. *J Clin Psychiatry.* 1988;49(9):333-337.

75. Lingford-Hughes A, Reid AG, Myers J, Feeney A, Hammers A, Taylor LG, Rosso L, Turkheimer F, Brooks DJ, Grasby P, Nutt DJ. A [11C]Ro15 4513 PET study suggests that alcohol dependence in man is associated with reduced alpha5 benzodiazepine receptors in limbic regions. *J Psychopharmacol.* 2012;26(2):273-281.

76. Kosten TR, O'Connor PG. Management of drug and alcohol withdrawal. *N Engl J Med.* 2003;348(18):1786-1795.

77. Parr JM, Kavanagh DJ, Cahill L, Mitchell G, Mc DYR. Effectiveness of current treatment approaches for benzodiazepine discontinuation: a meta-analysis. *Addiction.* 2009;104(1):13-24.

78. Arch JJ, Ayers CR. Which treatment worked better for whom? Moderators of group cognitive behavioral therapy versus adapted mindfulness based stress reduction for anxiety disorders. *Behav Res Ther.* 2013;51(8):434-442.

79. Otto MW, Smits JA, Reese HE. Cognitive-behavioral therapy for the treatment of anxiety disorders. *J Clin Psychiatry.* 2004;65 Suppl 5:34-41.

80. McHugh RK, Hearon BA, Otto MW. Cognitive behavioral therapy for substance use disorders. *Psychiatr Clin North Am.* 2010;33(3):511-525.

81. Carroll KM, Ball SA, Nich C, Martino S, Frankforter TL, Farentinos C, Kunkel LE, Mikulich-Gilbertson SK, Morgenstern J, Obert JL, Polcin D, Snead N, Woody GE, National Institute on Drug Abuse Clinical Trials N. Motivational interviewing to improve treatment engagement and outcome in individuals seeking treatment for substance abuse: a multisite effectiveness study. *Drug Alcohol Depend.* 2006;81(3):301-312.

82. Knight JR, Sherritt L, Van Hook S, Gates EC, Levy S, Chang G. Motivational interviewing for adolescent substance use: a pilot study. *J Adolesc Health.* 2005;37(2):167-169.

83. Dunn C. Brief motivational interviewing interventions targeting substance abuse in the acute care medical setting. *Semin Clin Neuropsychiatry.* 2003;8(3):188-196.

84. Beck AT, Wright FD. *Cognitive therapy of substance abuse*: Guilford Press; 2011.

85. RxList. Xanax: indications and dosage http://www.rxlist.com/xanax-drug/indications-dosage.htm.

86. Jones JD, Mogali S, Comer SD. Polydrug abuse: a review of opioid and benzodiazepine combination use. *Drug Alcohol Depend.* 2012;125(1-2):8-18.

87. Skolnick P, Rice KC, Barker JL, Paul SM. Interaction of barbiturates with benzodiazepine receptors in the central nervous system. *Brain Res.* 1982;233(1):143-156.

88. Chambers DM, Jefferson GC. Some observations on the mechanism of benzodiazepine-barbiturate interactions in the mouse. *Br J Pharmacol.* 1977;60(3):393-399.

89. Ellinwood EH, Jr., Eibergen RD, Kilbey MM. Stimulants: interaction with clinically relevant drugs. *Ann N Y Acad Sci.* 1976;281:393-408.

90. National Center for Health Statistics. Classification of Diseases and Injuries. ftp://ftp.cdc.gov/pub/Health_Statistics/NCHS/Publications/ICD-9/ucod.txt. Accessed June 7th, 2013.

91. Acute VCCSUPSV. Benzodiazepine- Comparison. http://www.vhpharmsci.com/vhformulary/tools/benzodiazepines-comparison.htm. Accessed June 17th, 2013.

92. Ray WA. Evaluating medication effects outside of clinical trials: new-user designs. *Am J Epidemiol.* 2003;158(9):915-920.

93. Beaulieu S, Saury S, Sareen J, Tremblay J, Schutz CG, McIntyre RS, Schaffer A, Canadian Network for M, Anxiety Treatments Task F. The Canadian Network for Mood and Anxiety Treatments (CANMAT) task force recommendations for the management of patients with mood disorders and comorbid substance use disorders. *Ann Clin Psychiatry.* 2012;24(1):38-55.

94. Dhalla IA, Persaud N, Juurlink DN. Facing up to the prescription opioid crisis. *BMJ.* 2011;343:d5142.

95. Davis CS, Pierce M, Dasgupta N. Evolution and convergence of state laws governing controlled substance prescription monitoring programs, 1998-2011. *Am J Public Health.* 2014;104(8):1389-1395.

96. Pradel V, Frauger E, Thirion X, Ronfle E, Lapierre V, Masut A, Coudert C, Blin O, Micallef J. Impact of a prescription monitoring program on doctor-shopping for high dosage buprenorphine. *Pharmacoepidemiol Drug Saf.* 2009;18(1):36-43.

97. Mumford GK, Evans SM, Fleishaker JC, Griffiths RR. Alprazolam absorption kinetics affects abuse liability. *Clin Pharmacol Ther.* 1995;57(3):356-365.

98. IMS National Prescription Audit PLUS. Top Therapeutic Classes by US Dispensed Prescriptions. ; 2011.

99. Paulose-Ram R, Safran MA, Jonas BS, Gu Q, Orwig D. Trends in psychotropic medication use among U.S. adults. *Pharmacoepidemiol Drug Saf.* 2007;16(5):560-570.

100. Paulozzi LJ, Budnitz DS, Xi Y. Increasing deaths from opioid analgesics in the United States. *Pharmacoepidemiol Drug Saf.* 2006;15(9):618-627.

101. Kuehn BM. Opioid prescriptions soar: increase in legitimate use as well as abuse. *JAMA.* 2007;297(3):249-251.

102. Wisniewski AM, Purdy CH, Blondell RD. The epidemiologic association between opioid prescribing, non-medical use, and emergency department visits. *J Addict Dis.* 2008;27(1):1-11.

103. McCabe SE, Cranford JA, West BT. Trends in prescription drug abuse and dependence, co-occurrence with other substance use disorders, and treatment utilization: results from two national surveys. *Addict Behav.* 2008;33(10):1297-1305.

104. Ciraulo DA, Sands BF, Shader RI. Critical review of liability for benzodiazepine abuse among alcoholics. *Am J Psychiatry.* 1988;145(12):1501-1506.

105. Kleber HD. Pharmacologic treatments for opioid dependence: detoxification and maintenance options. *Dialogues Clin Neurosci.* 2007;9(4):455-470.

106. Society BP. PHARMACOLOGICAL AND PHYSICAL INTERVENTIONS IN OPIOID DETOXIFICATION. In: (UK). NCCfMH, ed. *Drug Misuse: Opioid Detoxification. NICE Clinical Guidelines, No. 52.* Leicester (UK); 2008.

107. Nutt DJ. Overview of diagnosis and drug treatments of anxiety disorders. *CNS Spectr.* 2005;10(1):49-56.

108. Rothman KJ, Greenland S, Walker AM. Concepts of interaction. *Am J Epidemiol.* 1980;112(4):467-470.

109. Darroch J. Biologic synergism and parallelism. *Am J Epidemiol.* 1997;145(7):661-668.

110. Andersson T, Alfredsson L, Kallberg H, Zdravkovic S, Ahlbom A. Calculating measures of biological interaction. *Eur J Epidemiol.* 2005;20(7):575-579.

111. Zhang J, Xiao S, Zhou L. Mental disorders and suicide among young rural Chinese: a case-control psychological autopsy study. *Am J Psychiatry.* 2010;167(7):773-781.

112. Wicks S, Hjern A, Dalman C. Social risk or genetic liability for psychosis? A study of children born in Sweden and reared by adoptive parents. *Am J Psychiatry.* 2010;167(10):1240-1246.

113. Kalilani L, Atashili J. Measuring additive interaction using odds ratios. *Epidemiologic perspectives & innovations : EP+I.* 2006;3:5.

Appendices

Appendix 1: Attrition

Potential eligible individuals in the dataset during the 6 month ascertainment period (July-December 2003): **8, 922, 665**

Number who filed a claim for a benzodiazepine prescription during that period: **309,938**

Number who remained in the dataset after excluding individuals who did not meet the following inclusion criteria (enrolled in their insurance plan for the 6 months preceding and 12 month following an index benzodiazepine prescription; had a days' supply of less than or equal to 0, were dispensed less than 1 units of medication; had the outcome during the 6 month baseline): **231, 267**

Appendix 2: Abuse liability scores and comparative alprazolam dosage

Table A2.1. Abuse liability of commonly used benzodiazepines based on potency, half-life, clinical onset and therapeutic period.

Benzodiazepine	**potency**[68]	**Half-life**[68]	**Clinical onset**[91]*	**Abuse potential score**
Alprazolam	High	Short	intermediate	2+2+2=6
Alprazolam -XR	High	Long	intermediate	2+1+2=5
Lorazepam	High	Short	intermediate	2+2+2=6
Triazolam	High	Short	intermediate	2+2+2=6
Oxazepam	Low	Short	slow	1+2+1=4
Temazepam	Low	Short	slow	1+2+1=4
Chlordiazepoxide	Low	Long	intermediate	1+1+2=4
Diazepam	Low	Long	rapid	1+1+3=5
Flurazepam	Low	Long	rapid	1+1+3=5
Clorazepate	Low	Long	rapid	1+1+3=5
Midazolam	Low	Short	intermediate	1+2+2=5
Quazepam	Low	Long	Slow	1+1+1=3
Estazolam	High	Long	Slow	2+1+1=4

Table A2.2. Comparative oral doses of benzodiazepines[91]

Benzodiazepine	Comparative Oral Dose (mg)	Conversion factor for alprazolam equivalent dose
Alprazolam (Xanax)	0.5	1.000
Xanax-XR	0.5	1.000
Lorazepam (Ativan)	1	0.500
Triazolam (Halcion)	0.25	2.000
Clonazepam (Klonopin)	1	0.500
Oxazepam (Serax)	10	0.050
Temazepam (Restoril)	10	0.050
Chlordiazepoxide (Librium)	25	0.020
Diazepam (Valium)	5	0.100
Flurazepam (Dalmane)	15	0.033
Clorazepate	10	0.050
Midazolam	5	0.100
Prazepam	15	0.033
Quazepam	20	0.025
Halazepam	20	0.025
Estazolam	1.5	0.075

Appendix 3: List of ICD-9 codes used to create variables

Table A3.1. ICD-9 codes used to create compound diagnostic variables		
COMPOUND VARIABLE	**ICD-9 CODE**	**DESCRIPTION**
problem benzodiazepine use	All of 305.4	Nondependent sedative, hypnotic or anxiolytic abuse
	All of 304.1	Sedative, hypnotic or anxiolytic dependence
	E8532	Accidental poisoning by benzodiazepines
	9694	Poisoning by benzodiazepines
alcohol disorder	All of 303	Alcohol dependence syndrome
	All of 305.0	Nondependent alcohol abuse
	All of 291	Alcohol-induced mental disorders
	9773	Poisoning by alcohol deterrents
	All of 980	Toxic effect of alcohol
	E8601	Accidental poisoning by alcoholic beverages
drug use disorder	All of 292	Drug-induced mental disorders
	All of 304	Drug dependence
	All of 305	Nondependent abuse of drugs
	E850.0	Accidental poisoning by heroin
	E850.1	Accidental poisoning by methadone
	E850.2	Accidental poisoning by other opiates and related narcotics
	E851	Accidental poisoning by barbiturates
	E852	Accidental poisoning by other sedatives and hypnotics
anxiety disorders	29384	Anxiety disorder in conditions classified elsewhere
	All of 300.0	Anxiety states
	All of 300.2	Phobic disorders
	30921	Separation anxiety disorder
	300.7	Hypocondriasis
	308.3	Other acute reactions to stress
mood disorders	All of 296	Episodic mood disorders
	All of 298.0	Depressive type psychosis
	300.4	Dysthymic disorder
	301.13	Cyclothymic disorder
	All of 311	Depressive disorder not elsewhere classified
Insomnia	780.51	Insomnia with sleep apnea, unspecified
	780.52	Insomnia, unspecified
	307.41	Transient disorder of initiating or maintaining sleep
	307.42	Persistent disorder of initiating or maintaining sleep
	327.0	Organic insomnia
	327.00	Organic insomnia, unspecified
	327.01	Insomnia due to medical condition classified elsewhere
	327.02	Insomnia due to mental disorder
	327.09	Other organic insomnia

Appendix 4: Sample characteristics stratified by new and existing prescriptions

Table A4.1. Sample characteristics, stratified by new and existing prescriptions

Benzodiazepine characteristics[a]		NEW PRESCRIPTIONS ONLY (N= 114,347)				EXISTING PRESCRIPTIONS ONLY (N=116,920)			
		Sample		proportion with outcome[b]		Sample		proportion with outcome[b]	
		N or mean	%	N or mean	%	N or mean	%	N or mean	%
Age (mean years)		46.32	n/a	39.99	n/a	50.59	n/a	45.23	n/a
Sex	Male	35,366	31.22	79	0.22	36,640	31.34	191	0.52
	Female	77,915	68.78	159	0.20	80,280	68.66	383	0.48
Employment type	union	27,601	24.24	72	0.26	33,883	28.98	197	0.58
	not union	48,706	42.59	86	0.18	47,619	40.73	195	0.41
	other/unknown	38,040	33.27	120	0.32	35,418	30.29	182	0.51
region[c]	south	45,067	39.78	78	0.17	48,872	41.80	225	0.46
	northeast	9,349	8.25	21	0.22	8,151	6.97	39	0.48
	north central	33,253	29.35	82	0.25	37,178	31.80	178	0.48
	west	24,496	21.62	54	0.22	21,730	18.59	128	0.59
	unknown	1,116	0.99	3	0.27	989	0.85	4	0.40
Insomnia		1,398	1.23	3	0.21	2,100	1.80	24	1.14
any psychiatric diagnosis[d]		18,956	16.73	117	0.62	32,369	27.68	364	1.12

[a] During the 6 month lookback period
[b] Outcome is problem benzodiazepine use during the follow-up period

Appendix 5- relationship between potential confounders and prescription-related variables

Table A.5. Sample Characteristics- crude relationship to prescription-related predictors

Baseline characteristics		FREQUENCIES Crude relationship to															
		Dose[a]		Abuse Potential Score[b]		MPR[c,e]		Days supply[d,e]		Psychotherapy		Opioid prescription		Sedative prescription		Stimulant prescription	
		OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
age (mean years)		0.99	0.99-1.00	1.01	1.00-1.01	**1.01**	**1.01-1.01**	**1.03**	**1.03-1.03**	**0.99**	**0.99-0.99**	**1.01**	**1.01-1.01**	**1.01**	**1.01-1.01**	**0.98**	**0.98-0.98**
sex	male	*REF*		*REF*		*REF*		*REF*		*REF*		*REF*		*REF*		*REF*	
	female	**0.72**	**0.68-0.78**	**1.39**	**1.37-1.42**	**0.92**	**0.87-0.97**	**0.80**	**0.78-0.82**	**1.10**	**1.07-1.23**	**1.10**	**1.08-1.12**	**1.19**	**1.15-1.21**	1.05	0.99-1.11
employment type	union	*REF*		*REF*		*REF*		*REF*		*REF*		*REF*		*REF*		*REF*	
	not union	**1.13**	**1.03-1.23**	1.00	0.98-1.02	**0.77**	**0.72-0.82**	**0.77**	**0.75-0.79**	**0.66**	**0.64-0.68**	**0.80**	**0.79-0.82**	**0.90**	**0.87-0.93**	**0.65**	**0.61-0.69**
	other/ unknown	**1.36**	**1.24-1.48**	**0.79**	**0.77-0.81**	**1.00**	**0.94-1.07**	**0.68**	**0.66-0.70**	**0.83**	**0.81-0.86**	**0.80**	**0.78-0.81**	**0.87**	**0.84-0.89**	**0.61**	**0.57-0.66**
region	south	*REF*		*REF*		*REF*		*REF*		*REF*		*REF*		*REF*		*REF*	
	northeast	**0.72**	**0.62-0.84**	**1.17**	**1.13-1.22**	**0.74**	**0.66-0.84**	**0.81**	**0.77-0.85**	**1.54**	**1.47-1.61**	**0.56**	**0.54-0.58**	**0.77**	**0.74-0.81**	**0.92**	**0.83-1.02**
	north central	**0.73**	**0.67-0.80**	**1.05**	**1.03-1.07**	1.06	1.00-1.12	**1.12**	**1.10-1.15**	**1.57**	**1.53-1.62**	**0.92**	**0.90-0.94**	**0.80**	**0.78-0.82**	**1.17**	**1.10-1.24**
	west	**1.40**	**1.29-1.52**	**0.72**	**0.70-0.74**	**1.29**	**1.20-1.37**	**0.76**	**0.73-0.78**	**1.41**	**1.36-1.45**	**0.87**	**0.85-0.89**	**0.76**	**0.74-0.79**	**0.69**	**0.63-0.74**
	unknown	**0.66**	**0.43-1.02**	**0.85**	**0.77-0.93**	0.97	0.73-1.29	**0.97**	**0.86-1.11**	**1.12**	**0.98-1.27**	**0.81**	**0.74-0.89**	0.88	0.78-1.00	**0.72**	**0.52-0.99**
Psychiatric diagnosis		**1.76**	**1.64-1.90**	**1.43**	**1.40-1.46**	**1.78**	**1.69-1.88**	**1.30**	**1.26-1.33**	**574.21**	**530.28-622.27**	**1.09**	**1.07-1..11**	**2.30**	**2.24-2.36**	**4.54**	**4.31-4.79**
Insomnia		**1.04**	**0.79-1.37**	**0.91**	**0.85-0.97**	**1.44**	**1.23-1.70**	**0.82**	**0.75-0.89**	**1.39**	**1.28-1.51**	**1.11**	**1.03-1.19**	**4.43**	**4.14-4.75**	**1.10**	**0.90-1.35**
Benzodiazepine prescription history		**1.72**	**1.60-1.84**	**1.61**	**1.59-1.64**	**n/a**		**n/a**		**2.02**	**1.97-2.07**	**1.82**	**1.79-1.85**	**1.68**	**1.64-1.73**	**1.72**	**1.63-1.81**

[a]dose (≤4.0mgs vs >4mgs); [b] abuse potential (less than 6 vs 6); [c] mpr (1 vs >1); [d]days supply is binary (≤60 days vs > 60 days);
[e]MPR and Days supply only in existing prescription

Appendix 6: Sensitivity analyses

Predictors		LOGISTIC REGRESSION RESULTS FROM FULLY ADJUSTED MODEL (demos, insomnia, psych disorder[c], benzo hx)																	
		Among total study sample (n=231,267)			**Among those not prescribed other anxiolytics (n=198,699**			**For benzo-specific outcomes (n=492)[a]**			**For non benzo-specific outcomes (n=389)[b]**			**For new prescriptions only (n=114,347)**			**For existing prescriptions only (n=116,920)**		
		OR	*lower 95% CI*	*upper 95% CI*	*OR*	*lower 95% CI*	*upper 95% CI*	*OR*	*lower 95% CI*	*upper 95% CI*	*OR*	*lower 95% CI*	*upper 95% CI*	*OR*	*lower 95% CI*	*upper 95% CI*	*OR*	*lower 95% CI*	*upper 95% CI*
Dose (alprazolam equivalent mgs)	≥1.5	*REF*			*REF*			*REF*			*REF*			*REF*					
	1.5-4.0	**2.20**	**1.90**	**2.55**	**2.29**	**1.92**	**2.72**	**2.01**	**1.65**	**2.44**	**2.50**	**2.01**	**3.12**	**2.12**	**1.60**	**2.82**	**2.25**	**1.89**	**2.68**
	>4.0	**3.70**	**2.71**	**5.06**	**4.46**	**3.14**	**6.32**	**2.96**	**1.91**	**4.59**	**4.66**	**3.03**	**7.15**	2.19	0.90	5.37	**4.11**	**2.94**	**5.74**
Abuse potential score		1.02	1.02	0.91	1.09	0.95	1.25	1.06	0.91	1.23	1.00	0.85	1.18	0.94	0.77	1.15	1.06	0.92	1.21
Medication Possession Ratio**	≤0.5	*REF*			*REF*			*REF*			*REF*								
	0.5-1	**1.83**	**1.53**	**2.20**	**1.92**	**1.55**	**2.38**	**1.57**	**1.24**	**2.00**	**2.13**	**1.64**	**2.78**		n/a[d]			n/a[d]	
	>1	**3.46**	**2.70**	**4.46**	**3.97**	**2.94**	**5.37**	**2.60**	**1.83**	**3.71**	**4.53**	**3.20**	**6.41**						
Days supply in baseline**	≤30	*REF*			*REF*			*REF*			*REF*								
	30-60	1.36	1.00	1.85	1.36	0.94	1.95	1.24	0.84	1.84	1.60	1.00	2.55		n/a[d]			n/a[d]	
	61-90	**1.44**	**1.05**	**1.98**	1.30	0.88	1.92	1.38	0.92	2.06	**1.66**	**1.02**	**2.69**						
	91-120	**1.65**	**1.19**	**2.28**	**1.71**	**1.17**	**2.50**	**1.53**	**1.01**	**2.31**	**1.86**	**1.13**	**3.06**						
	121-180	**2.45**	**1.91**	**3.13**	**2.47**	**1.85**	**3.30**	**1.94**	**1.41**	**2.68**	**3.24**	**2.22**	**4.72**						
	>180	**4.16**	**3.10**	**5.58**	**4.63**	**3.26**	**6.56**	**3.01**	**2.01**	**4.49**	**5.96**	**3.88**	**9.15**						
Psychotherapy[c]		**1.39**	**1.12**	**1.72**	1.25	0.97	1.60	**1.51**	**1.14**	**1.99**	**1.28**	**0.94**	**1.77**	1.34	0.89	2.00	**1.42**	**1.11**	**1.83**
Opioid prescription[c]		**2.45**	**2.12**	**2.83**	**2.34**	**1.98**	**2.76**	**1.86**	**1.55**	**2.24**	**3.59**	**2.86**	**4.50**	**2.82**	**2.18**	**3.65**	**2.29**	**1.93**	**2.72**
Sedative prescription[c]		**1.76**	**1.50**	**2.06**		n/a		**1.53**	**1.23**	**1.90**	**2.18**	**1.74**	**2.74**	**2.05**	**1.50**	**2.81**	**1.67**	**1.40**	**2.01**
Stimulant prescription[c]		1.28	0.95	1.72	**1.46**	**1.03**	**2.06**	1.10	0.74	1.65	1.41	0.92	2.17	0.92	0.46	1.81	**1.41**	**1.02**	**1.95**
Alcohol disorder		**3.76**	**2.62**	**5.40**	**2.89**	**1.85**	**4.53**	**2.92**	**1.77**	**4.83**	**3.33**	**2.04**	**5.43**	**4.13**	**2.22**	**7.68**	**2.88**	**1.85**	**4.47**
Drug disorder		**3.27**	**2.53**	**4.23**	**3.28**	**2.41**	**4.48**	**2.29**	**1.59**	**3.30**	**4.69**	**3.34**	**6.57**	**3.20**	**1.98**	**5.18**	**3.21**	**2.38**	**4.33**
Anxiety disorder		**1.59**	**1.31**	**1.94**	1.09	0.83	1.42	1.02	0.77	1.37	**1.48**	**1.09**	**2.01**	1.40	0.90	2.16	1.11	0.87	1.42
Mood disorder		**3.54**	**3.06**	**4.10**	**1.81**	**1.41**	**2.33**	**2.50**	**1.89**	**3.12**	**1.66**	**1.23**	**2.25**	**2.30**	**1.53**	**3.46**	**2.03**	**1.59**	**2.59**

[a]Benzodiazepine specific codes include ICD-9 codes E853.2 or 969.4 (benzodiazepine poisoning), [b]benzodiazepine non-specific codes include ICD-9 codes 305.4, 305.40, 305.41, 305.42, 305.43, or 304.1, 304.10, 304.11, 304.12 and 304.13 (anxiolytic abuse/dependence).

[c] Psych disorder is a binary variable (any psych disorder) in analyses involving prescription related characteristics (dose, abuse potential, MPR, days supplied, psychotherapy, opioid prescription, sedative prescription, stimulant prescription. Analyses that include alcohol, drug, anxiety and mood disorders include four separate variables to represent these disorders

[d]MPR and days supply in baseline only considered in the existing prescription population, therefore a comparison of results between new and existing prescriptions is not applicable

Appendix 7: full models for all primary analyses

Tables A7.1. Dose, adjusting for demographics and insomnia

Model Fit Statistics

Criterion	Intercept Only	Intercept and Covariates
AIC	10794.198	10437.777
SC	10804.545	10551.591
-2 Log L	10792.198	10415.777

Testing Global Null Hypothesis: BETA=0

Test	Chi-Square	DF	Pr > ChiSq
Likelihood Ratio	376.4207	10	<.0001
Score	456.3313	10	<.0001
Wald	419.9228	10	<.0001

Type 3 Analysis of Effects

Effect	DF	Wald Chi-Square	Pr > ChiSq
dosecat	2	220.9489	<.0001
AGE	1	159.3975	<.0001
REGION	4	1.5556	0.8167
unioncat	2	30.7233	<.0001
insom1	1	17.3583	<.0001

Analysis of Maximum Likelihood Estimates

Parameter		DF	Estimate	Standard Error	Wald Chi-Square	Pr > ChiSq
Intercept		1	-3.1098	0.1752	315.1547	<.0001
dosecat	**2**	1	0.0816	0.0658	1.5379	0.2149
dosecat	**3**	1	0.7683	0.1034	55.1735	<.0001
AGE		1	-0.0339	0.00269	159.3975	<.0001
REGION	**1**	1	0.0402	0.1314	0.0936	0.7597
REGION	**2**	1	-0.0240	0.1009	0.0566	0.8119
REGION	**4**	1	0.0896	0.1128	0.6307	0.4271
REGION	**5**	1	-0.0734	0.3061	0.0575	0.8106
unioncat	**2**	1	-0.2342	0.0538	18.9418	<.0001

Analysis of Maximum Likelihood Estimates						
Parameter		**DF**	**Estimate**	**Standard Error**	**Wald Chi-Square**	**Pr > ChiSq**
unioncat	**3**	1	-0.0534	0.0612	0.7638	0.3821
insom1	**1**	1	0.4104	0.0985	17.3583	<.0001

Odds Ratio Estimates			
Effect	**Point Estimate**	**95% Wald Confidence Limits**	
dosecat 2 vs 1	2.538	2.190	2.941
dosecat 3 vs 1	5.044	3.705	6.866
AGE	0.967	0.962	0.972
REGION 1 vs 3	1.075	0.813	1.422
REGION 2 vs 3	1.008	0.840	1.211
REGION 4 vs 3	1.130	0.916	1.393
REGION 5 vs 3	0.960	0.452	2.037
unioncat 2 vs 1	0.593	0.493	0.714
unioncat 3 vs 1	0.711	0.577	0.877
insom1 1 vs 0	2.272	1.544	3.343

Association of Predicted Probabilities and Observed Responses			
Percent Concordant	55.7	**Somers' D**	0.347
Percent Discordant	21.0	**Gamma**	0.453
Percent Tied	23.2	**Tau-a**	0.002
Pairs	186263868	**c**	0.674

Tables A7.2. Abuse potential, adjusting for demographics and insomnia

Model Fit Statistics

Criterion	Intercept Only	Intercept and Covariates
AIC	10794.198	10620.475
SC	10804.545	10723.942
-2 Log L	10792.198	10600.475

Testing Global Null Hypothesis: BETA=0

Test	Chi-Square	DF	Pr > ChiSq
Likelihood Ratio	191.7230	9	<.0001
Score	215.4414	9	<.0001
Wald	210.9044	9	<.0001

Type 3 Analysis of Effects

Effect	DF	Wald Chi-Square	Pr > ChiSq
ab_pot1	1	6.6217	0.0101
AGE	1	164.1480	<.0001
REGION	4	3.5736	0.4668
unioncat	2	33.5310	<.0001
insom1	1	16.5453	<.0001

Analysis of Maximum Likelihood Estimates

Parameter		DF	Estimate	Standard Error	Wald Chi-Square	Pr > ChiSq
Intercept		1	-4.5387	0.3686	151.6362	<.0001
ab_pot1		1	0.1524	0.0592	6.6217	0.0101
AGE		1	-0.0340	0.00265	164.1480	<.0001
REGION	**1**	1	-0.00978	0.1314	0.0055	0.9407
REGION	**2**	1	-0.0456	0.1008	0.2043	0.6512
REGION	**4**	1	0.1603	0.1125	2.0311	0.1541
REGION	**5**	1	-0.0857	0.3060	0.0785	0.7793
unioncat	**2**	1	-0.2399	0.0537	19.9311	<.0001
unioncat	**3**	1	-0.0639	0.0609	1.0993	0.2944
insom1	**1**	1	0.4002	0.0984	16.5453	<.0001

Odds Ratio Estimates

Effect	Point Estimate	95% Wald Confidence Limits	
ab_pot1	1.165	1.037	1.308
AGE	0.967	0.962	0.972
REGION 1 vs 3	1.009	0.763	1.335
REGION 2 vs 3	0.974	0.811	1.169
REGION 4 vs 3	1.197	0.971	1.474
REGION 5 vs 3	0.936	0.441	1.985
unioncat 2 vs 1	0.581	0.483	0.698
unioncat 3 vs 1	0.692	0.562	0.853
insom1 1 vs 0	2.226	1.514	3.274

Association of Predicted Probabilities and Observed Responses			
Percent Concordant	44.4	**Somers' D**	0.246
Percent Discordant	19.8	**Gamma**	0.382
Percent Tied	35.8	**Tau-a**	0.002
Pairs	186263868	**c**	0.623

Tables A7.3. MPR, adjusting for demographics and insomnia

Model Fit Statistics

Criterion	Intercept Only	Intercept and Covariates
AIC	7250.652	6942.805
SC	7260.322	7049.167
-2 Log L	7248.652	6920.805

Testing Global Null Hypothesis: BETA=0

Test	Chi-Square	DF	Pr > ChiSq
Likelihood Ratio	327.8475	10	<.0001
Score	385.8373	10	<.0001
Wald	366.0700	10	<.0001

Type 3 Analysis of Effects

Effect	DF	Wald Chi-Square	Pr > ChiSq
mprcat	2	140.6120	<.0001
AGE	1	224.7606	<.0001
REGION	4	6.0523	0.1953
unioncat	2	21.4110	<.0001
insom1	1	12.7914	0.0003

Analysis of Maximum Likelihood Estimates

Parameter		DF	Estimate	Standard Error	Wald Chi-Square	Pr > ChiSq
Intercept		1	-2.0900	0.2164	93.3022	<.0001
mprcat	**2**	1	-0.0150	0.0600	0.0625	0.8026
mprcat	**3**	1	0.7290	0.0789	85.3457	<.0001
AGE		1	-0.0535	0.00357	224.7606	<.0001
REGION	**1**	1	0.0561	0.1666	0.1135	0.7362
REGION	**2**	1	-0.1079	0.1287	0.7025	0.4020
REGION	**4**	1	0.2323	0.1417	2.6854	0.1013
REGION	**5**	1	-0.1822	0.4047	0.2026	0.6526
unioncat	**2**	1	-0.2289	0.0644	12.6383	0.0004
unioncat	**3**	1	-0.0577	0.0730	0.6242	0.4295

Analysis of Maximum Likelihood Estimates						
Parameter		**DF**	**Estimate**	**Standard Error**	**Wald Chi-Square**	**Pr > ChiSq**
insom1	**0**	1	-0.3774	0.1055	12.7914	0.0003

Odds Ratio Estimates			
Effect	**Point Estimate**	**95% Wald Confidence Limits**	
mprcat 2 vs 1	2.012	1.680	2.409
mprcat 3 vs 1	4.233	3.296	5.438
AGE	0.948	0.941	0.955
REGION 1 vs 3	1.056	0.749	1.489
REGION 2 vs 3	0.896	0.721	1.114
REGION 4 vs 3	1.259	0.982	1.615
REGION 5 vs 3	0.832	0.308	2.247
unioncat 2 vs 1	0.597	0.480	0.744
unioncat 3 vs 1	0.709	0.553	0.909
insom1 0 vs 1	0.470	0.311	0.711

Association of Predicted Probabilities and Observed Responses			
Percent Concordant	61.4	**Somers' D**	0.391
Percent Discordant	22.3	**Gamma**	0.467
Percent Tied	16.3	**Tau-a**	0.004
Pairs	66782604	**c**	0.696

Tables A7.4. Number of days, adjusting for demographics and insomnia

Model Fit Statistics		
Criterion	**Intercept Only**	**Intercept and Covariates**
AIC	7250.652	6931.919
SC	7260.322	7067.288
-2 Log L	7248.652	6903.919

Testing Global Null Hypothesis: BETA=0			
Test	**Chi-Square**	**DF**	**Pr > ChiSq**
Likelihood Ratio	344.7334	13	<.0001
Score	402.9702	13	<.0001
Wald	382.2982	13	<.0001

Type 3 Analysis of Effects			
Effect	**DF**	**Wald Chi-Square**	**Pr > ChiSq**
monthsuppcat	5	153.8806	<.0001
AGE	1	234.2954	<.0001
REGION	4	6.6436	0.1560
unioncat	2	20.8775	<.0001
insom1	1	13.0804	0.0003

Analysis of Maximum Likelihood Estimates						
Parameter		**DF**	**Estimate**	**Standard Error**	**Wald Chi-Square**	**Pr > ChiSq**
Intercept		1	-2.2596	0.2157	109.7271	<.0001
monthsuppcat	**2**	1	-0.3152	0.1080	8.5171	0.0035
monthsuppcat	**3**	1	-0.2472	0.1121	4.8599	0.0275
monthsuppcat	**4**	1	-0.0608	0.1160	0.2746	0.6002
monthsuppcat	**5**	1	0.3369	0.0749	20.2444	<.0001
monthsuppcat	**6**	1	0.9720	0.1001	94.2124	<.0001
AGE		1	-0.0550	0.00360	234.2954	<.0001
REGION	**1**	1	0.0597	0.1666	0.1283	0.7202
REGION	**2**	1	-0.1125	0.1287	0.7644	0.3819
REGION	**4**	1	0.2432	0.1419	2.9382	0.0865
REGION	**5**	1	-0.1879	0.4048	0.2156	0.6424

Analysis of Maximum Likelihood Estimates						
Parameter		**DF**	**Estimate**	**Standard Error**	**Wald Chi-Square**	**Pr > ChiSq**
unioncat	**2**	1	-0.2284	0.0644	12.5716	0.0004
unioncat	**3**	1	-0.0529	0.0731	0.5236	0.4693
insom1	**0**	1	-0.3818	0.1056	13.0804	0.0003

Odds Ratio Estimates			
Effect	**Point Estimate**	**95% Wald Confidence Limits**	
monthsuppcat 2 vs 1	1.449	1.066	1.968
monthsuppcat 3 vs 1	1.550	1.130	2.127
monthsuppcat 4 vs 1	1.868	1.351	2.582
monthsuppcat 5 vs 1	2.781	2.176	3.554
monthsuppcat 6 vs 1	5.247	3.918	7.028
AGE	0.946	0.940	0.953
REGION 1 vs 3	1.064	0.755	1.500
REGION 2 vs 3	0.896	0.721	1.113
REGION 4 vs 3	1.278	0.996	1.640
REGION 5 vs 3	0.831	0.308	2.244
unioncat 2 vs 1	0.601	0.482	0.748
unioncat 3 vs 1	0.716	0.558	0.918
insom1 0 vs 1	0.466	0.308	0.705

Association of Predicted Probabilities and Observed Responses			
Percent Concordant	62.6	**Somers' D**	0.409
Percent Discordant	21.7	**Gamma**	0.485
Percent Tied	15.6	**Tau-a**	0.004
Pairs	66782604	**c**	0.705

Tables A7.5. Psychotherapy, adjusting for demographics and insomnia

Model Fit Statistics		
Criterion	**Intercept Only**	**Intercept and Covariates**
AIC	10794.198	10277.986
SC	10804.545	10381.453
-2 Log L	10792.198	10257.986

Testing Global Null Hypothesis: BETA=0			
Test	**Chi-Square**	**DF**	**Pr > ChiSq**
Likelihood Ratio	534.2118	9	<.0001
Score	696.4542	9	<.0001
Wald	600.9126	9	<.0001

Type 3 Analysis of Effects			
Effect	**DF**	**Wald Chi-Square**	**Pr > ChiSq**
psychotherapy1	1	392.2460	<.0001
AGE	1	128.4165	<.0001
REGION	4	3.6243	0.4592
unioncat	2	22.2298	<.0001
insom1	1	12.1703	0.0005

Analysis of Maximum Likelihood Estimates						
Parameter		**DF**	**Estimate**	**Standard Error**	**Wald Chi-Square**	**Pr > ChiSq**
Intercept		1	-3.5794	0.1704	441.3173	<.0001
psychotherapy1	**1**	1	0.7090	0.0358	392.2460	<.0001
AGE		1	-0.0308	0.00272	128.4165	<.0001
REGION	**1**	1	-0.0577	0.1316	0.1922	0.6611
REGION	**2**	1	-0.0819	0.1014	0.6529	0.4191
REGION	**4**	1	0.1330	0.1132	1.3812	0.2399
REGION	**5**	1	-0.0342	0.3063	0.0124	0.9112
unioncat	**2**	1	-0.1873	0.0539	12.0567	0.0005
unioncat	**3**	1	-0.0675	0.0618	1.1916	0.2750

Analysis of Maximum Likelihood Estimates						
Parameter		**DF**	**Estimate**	**Standard Error**	**Wald Chi-Square**	**Pr > ChiSq**
insom1	**1**	1	0.3442	0.0987	12.1703	0.0005

Odds Ratio Estimates			
Effect	**Point Estimate**	**95% Wald Confidence Limits**	
psychotherapy1 1 vs 0	4.129	3.589	4.751
AGE	0.970	0.965	0.975
REGION 1 vs 3	0.906	0.685	1.199
REGION 2 vs 3	0.885	0.736	1.063
REGION 4 vs 3	1.097	0.889	1.353
REGION 5 vs 3	0.928	0.437	1.970
unioncat 2 vs 1	0.643	0.534	0.774
unioncat 3 vs 1	0.725	0.586	0.895
insom1 1 vs 0	1.991	1.352	2.930

Association of Predicted Probabilities and Observed Responses			
Percent Concordant	61.0	**Somers' D**	0.425
Percent Discordant	18.5	**Gamma**	0.534
Percent Tied	20.5	**Tau-a**	0.003
Pairs	186263868	**c**	0.712

Tables A7.6. Opioid prescription , adjusting for demographics and insomnia

Model Fit Statistics		
Criterion	**Intercept Only**	**Intercept and Covariates**
AIC	10794.198	10425.070
SC	10804.545	10528.537
-2 Log L	10792.198	10405.070

Testing Global Null Hypothesis: BETA=0			
Test	**Chi-Square**	**DF**	**Pr > ChiSq**
Likelihood Ratio	387.1283	9	<.0001
Score	413.3382	9	<.0001
Wald	392.0638	9	<.0001

Type 3 Analysis of Effects			
Effect	**DF**	**Wald Chi-Square**	**Pr > ChiSq**
opioids1	1	198.5731	<.0001
AGE	1	192.1918	<.0001
REGION	4	3.9258	0.4161
unioncat	2	26.9209	<.0001
insom1	1	14.3879	0.0001

Analysis of Maximum Likelihood Estimates						
Parameter		**DF**	**Estimate**	**Standard Error**	**Wald Chi-Square**	**Pr > ChiSq**
Intercept		1	-3.4793	0.1700	419.0251	<.0001
opioids1	**1**	1	0.5093	0.0361	198.5731	<.0001
AGE		1	-0.0378	0.00273	192.1918	<.0001
REGION	**1**	1	0.0927	0.1316	0.4965	0.4810
REGION	**2**	1	-0.0461	0.1012	0.2075	0.6488
REGION	**4**	1	0.1138	0.1127	1.0201	0.3125
REGION	**5**	1	-0.0919	0.3061	0.0900	0.7641
unioncat	**2**	1	-0.2286	0.0539	17.9850	<.0001
unioncat	**3**	1	-0.0347	0.0612	0.3214	0.5707
insom1	**1**	1	0.3736	0.0985	14.3879	0.0001

Odds Ratio Estimates

Effect	Point Estimate	95% Wald Confidence Limits	
opioids1 1 vs 0	2.769	2.403	3.190
AGE	0.963	0.958	0.968
REGION 1 vs 3	1.175	0.888	1.555
REGION 2 vs 3	1.023	0.851	1.229
REGION 4 vs 3	1.200	0.974	1.479
REGION 5 vs 3	0.977	0.460	2.074
unioncat 2 vs 1	0.611	0.508	0.736
unioncat 3 vs 1	0.742	0.602	0.916
insom1 1 vs 0	2.111	1.435	3.106

Association of Predicted Probabilities and Observed Responses			
Percent Concordant	58.4	**Somers' D**	0.363
Percent Discordant	22.1	**Gamma**	0.451
Percent Tied	19.6	**Tau-a**	0.003
Pairs	186263868	**c**	0.682

Tables A7.7. Sedative prescription, adjusting for demographics and insomnia

Model Fit Statistics		
Criterion	**Intercept Only**	**Intercept and Covariates**
AIC	10794.198	10520.018
SC	10804.545	10623.485
-2 Log L	10792.198	10500.018

Testing Global Null Hypothesis: BETA=0			
Test	**Chi-Square**	**DF**	**Pr > ChiSq**
Likelihood Ratio	292.1801	9	<.0001
Score	337.1959	9	<.0001
Wald	323.7199	9	<.0001

Type 3 Analysis of Effects			
Effect	**DF**	**Wald Chi-Square**	**Pr > ChiSq**
sedatives1	1	124.1131	<.0001
AGE	1	178.3536	<.0001
REGION	4	3.7589	0.4396
unioncat	2	30.0875	<.0001
insom1	1	6.4326	0.0112

Analysis of Maximum Likelihood Estimates						
Parameter		**DF**	**Estimate**	**Standard Error**	**Wald Chi-Square**	**Pr > ChiSq**
Intercept		1	-3.4781	0.1692	422.3248	<.0001
sedatives1	**1**	1	0.4478	0.0402	124.1131	<.0001
AGE		1	-0.0355	0.00266	178.3536	<.0001
REGION	**1**	1	0.0104	0.1313	0.0062	0.9372
REGION	**2**	1	-0.0252	0.1009	0.0622	0.8031
REGION	**4**	1	0.1546	0.1122	1.8974	0.1684
REGION	**5**	1	-0.0944	0.3061	0.0952	0.7577
unioncat	**2**	1	-0.2304	0.0537	18.4073	<.0001
unioncat	**3**	1	-0.0551	0.0607	0.8222	0.3645

Analysis of Maximum Likelihood Estimates						
Parameter		**DF**	**Estimate**	**Standard Error**	**Wald Chi-Square**	**Pr > ChiSq**
insom1	**1**	1	0.2522	0.0994	6.4326	0.0112

Odds Ratio Estimates			
Effect	**Point Estimate**	**95% Wald Confidence Limits**	
sedatives1 1 vs 0	2.449	2.092	2.867
AGE	0.965	0.960	0.970
REGION 1 vs 3	1.057	0.799	1.398
REGION 2 vs 3	1.020	0.850	1.225
REGION 4 vs 3	1.221	0.992	1.504
REGION 5 vs 3	0.952	0.449	2.021
unioncat 2 vs 1	0.597	0.496	0.718
unioncat 3 vs 1	0.711	0.577	0.876
insom1 1 vs 0	1.656	1.121	2.445

Association of Predicted Probabilities and Observed Responses			
Percent Concordant	51.0	**Somers' D**	0.298
Percent Discordant	21.2	**Gamma**	0.412
Percent Tied	27.8	**Tau-a**	0.002
Pairs	186263868	**c**	0.649

Tables A7.8. Stimulant prescription, adjusting for demographics and insomnia

Model Fit Statistics		
Criterion	**Intercept Only**	**Intercept and Covariates**
AIC	10794.198	10605.597
SC	10804.545	10709.064
-2 Log L	10792.198	10585.597

Testing Global Null Hypothesis: BETA=0			
Test	**Chi-Square**	**DF**	**Pr > ChiSq**
Likelihood Ratio	206.6007	9	<.0001
Score	243.0057	9	<.0001
Wald	236.3350	9	<.0001

Type 3 Analysis of Effects			
Effect	**DF**	**Wald Chi-Square**	**Pr > ChiSq**
stimulants1	1	26.9277	<.0001
AGE	1	155.4168	<.0001
REGION	4	3.4148	0.4910
unioncat	2	31.3217	<.0001
insom1	1	15.9012	<.0001

Analysis of Maximum Likelihood Estimates						
Parameter		**DF**	**Estimate**	**Standard Error**	**Wald Chi-Square**	**Pr > ChiSq**
Intercept		1	-3.3790	0.1771	363.9079	<.0001
stimulants1	**1**	1	0.3864	0.0745	26.9277	<.0001
AGE		1	-0.0329	0.00264	155.4168	<.0001
REGION	**1**	1	-0.00037	0.1313	0.0000	0.9978
REGION	**2**	1	-0.0472	0.1009	0.2187	0.6400
REGION	**4**	1	0.1531	0.1124	1.8549	0.1732
REGION	**5**	1	-0.0824	0.3060	0.0726	0.7876
unioncat	**2**	1	-0.2321	0.0538	18.6336	<.0001
unioncat	**3**	1	-0.0621	0.0609	1.0376	0.3084
insom1	**1**	1	0.3922	0.0984	15.9012	<.0001

Odds Ratio Estimates

Effect	Point Estimate	95% Wald Confidence Limits	
stimulants1 1 vs 0	2.166	1.618	2.900
AGE	0.968	0.963	0.973
REGION 1 vs 3	1.023	0.774	1.353
REGION 2 vs 3	0.976	0.813	1.172
REGION 4 vs 3	1.193	0.968	1.469
REGION 5 vs 3	0.942	0.444	2.000
unioncat 2 vs 1	0.591	0.491	0.711
unioncat 3 vs 1	0.700	0.568	0.863
insom1 1 vs 0	2.191	1.490	3.222

Association of Predicted Probabilities and Observed Responses			
Percent Concordant	44.7	**Somers' D**	0.252
Percent Discordant	19.6	**Gamma**	0.391
Percent Tied	35.7	**Tau-a**	0.002
Pairs	186263868	**c**	0.626

A7.9. Dose, adjusting for demographics, insomnia and psychiatric disorders

Model Fit Statistics		
Criterion	**Intercept Only**	**Intercept and Covariates**
AIC	10794.198	10024.724
SC	10804.545	10148.884
-2 Log L	10792.198	10000.724

Testing Global Null Hypothesis: BETA=0			
Test	**Chi-Square**	**DF**	**Pr > ChiSq**
Likelihood Ratio	791.4741	11	<.0001
Score	980.7801	11	<.0001
Wald	818.6429	11	<.0001

Type 3 Analysis of Effects			
Effect	**DF**	**Wald Chi-Square**	**Pr > ChiSq**
dosecat	2	177.6538	<.0001
AGE	1	113.1300	<.0001
REGION	4	1.5397	0.8196
unioncat	2	22.6110	<.0001
insom1	1	0.0292	0.8644
psychdiag1	1	418.3759	<.0001

Analysis of Maximum Likelihood Estimates						
Parameter		**DF**	**Estimate**	**Standard Error**	**Wald Chi-Square**	**Pr > ChiSq**
Intercept		1	-3.6353	0.1821	398.6573	<.0001
dosecat	**2**	1	0.0954	0.0660	2.0905	0.1482
dosecat	**3**	1	0.6623	0.1039	40.6257	<.0001
AGE		1	-0.0296	0.00279	113.1300	<.0001
REGION	**1**	1	-0.00456	0.1317	0.0012	0.9724
REGION	**2**	1	-0.0587	0.1013	0.3358	0.5623
REGION	**4**	1	0.0876	0.1135	0.5965	0.4399
REGION	**5**	1	-0.0423	0.3066	0.0190	0.8903
unioncat	**2**	1	-0.1931	0.0540	12.8093	0.0003
unioncat	**3**	1	-0.0609	0.0619	0.9676	0.3253

Analysis of Maximum Likelihood Estimates						
Parameter		**DF**	**Estimate**	**Standard Error**	**Wald Chi-Square**	**Pr > ChiSq**
insom1	**1**	1	-0.0170	0.0997	0.0292	0.8644
psychdiag1	**1**	1	0.7478	0.0366	418.3759	<.0001

Odds Ratio Estimates			
Effect	**Point Estimate**	**95% Wald Confidence Limits**	
dosecat 2 vs 1	2.347	2.024	2.721
dosecat 3 vs 1	4.137	3.035	5.641
AGE	0.971	0.966	0.976
REGION 1 vs 3	0.978	0.739	1.294
REGION 2 vs 3	0.926	0.771	1.113
REGION 4 vs 3	1.072	0.869	1.323
REGION 5 vs 3	0.942	0.443	2.001
unioncat 2 vs 1	0.639	0.531	0.770
unioncat 3 vs 1	0.730	0.590	0.902
insom1 1 vs 0	0.967	0.654	1.429
psychdiag1 1 vs 0	4.462	3.867	5.150

Association of Predicted Probabilities and Observed Responses			
Percent Concordant	66.0	**Somers' D**	0.488
Percent Discordant	17.2	**Gamma**	0.586
Percent Tied	16.8	**Tau-a**	0.003
Pairs	186263868	**c**	0.744

A7.10. Abuse potential, adjusting for demographics, insomnia and psychiatric disorders

Model Fit Statistics		
Criterion	**Intercept Only**	**Intercept and Covariates**
AIC	10794.198	10179.283
SC	10804.545	10293.097
-2 Log L	10792.198	10157.283

Testing Global Null Hypothesis: BETA=0			
Test	**Chi-Square**	**DF**	**Pr > ChiSq**
Likelihood Ratio	634.9144	10	<.0001
Score	774.6761	10	<.0001
Wald	646.3061	10	<.0001

Type 3 Analysis of Effects			
Effect	**DF**	**Wald Chi-Square**	**Pr > ChiSq**
ab_pot1	1	1.2525	0.2631
AGE	1	109.3045	<.0001
REGION	4	3.6636	0.4534
unioncat	2	25.4256	<.0001
insom1	1	0.2520	0.6156
psychdiag1	1	448.3977	<.0001

Analysis of Maximum Likelihood Estimates						
Parameter		**DF**	**Estimate**	**Standard Error**	**Wald Chi-Square**	**Pr > ChiSq**
Intercept		1	-4.5623	0.3646	156.5825	<.0001
ab_pot1		1	0.0646	0.0577	1.2525	0.2631
AGE		1	-0.0288	0.00275	109.3045	<.0001
REGION	**1**	1	-0.0482	0.1316	0.1342	0.7141
REGION	**2**	1	-0.0791	0.1012	0.6114	0.4342
REGION	**4**	1	0.1388	0.1132	1.5045	0.2200
REGION	**5**	1	-0.0535	0.3064	0.0305	0.8613
unioncat	**2**	1	-0.1996	0.0539	13.7301	0.0002
unioncat	**3**	1	-0.0725	0.0616	1.3844	0.2394
insom1	**1**	1	-0.0500	0.0996	0.2520	0.6156
psychdiag1	**1**	1	0.7748	0.0366	448.3977	<.0001

Odds Ratio Estimates			
Effect	**Point Estimate**	**95% Wald Confidence Limits**	
ab_pot1	1.067	0.953	1.194
AGE	0.972	0.966	0.977
REGION 1 vs 3	0.914	0.690	1.209
REGION 2 vs 3	0.886	0.737	1.065
REGION 4 vs 3	1.102	0.893	1.359
REGION 5 vs 3	0.909	0.428	1.930
unioncat 2 vs 1	0.624	0.518	0.751
unioncat 3 vs 1	0.708	0.574	0.875
insom1 1 vs 0	0.905	0.612	1.337
psychdiag1 1 vs 0	4.709	4.080	5.435

Association of Predicted Probabilities and Observed Responses			
Percent Concordant	64.3	**Somers' D**	0.461
Percent Discordant	18.1	**Gamma**	0.560
Percent Tied	17.6	**Tau-a**	0.003
Pairs	186263868	**c**	0.731

A7.11. MPR, adjusting for demographics, insomnia and psychiatric disorders

Model Fit Statistics

Criterion	Intercept Only	Intercept and Covariates
AIC	7250.652	6737.460
SC	7260.322	6853.491
-2 Log L	7248.652	6713.460

Testing Global Null Hypothesis: BETA=0

Test	Chi-Square	DF	Pr > ChiSq
Likelihood Ratio	535.1925	11	<.0001
Score	626.3327	11	<.0001
Wald	542.0438	11	<.0001

Type 3 Analysis of Effects

Effect	DF	Wald Chi-Square	Pr > ChiSq
mprcat	2	102.5729	<.0001
AGE	1	142.6461	<.0001
REGION	4	6.2310	0.1825
unioncat	2	17.1220	0.0002
psychdiag1	1	200.1972	<.0001
insom1	1	0.3509	0.5536

Analysis of Maximum Likelihood Estimates

Parameter		DF	Estimate	Standard Error	Wald Chi-Square	Pr > ChiSq
Intercept		1	-2.8092	0.2289	150.6828	<.0001
mprcat	**2**	1	-0.0111	0.0601	0.0341	0.8536
mprcat	**3**	1	0.6264	0.0794	62.2426	<.0001
AGE		1	-0.0447	0.00374	142.6461	<.0001
REGION	**1**	1	0.0174	0.1669	0.0109	0.9167
REGION	**2**	1	-0.1241	0.1291	0.9241	0.3364
REGION	**4**	1	0.2246	0.1424	2.4872	0.1148
REGION	**5**	1	-0.1789	0.4054	0.1947	0.6590
unioncat	**2**	1	-0.1936	0.0645	9.0064	0.0027
unioncat	**3**	1	-0.0710	0.0737	0.9281	0.3354

Analysis of Maximum Likelihood Estimates						
Parameter		**DF**	**Estimate**	**Standard Error**	**Wald Chi-Square**	**Pr > ChiSq**
psychdiag1	**1**	1	0.6362	0.0450	200.1972	<.0001
insom1	**0**	1	-0.0632	0.1067	0.3509	0.5536

Odds Ratio Estimates			
Effect	**Point Estimate**	**95% Wald Confidence Limits**	
mprcat 2 vs 1	1.830	1.527	2.193
mprcat 3 vs 1	3.462	2.689	4.456
AGE	0.956	0.949	0.963
REGION 1 vs 3	0.957	0.678	1.352
REGION 2 vs 3	0.831	0.668	1.034
REGION 4 vs 3	1.178	0.918	1.512
REGION 5 vs 3	0.787	0.291	2.128
unioncat 2 vs 1	0.632	0.508	0.788
unioncat 3 vs 1	0.715	0.556	0.919
psychdiag1 1 vs 0	3.569	2.992	4.257
insom1 0 vs 1	0.881	0.580	1.339

Association of Predicted Probabilities and Observed Responses			
Percent Concordant	70.2	**Somers' D**	0.514
Percent Discordant	18.8	**Gamma**	0.578
Percent Tied	11.0	**Tau-a**	0.005
Pairs	66782604	**c**	0.757

A7.12. Number of days, adjusting for demographics, insomnia and psychiatric disorders

Model Fit Statistics

Criterion	Intercept Only	Intercept and Covariates
AIC	7250.652	6729.634
SC	7260.322	6874.673
-2 Log L	7248.652	6699.634

Testing Global Null Hypothesis: BETA=0

Test	Chi-Square	DF	Pr > ChiSq
Likelihood Ratio	549.0180	14	<.0001
Score	640.0076	14	<.0001
Wald	554.6177	14	<.0001

Type 3 Analysis of Effects

Effect	DF	Wald Chi-Square	Pr > ChiSq
monthsuppcat	5	114.5074	<.0001
AGE	1	149.3553	<.0001
REGION	4	6.7363	0.1505
unioncat	2	16.6244	0.0002
psychdiag1	1	197.2197	<.0001
insom1	1	0.4367	0.5087

Analysis of Maximum Likelihood Estimates

Parameter		DF	Estimate	Standard Error	Wald Chi-Square	Pr > ChiSq
Intercept		1	-2.9539	0.2276	168.4494	<.0001
monthsuppcat	**2**	1	-0.2747	0.1082	6.4433	0.0111
monthsuppcat	**3**	1	-0.2162	0.1123	3.7060	0.0542
monthsuppcat	**4**	1	-0.0818	0.1161	0.4963	0.4811
monthsuppcat	**5**	1	0.3122	0.0751	17.2873	<.0001
monthsuppcat	**6**	1	0.8428	0.1008	69.9493	<.0001
AGE		1	-0.0460	0.00376	149.3553	<.0001
REGION	**1**	1	0.0207	0.1669	0.0154	0.9011
REGION	**2**	1	-0.1293	0.1292	1.0026	0.3167
REGION	**4**	1	0.2357	0.1426	2.7335	0.0983
REGION	**5**	1	-0.1837	0.4055	0.2052	0.6505

Analysis of Maximum Likelihood Estimates						
Parameter		**DF**	**Estimate**	**Standard Error**	**Wald Chi-Square**	**Pr > ChiSq**
unioncat	**2**	1	-0.1931	0.0645	8.9531	0.0028
unioncat	**3**	1	-0.0663	0.0738	0.8076	0.3688
psychdiag1	**1**	1	0.6317	0.0450	197.2197	<.0001
insom1	**0**	1	-0.0705	0.1067	0.4367	0.5087

Odds Ratio Estimates			
Effect	**Point Estimate**	**95% Wald Confidence Limits**	
monthsuppcat 2 vs 1	1.360	1.001	1.848
monthsuppcat 3 vs 1	1.442	1.051	1.980
monthsuppcat 4 vs 1	1.650	1.192	2.282
monthsuppcat 5 vs 1	2.446	1.912	3.129
monthsuppcat 6 vs 1	4.158	3.098	5.582
AGE	0.955	0.948	0.962
REGION 1 vs 3	0.965	0.683	1.362
REGION 2 vs 3	0.830	0.668	1.033
REGION 4 vs 3	1.196	0.932	1.536
REGION 5 vs 3	0.786	0.291	2.128
unioncat 2 vs 1	0.636	0.511	0.792
unioncat 3 vs 1	0.722	0.562	0.928
psychdiag1 1 vs 0	3.538	2.966	4.220
insom1 0 vs 1	0.868	0.572	1.320

Association of Predicted Probabilities and Observed Responses			
Percent Concordant	70.8	**Somers' D**	0.524
Percent Discordant	18.5	**Gamma**	0.587
Percent Tied	10.7	**Tau-a**	0.005
Pairs	66782604	**c**	0.762

A7.13. Psychotherapy, adjusting for demographics, insomnia and psychiatric disorders

Model Fit Statistics		
Criterion	**Intercept Only**	**Intercept and Covariates**
AIC	10794.198	10168.020
SC	10804.545	10281.834
-2 Log L	10792.198	10146.020

Testing Global Null Hypothesis: BETA=0			
Test	**Chi-Square**	**DF**	**Pr > ChiSq**
Likelihood Ratio	646.1778	10	<.0001
Score	803.4478	10	<.0001
Wald	663.8594	10	<.0001

Type 3 Analysis of Effects			
Effect	**DF**	**Wald Chi-Square**	**Pr > ChiSq**
psychotherapy1	1	11.9091	0.0006
AGE	1	111.4931	<.0001
REGION	4	3.7993	0.4338
unioncat	2	23.1054	<.0001
insom1	1	0.0957	0.7571
psychdiag1	1	135.6349	<.0001

Analysis of Maximum Likelihood Estimates						
Parameter		**DF**	**Estimate**	**Standard Error**	**Wald Chi-Square**	**Pr > ChiSq**
Intercept		1	-4.0575	0.1791	513.4037	<.0001
psychotherapy1	**1**	1	0.1866	0.0541	11.9091	0.0006
AGE		1	-0.0290	0.00275	111.4931	<.0001
REGION	**1**	1	-0.0555	0.1316	0.1775	0.6735
REGION	**2**	1	-0.0835	0.1013	0.6796	0.4097
REGION	**4**	1	0.1336	0.1132	1.3933	0.2378
REGION	**5**	1	-0.0428	0.3064	0.0195	0.8890
unioncat	**2**	1	-0.1893	0.0540	12.3010	0.0005
unioncat	**3**	1	-0.0718	0.0618	1.3505	0.2452

Analysis of Maximum Likelihood Estimates						
Parameter		**DF**	**Estimate**	**Standard Error**	**Wald Chi-Square**	**Pr > ChiSq**
insom1	**1**	1	0.0318	0.1027	0.0957	0.7571
psychdiag1	**1**	1	0.6414	0.0551	135.6349	<.0001

Odds Ratio Estimates			
Effect	**Point Estimate**	**95% Wald Confidence Limits**	
psychotherapy1 1 vs 0	1.452	1.175	1.795
AGE	0.971	0.966	0.977
REGION 1 vs 3	0.902	0.681	1.193
REGION 2 vs 3	0.877	0.729	1.054
REGION 4 vs 3	1.089	0.883	1.344
REGION 5 vs 3	0.913	0.430	1.939
unioncat 2 vs 1	0.637	0.529	0.767
unioncat 3 vs 1	0.717	0.580	0.886
insom1 1 vs 0	1.066	0.713	1.593
psychdiag1 1 vs 0	3.607	2.906	4.476

Association of Predicted Probabilities and Observed Responses			
Percent Concordant	64.5	**Somers' D**	0.465
Percent Discordant	17.9	**Gamma**	0.565
Percent Tied	17.6	**Tau-a**	0.003
Pairs	186263868	**c**	0.733

A7.14. Opioid prescription, adjusting for demographics, insomnia and psychiatric disorders

Model Fit Statistics		
Criterion	**Intercept Only**	**Intercept and Covariates**
AIC	10794.198	9993.178
SC	10804.545	10106.992
-2 Log L	10792.198	9971.178

Testing Global Null Hypothesis: BETA=0			
Test	**Chi-Square**	**DF**	**Pr > ChiSq**
Likelihood Ratio	821.0196	10	<.0001
Score	962.1598	10	<.0001
Wald	816.5572	10	<.0001

Type 3 Analysis of Effects			
Effect	**DF**	**Wald Chi-Square**	**Pr > ChiSq**
opioids1	1	183.8162	<.0001
AGE	1	134.1496	<.0001
REGION	4	2.4001	0.6626
unioncat	2	19.2203	<.0001
insom1	1	0.3682	0.5440
psychdiag1	1	438.2071	<.0001

Analysis of Maximum Likelihood Estimates						
Parameter		**DF**	**Estimate**	**Standard Error**	**Wald Chi-Square**	**Pr > ChiSq**
Intercept		1	-3.9753	0.1764	507.9890	<.0001
opioids1	**1**	1	0.4908	0.0362	183.8162	<.0001
AGE		1	-0.0328	0.00283	134.1496	<.0001
REGION	**1**	1	0.0478	0.1319	0.1314	0.7169
REGION	**2**	1	-0.0804	0.1015	0.6275	0.4283
REGION	**4**	1	0.0940	0.1134	0.6863	0.4074
REGION	**5**	1	-0.0464	0.3066	0.0229	0.8796
unioncat	**2**	1	-0.1870	0.0540	11.9798	0.0005
unioncat	**3**	1	-0.0420	0.0619	0.4602	0.4975
insom1	**1**	1	-0.0605	0.0996	0.3682	0.5440
psychdiag1	**1**	1	0.7642	0.0365	438.2071	<.0001

Odds Ratio Estimates			
Effect	**Point Estimate**	**95% Wald Confidence Limits**	
opioids1 1 vs 0	2.668	2.315	3.075
AGE	0.968	0.962	0.973
REGION 1 vs 3	1.065	0.804	1.410
REGION 2 vs 3	0.937	0.779	1.127
REGION 4 vs 3	1.115	0.904	1.376
REGION 5 vs 3	0.969	0.456	2.059
unioncat 2 vs 1	0.660	0.548	0.795
unioncat 3 vs 1	0.763	0.616	0.943
insom1 1 vs 0	0.886	0.600	1.310
psychdiag1 1 vs 0	4.611	3.996	5.320

Association of Predicted Probabilities and Observed Responses			
Percent Concordant	68.2	**Somers' D**	0.515
Percent Discordant	16.7	**Gamma**	0.606
Percent Tied	15.1	**Tau-a**	0.004
Pairs	186263868	**c**	0.757

A7.15. Sedative prescription, adjusting for demographics, insomnia and psychiatric disorders

Model Fit Statistics

Criterion	Intercept Only	Intercept and Covariates
AIC	10794.198	10126.509
SC	10804.545	10240.323
-2 Log L	10792.198	10104.509

Testing Global Null Hypothesis: BETA=0

Test	Chi-Square	DF	Pr > ChiSq
Likelihood Ratio	687.6884	10	<.0001
Score	843.6852	10	<.0001
Wald	707.2826	10	<.0001

Type 3 Analysis of Effects

Effect	DF	Wald Chi-Square	Pr > ChiSq
sedatives1	1	59.3315	<.0001
AGE	1	119.4284	<.0001
REGION	4	3.0071	0.5566
unioncat	2	23.5072	<.0001
insom1	1	1.5110	0.2190
psychdiag1	1	398.2650	<.0001

Analysis of Maximum Likelihood Estimates

Parameter		DF	Estimate	Standard Error	Wald Chi-Square	Pr > ChiSq
Intercept		1	-4.0155	0.1764	518.1835	<.0001
sedatives1	**1**	1	0.3131	0.0407	59.3315	<.0001
AGE		1	-0.0303	0.00277	119.4284	<.0001
REGION	**1**	1	-0.0316	0.1316	0.0577	0.8102
REGION	**2**	1	-0.0648	0.1013	0.4099	0.5220
REGION	**4**	1	0.1394	0.1129	1.5228	0.2172
REGION	**5**	1	-0.0605	0.3065	0.0390	0.8434
unioncat	**2**	1	-0.1943	0.0539	13.0181	0.0003
unioncat	**3**	1	-0.0661	0.0615	1.1557	0.2824
insom1	**1**	1	-0.1229	0.1000	1.5110	0.2190

Analysis of Maximum Likelihood Estimates					
Parameter	**DF**	**Estimate**	**Standard Error**	**Wald Chi-Square**	**Pr > ChiSq**
psychdiag1 1	1	0.7379	0.0370	398.2650	<.0001

Odds Ratio Estimates			
Effect	**Point Estimate**	**95% Wald Confidence Limits**	
sedatives1 1 vs 0	1.871	1.595	2.194
AGE	0.970	0.965	0.975
REGION 1 vs 3	0.952	0.719	1.260
REGION 2 vs 3	0.921	0.766	1.107
REGION 4 vs 3	1.129	0.916	1.393
REGION 5 vs 3	0.925	0.435	1.965
unioncat 2 vs 1	0.635	0.527	0.764
unioncat 3 vs 1	0.721	0.584	0.891
insom1 1 vs 0	0.782	0.528	1.157
psychdiag1 1 vs 0	4.375	3.784	5.057

Association of Predicted Probabilities and Observed Responses			
Percent Concordant	65.7	**Somers' D**	0.480
Percent Discordant	17.8	**Gamma**	0.574
Percent Tied	16.5	**Tau-a**	0.003
Pairs	186263868	**c**	0.740

A7.16. Stimulant prescription, adjusting for demographics, insomnia and psychiatric disorders

Model Fit Statistics

Criterion	Intercept Only	Intercept and Covariates
AIC	10794.198	10177.374
SC	10804.545	10291.188
-2 Log L	10792.198	10155.374

Testing Global Null Hypothesis: BETA=0

Test	Chi-Square	DF	Pr > ChiSq
Likelihood Ratio	636.8241	10	<.0001
Score	781.1616	10	<.0001
Wald	650.9131	10	<.0001

Type 3 Analysis of Effects

Effect	DF	Wald Chi-Square	Pr > ChiSq
stimulants1	1	3.4342	0.0639
AGE	1	106.9380	<.0001
REGION	4	3.5318	0.4731
unioncat	2	24.7990	<.0001
insom1	1	0.2455	0.6203
psychdiag1	1	436.4948	<.0001

Analysis of Maximum Likelihood Estimates

Parameter		DF	Estimate	Standard Error	Wald Chi-Square	Pr > ChiSq
Intercept		1	-4.0861	0.1856	484.8670	<.0001
stimulants1	**1**	1	0.1394	0.0752	3.4342	0.0639
AGE		1	-0.0285	0.00275	106.9380	<.0001
REGION	**1**	1	-0.0429	0.1316	0.1066	0.7441
REGION	**2**	1	-0.0787	0.1013	0.6041	0.4370
REGION	**4**	1	0.1369	0.1131	1.4635	0.2264
REGION	**5**	1	-0.0541	0.3064	0.0312	0.8598
unioncat	**2**	1	-0.1970	0.0539	13.3637	0.0003
unioncat	**3**	1	-0.0722	0.0617	1.3716	0.2415
insom1	**1**	1	-0.0493	0.0996	0.2455	0.6203

Analysis of Maximum Likelihood Estimates					
Parameter	**DF**	**Estimate**	**Standard Error**	**Wald Chi-Square**	**Pr > ChiSq**
psychdiag1 1	1	0.7694	0.0368	436.4948	<.0001

Odds Ratio Estimates			
Effect	**Point Estimate**	**95% Wald Confidence Limits**	
stimulants1 1 vs 0	1.322	0.984	1.775
AGE	0.972	0.967	0.977
REGION 1 vs 3	0.921	0.696	1.219
REGION 2 vs 3	0.889	0.740	1.068
REGION 4 vs 3	1.103	0.894	1.360
REGION 5 vs 3	0.911	0.429	1.935
unioncat 2 vs 1	0.627	0.521	0.755
unioncat 3 vs 1	0.711	0.575	0.878
insom1 1 vs 0	0.906	0.613	1.339
psychdiag1 1 vs 0	4.659	4.033	5.383

Association of Predicted Probabilities and Observed Responses			
Percent Concordant	64.1	**Somers' D**	0.460
Percent Discordant	18.2	**Gamma**	0.559
Percent Tied	17.7	**Tau-a**	0.003
Pairs	186263868	**c**	0.730

A7.17. Dose, adjusting for demographics, insomnia, psychiatric disorders and benzodiazepine prescription history

Model Fit Statistics		
Criterion	**Intercept Only**	**Intercept and Covariates**
AIC	10794.198	9934.948
SC	10804.545	10069.456
-2 Log L	10792.198	9908.948

Testing Global Null Hypothesis: BETA=0			
Test	**Chi-Square**	**DF**	**Pr > ChiSq**
Likelihood Ratio	883.2495	12	<.0001
Score	1069.5012	12	<.0001
Wald	899.7199	12	<.0001

Type 3 Analysis of Effects			
Effect	**DF**	**Wald Chi-Square**	**Pr > ChiSq**
dosecat	2	149.6493	<.0001
AGE	1	158.6439	<.0001
REGION	4	1.9757	0.7402
unioncat	2	20.5719	<.0001
insom1	1	0.0132	0.9084
psychdiag1	1	332.4121	<.0001
benzo_bl1	1	85.3827	<.0001

Analysis of Maximum Likelihood Estimates						
Parameter		**DF**	**Estimate**	**Standard Error**	**Wald Chi-Square**	**Pr > ChiSq**
Intercept		1	-3.4328	0.1835	349.9422	<.0001
dosecat	**2**	1	0.0888	0.0661	1.8054	0.1791
dosecat	**3**	1	0.6103	0.1041	34.3475	<.0001
AGE		1	-0.0367	0.00291	158.6439	<.0001
REGION	**1**	1	0.0105	0.1317	0.0064	0.9364
REGION	**2**	1	-0.0624	0.1013	0.3792	0.5380
REGION	**4**	1	0.1035	0.1135	0.8321	0.3617
REGION	**5**	1	-0.0436	0.3068	0.0202	0.8871
unioncat	**2**	1	-0.1889	0.0540	12.2469	0.0005

Analysis of Maximum Likelihood Estimates						
Parameter		**DF**	**Estimate**	**Standard Error**	**Wald Chi-Square**	**Pr > ChiSq**
unioncat	**3**	1	-0.0499	0.0618	0.6523	0.4193
insom1	**1**	1	-0.0115	0.0998	0.0132	0.9084
psychdiag1	**1**	1	0.6789	0.0372	332.4121	<.0001
benzo_bl1	**1**	1	0.3772	0.0408	85.3827	<.0001

Odds Ratio Estimates			
Effect	**Point Estimate**	**95% Wald Confidence Limits**	
dosecat 2 vs 1	2.199	1.895	2.551
dosecat 3 vs 1	3.704	2.714	5.055
AGE	0.964	0.959	0.970
REGION 1 vs 3	1.019	0.769	1.349
REGION 2 vs 3	0.947	0.788	1.138
REGION 4 vs 3	1.118	0.906	1.380
REGION 5 vs 3	0.965	0.454	2.052
unioncat 2 vs 1	0.652	0.542	0.785
unioncat 3 vs 1	0.749	0.606	0.926
insom1 1 vs 0	0.977	0.661	1.445
psychdiag1 1 vs 0	3.888	3.360	4.499
benzo_bl1 1 vs 0	2.126	1.812	2.495

Association of Predicted Probabilities and Observed Responses			
Percent Concordant	68.8	**Somers' D**	0.526
Percent Discordant	16.2	**Gamma**	0.619
Percent Tied	15.0	**Tau-a**	0.004
Pairs	186263868	**c**	0.763

A7.18. Abuse potential, adjusting for demographics, insomnia, psychiatric disorders and benzodiazepine prescription history

Model Fit Statistics		
Criterion	**Intercept Only**	**Intercept and Covariates**
AIC	10794.198	10067.465
SC	10804.545	10191.625
-2 Log L	10792.198	10043.465

Testing Global Null Hypothesis: BETA=0			
Test	**Chi-Square**	**DF**	**Pr > ChiSq**
Likelihood Ratio	748.7331	11	<.0001
Score	880.3529	11	<.0001
Wald	745.2508	11	<.0001

Type 3 Analysis of Effects			
Effect	**DF**	**Wald Chi-Square**	**Pr > ChiSq**
ab_pot1	1	0.1445	0.7038
AGE	1	161.5806	<.0001
REGION	4	3.5653	0.4680
unioncat	2	23.3112	<.0001
insom1	1	0.2327	0.6295
psychdiag1	1	357.1718	<.0001
benzo_bl1	1	104.9388	<.0001

Analysis of Maximum Likelihood Estimates						
Parameter		**DF**	**Estimate**	**Standard Error**	**Wald Chi-Square**	**Pr > ChiSq**
Intercept		1	-4.0554	0.3651	123.4150	<.0001
ab_pot1		1	0.0218	0.0573	0.1445	0.7038
AGE		1	-0.0366	0.00288	161.5806	<.0001
REGION	**1**	1	-0.0283	0.1317	0.0461	0.8299
REGION	**2**	1	-0.0816	0.1012	0.6499	0.4201
REGION	**4**	1	0.1434	0.1132	1.6028	0.2055
REGION	**5**	1	-0.0471	0.3065	0.0236	0.8780

Analysis of Maximum Likelihood Estimates						
Parameter		**DF**	**Estimate**	**Standard Error**	**Wald Chi-Square**	**Pr > ChiSq**
unioncat	**2**	1	-0.1962	0.0539	13.2506	0.0003
unioncat	**3**	1	-0.0609	0.0616	0.9757	0.3233
insom1	**1**	1	-0.0481	0.0997	0.2327	0.6295
psychdiag1	**1**	1	0.7025	0.0372	357.1718	<.0001
benzo_bl1	**1**	1	0.4160	0.0406	104.9388	<.0001

Odds Ratio Estimates			
Effect	**Point Estimate**	**95% Wald Confidence Limits**	
ab_pot1	1.022	0.913	1.143
AGE	0.964	0.959	0.969
REGION 1 vs 3	0.959	0.724	1.269
REGION 2 vs 3	0.909	0.757	1.093
REGION 4 vs 3	1.139	0.923	1.405
REGION 5 vs 3	0.941	0.443	2.000
unioncat 2 vs 1	0.635	0.528	0.765
unioncat 3 vs 1	0.728	0.589	0.899
insom1 1 vs 0	0.908	0.614	1.343
psychdiag1 1 vs 0	4.075	3.523	4.715
benzo_bl1 1 vs 0	2.298	1.960	2.694

Association of Predicted Probabilities and Observed Responses			
Percent Concordant	66.4	**Somers' D**	0.489
Percent Discordant	17.6	**Gamma**	0.582
Percent Tied	16.0	**Tau-a**	0.003
Pairs	186263868	**c**	0.744

A7.19. Psychotherapy, adjusting for demographics, insomnia, psychiatric disorders and benzodiazepine prescription history

Model Fit Statistics		
Criterion	**Intercept Only**	**Intercept and Covariates**
AIC	10794.198	10057.936
SC	10804.545	10182.097
-2 Log L	10792.198	10033.936

Testing Global Null Hypothesis: BETA=0			
Test	**Chi-Square**	**DF**	**Pr > ChiSq**
Likelihood Ratio	758.2615	11	<.0001
Score	906.9306	11	<.0001
Wald	760.7573	11	<.0001

Type 3 Analysis of Effects			
Effect	**DF**	**Wald Chi-Square**	**Pr > ChiSq**
psychotherapy1	1	9.2439	0.0024
AGE	1	163.4722	<.0001
REGION	4	3.7087	0.4469
unioncat	2	21.3190	<.0001
insom1	1	0.0680	0.7943
psychdiag1	1	110.7919	<.0001
benzo_bl1	1	103.4347	<.0001

Analysis of Maximum Likelihood Estimates						
Parameter		**DF**	**Estimate**	**Standard Error**	**Wald Chi-Square**	**Pr > ChiSq**
Intercept		1	-3.8048	0.1810	441.9703	<.0001
psychotherapy1	**1**	1	0.1646	0.0541	9.2439	0.0024
AGE		1	-0.0368	0.00288	163.4722	<.0001
REGION	**1**	1	-0.0376	0.1317	0.0816	0.7751
REGION	**2**	1	-0.0869	0.1013	0.7364	0.3908
REGION	**4**	1	0.1413	0.1132	1.5582	0.2119
REGION	**5**	1	-0.0349	0.3065	0.0130	0.9093
unioncat	**2**	1	-0.1873	0.0540	12.0419	0.0005
unioncat	**3**	1	-0.0597	0.0617	0.9343	0.3337

Analysis of Maximum Likelihood Estimates						
Parameter		**DF**	**Estimate**	**Standard Error**	**Wald Chi-Square**	**Pr > ChiSq**
insom1	**1**	1	0.0268	0.1027	0.0680	0.7943
psychdiag1	**1**	1	0.5831	0.0554	110.7919	<.0001
benzo_bl1	**1**	1	0.4127	0.0406	103.4347	<.0001

Odds Ratio Estimates			
Effect	**Point Estimate**	**95% Wald Confidence Limits**	
psychotherapy1 1 vs 0	1.390	1.124	1.718
AGE	0.964	0.958	0.969
REGION 1 vs 3	0.946	0.714	1.252
REGION 2 vs 3	0.900	0.749	1.082
REGION 4 vs 3	1.131	0.917	1.395
REGION 5 vs 3	0.948	0.446	2.015
unioncat 2 vs 1	0.648	0.538	0.780
unioncat 3 vs 1	0.736	0.596	0.909
insom1 1 vs 0	1.055	0.705	1.578
psychdiag1 1 vs 0	3.210	2.583	3.988
benzo_bl1 1 vs 0	2.283	1.947	2.677

Association of Predicted Probabilities and Observed Responses			
Percent Concordant	66.7	**Somers' D**	0.493
Percent Discordant	17.4	**Gamma**	0.586
Percent Tied	15.9	**Tau-a**	0.003
Pairs	186263868	**c**	0.747

A7.20. Opioid prescription, adjusting for demographics, insomnia, psychiatric disorders and benzodiazepine prescription history

Model Fit Statistics		
Criterion	**Intercept Only**	**Intercept and Covariates**
AIC	10794.198	9913.664
SC	10804.545	10037.825
-2 Log L	10792.198	9889.664

Testing Global Null Hypothesis: BETA=0			
Test	**Chi-Square**	**DF**	**Pr > ChiSq**
Likelihood Ratio	902.5336	11	<.0001
Score	1036.3809	11	<.0001
Wald	883.5737	11	<.0001

Type 3 Analysis of Effects			
Effect	**DF**	**Wald Chi-Square**	**Pr > ChiSq**
opioids1	1	150.7869	<.0001
AGE	1	176.4366	<.0001
REGION	4	2.8271	0.5872
unioncat	2	18.0296	0.0001
insom1	1	0.2972	0.5856
psychdiag1	1	360.6459	<.0001
benzo_bl1	1	75.9780	<.0001

Analysis of Maximum Likelihood Estimates						
Parameter		**DF**	**Estimate**	**Standard Error**	**Wald Chi-Square**	**Pr > ChiSq**
Intercept		1	-3.7655	0.1781	447.0792	<.0001
opioids1	**1**	1	0.4479	0.0365	150.7869	<.0001
AGE		1	-0.0391	0.00295	176.4366	<.0001
REGION	**1**	1	0.0580	0.1319	0.1930	0.6604
REGION	**2**	1	-0.0809	0.1015	0.6350	0.4255
REGION	**4**	1	0.0985	0.1134	0.7540	0.3852
REGION	**5**	1	-0.0392	0.3067	0.0164	0.8982
unioncat	**2**	1	-0.1846	0.0540	11.6689	0.0006

Analysis of Maximum Likelihood Estimates						
Parameter		**DF**	**Estimate**	**Standard Error**	**Wald Chi-Square**	**Pr > ChiSq**
unioncat	**3**	1	-0.0340	0.0619	0.3017	0.5828
insom1	**1**	1	-0.0544	0.0997	0.2972	0.5856
psychdiag1	**1**	1	0.7041	0.0371	360.6459	<.0001
benzo_bl1	**1**	1	0.3553	0.0408	75.9780	<.0001

Odds Ratio Estimates			
Effect	**Point Estimate**	**95% Wald Confidence Limits**	
opioids1 1 vs 0	2.449	2.123	2.826
AGE	0.962	0.956	0.967
REGION 1 vs 3	1.099	0.829	1.456
REGION 2 vs 3	0.956	0.795	1.150
REGION 4 vs 3	1.144	0.927	1.412
REGION 5 vs 3	0.997	0.469	2.120
unioncat 2 vs 1	0.668	0.555	0.805
unioncat 3 vs 1	0.777	0.628	0.961
insom1 1 vs 0	0.897	0.607	1.326
psychdiag1 1 vs 0	4.088	3.535	4.728
benzo_bl1 1 vs 0	2.035	1.735	2.388

Association of Predicted Probabilities and Observed Responses			
Percent Concordant	69.7	**Somers' D**	0.538
Percent Discordant	16.0	**Gamma**	0.627
Percent Tied	14.3	**Tau-a**	0.004
Pairs	186263868	**c**	0.769

A7.21. Sedative prescription, adjusting for demographics, insomnia, psychiatric disorders and benzodiazepine prescription history

Model Fit Statistics		
Criterion	**Intercept Only**	**Intercept and Covariates**
AIC	10794.198	10023.201
SC	10804.545	10147.361
-2 Log L	10792.198	9999.201

Testing Global Null Hypothesis: BETA=0			
Test	**Chi-Square**	**DF**	**Pr > ChiSq**
Likelihood Ratio	792.9969	11	<.0001
Score	940.3801	11	<.0001
Wald	797.6907	11	<.0001

Type 3 Analysis of Effects			
Effect	**DF**	**Wald Chi-Square**	**Pr > ChiSq**
sedatives1	1	48.2681	<.0001
AGE	1	168.8293	<.0001
REGION	4	3.2733	0.5132
unioncat	2	21.6388	<.0001
insom1	1	1.1612	0.2812
psychdiag1	1	321.6823	<.0001
benzo_bl1	1	97.3388	<.0001

Analysis of Maximum Likelihood Estimates						
Parameter		**DF**	**Estimate**	**Standard Error**	**Wald Chi-Square**	**Pr > ChiSq**
Intercept		1	-3.7776	0.1780	450.6103	<.0001
sedatives1	**1**	1	0.2823	0.0406	48.2681	<.0001
AGE		1	-0.0376	0.00289	168.8293	<.0001
REGION	**1**	1	-0.0155	0.1316	0.0138	0.9065
REGION	**2**	1	-0.0688	0.1013	0.4614	0.4970
REGION	**4**	1	0.1438	0.1130	1.6197	0.2031
REGION	**5**	1	-0.0536	0.3066	0.0306	0.8611
unioncat	**2**	1	-0.1917	0.0539	12.6550	0.0004

Analysis of Maximum Likelihood Estimates						
Parameter		**DF**	**Estimate**	**Standard Error**	**Wald Chi-Square**	**Pr > ChiSq**
unioncat	**3**	1	-0.0545	0.0615	0.7848	0.3757
insom1	**1**	1	-0.1078	0.1000	1.1612	0.2812
psychdiag1	**1**	1	0.6718	0.0375	321.6823	<.0001
benzo_bl1	**1**	1	0.4002	0.0406	97.3388	<.0001

Odds Ratio Estimates			
Effect	**Point Estimate**	**95% Wald Confidence Limits**	
sedatives1 1 vs 0	1.759	1.500	2.062
AGE	0.963	0.958	0.969
REGION 1 vs 3	0.990	0.748	1.311
REGION 2 vs 3	0.939	0.781	1.129
REGION 4 vs 3	1.161	0.942	1.432
REGION 5 vs 3	0.953	0.449	2.026
unioncat 2 vs 1	0.645	0.536	0.777
unioncat 3 vs 1	0.740	0.600	0.914
insom1 1 vs 0	0.806	0.545	1.193
psychdiag1 1 vs 0	3.833	3.309	4.439
benzo_bl1 1 vs 0	2.227	1.899	2.610

Association of Predicted Probabilities and Observed Responses			
Percent Concordant	67.2	**Somers' D**	0.500
Percent Discordant	17.2	**Gamma**	0.593
Percent Tied	15.7	**Tau-a**	0.004
Pairs	186263868	**c**	0.750

A7.22. Stimulant prescription, adjusting for demographics, insomnia, psychiatric disorders and benzodiazepine prescription history

Model Fit Statistics

Criterion	Intercept Only	Intercept and Covariates
AIC	10794.198	10065.132
SC	10804.545	10189.292
-2 Log L	10792.198	10041.132

Testing Global Null Hypothesis: BETA=0

Test	Chi-Square	DF	Pr > ChiSq
Likelihood Ratio	751.0661	11	<.0001
Score	886.2600	11	<.0001
Wald	749.4706	11	<.0001

Type 3 Analysis of Effects

Effect	DF	Wald Chi-Square	Pr > ChiSq
stimulants1	1	2.6472	0.1037
AGE	1	159.1212	<.0001
REGION	4	3.6206	0.4598
unioncat	2	22.8331	<.0001
insom1	1	0.2030	0.6523
psychdiag1	1	347.1632	<.0001
benzo_bl1	1	105.3111	<.0001

Analysis of Maximum Likelihood Estimates

Parameter		DF	Estimate	Standard Error	Wald Chi-Square	Pr > ChiSq
Intercept		1	-3.8295	0.1874	417.3872	<.0001
stimulants1	**1**	1	0.1223	0.0752	2.6472	0.1037
AGE		1	-0.0364	0.00288	159.1212	<.0001
REGION	**1**	1	-0.0264	0.1316	0.0404	0.8408
REGION	**2**	1	-0.0827	0.1013	0.6670	0.4141
REGION	**4**	1	0.1441	0.1131	1.6223	0.2028
REGION	**5**	1	-0.0455	0.3065	0.0220	0.8820
unioncat	**2**	1	-0.1943	0.0539	12.9984	0.0003
unioncat	**3**	1	-0.0602	0.0616	0.9555	0.3283

Analysis of Maximum Likelihood Estimates						
Parameter		**DF**	**Estimate**	**Standard Error**	**Wald Chi-Square**	**Pr > ChiSq**
insom1	**1**	1	-0.0449	0.0997	0.2030	0.6523
psychdiag1	**1**	1	0.6966	0.0374	347.1632	<.0001
benzo_bl1	**1**	1	0.4159	0.0405	105.3111	<.0001

Odds Ratio Estimates			
Effect	**Point Estimate**	**95% Wald Confidence Limits**	
stimulants1 1 vs 0	1.277	0.951	1.715
AGE	0.964	0.959	0.970
REGION 1 vs 3	0.964	0.728	1.276
REGION 2 vs 3	0.911	0.758	1.095
REGION 4 vs 3	1.143	0.926	1.410
REGION 5 vs 3	0.945	0.445	2.009
unioncat 2 vs 1	0.638	0.530	0.768
unioncat 3 vs 1	0.730	0.591	0.902
insom1 1 vs 0	0.914	0.618	1.351
psychdiag1 1 vs 0	4.028	3.479	4.664
benzo_bl1 1 vs 0	2.297	1.960	2.693

Association of Predicted Probabilities and Observed Responses			
Percent Concordant	66.4	**Somers' D**	0.489
Percent Discordant	17.5	**Gamma**	0.582
Percent Tied	16.1	**Tau-a**	0.003
Pairs	186263868	**c**	0.744

A7.23. Alcohol disorder, adjusting for demographics

Model Fit Statistics		
Criterion	**Intercept Only**	**Intercept and Covariates**
AIC	10794.198	10521.312
SC	10804.545	10614.432
-2 Log L	10792.198	10503.312

Testing Global Null Hypothesis: BETA=0			
Test	**Chi-Square**	**DF**	**Pr > ChiSq**
Likelihood Ratio	288.8859	8	<.0001
Score	530.1053	8	<.0001
Wald	396.6879	8	<.0001

Type 3 Analysis of Effects			
Effect	**DF**	**Wald Chi-Square**	**Pr > ChiSq**
aud1	1	207.1461	<.0001
AGE	1	165.6192	<.0001
REGION	4	2.6253	0.6223
unioncat	2	29.0497	<.0001

Analysis of Maximum Likelihood Estimates						
Parameter		**DF**	**Estimate**	**Standard Error**	**Wald Chi-Square**	**Pr > ChiSq**
Intercept		1	-2.9378	0.1602	336.3344	<.0001
aud1	**1**	1	1.1683	0.0812	207.1461	<.0001
AGE		1	-0.0341	0.00265	165.6192	<.0001
REGION	**1**	1	-0.00404	0.1314	0.0009	0.9755
REGION	**2**	1	-0.0498	0.1011	0.2433	0.6218
REGION	**4**	1	0.1373	0.1128	1.4832	0.2233
REGION	**5**	1	-0.0835	0.3062	0.0744	0.7851
unioncat	**2**	1	-0.2244	0.0539	17.3205	<.0001
unioncat	**3**	1	-0.0595	0.0613	0.9440	0.3313

Odds Ratio Estimates

Effect	Point Estimate	95% Wald Confidence Limits	
aud1 1 vs 0	10.345	7.526	14.221
AGE	0.966	0.961	0.972
REGION 1 vs 3	0.996	0.753	1.317
REGION 2 vs 3	0.951	0.792	1.143
REGION 4 vs 3	1.147	0.930	1.415
REGION 5 vs 3	0.920	0.433	1.953
unioncat 2 vs 1	0.602	0.500	0.724
unioncat 3 vs 1	0.709	0.575	0.875

Association of Predicted Probabilities and Observed Responses			
Percent Concordant	44.0	**Somers' D**	0.258
Percent Discordant	18.3	**Gamma**	0.413
Percent Tied	37.7	**Tau-a**	0.002
Pairs	186263868	**c**	0.629

A7.24. Drug disorder, adjusting for demographics and insomnia

Model Fit Statistics		
Criterion	**Intercept Only**	**Intercept and Covariates**
AIC	10794.198	10460.189
SC	10804.545	10563.656
-2 Log L	10792.198	10440.189

Testing Global Null Hypothesis: BETA=0			
Test	**Chi-Square**	**DF**	**Pr > ChiSq**
Likelihood Ratio	352.0087	9	<.0001
Score	586.8294	9	<.0001
Wald	474.9892	9	<.0001

Type 3 Analysis of Effects			
Effect	**DF**	**Wald Chi-Square**	**Pr > ChiSq**
dud1	1	259.2799	<.0001
AGE	1	155.2759	<.0001
REGION	4	2.8342	0.5859
unioncat	2	27.6460	<.0001
insom1	1	13.9437	0.0002

Analysis of Maximum Likelihood Estimates						
Parameter		**DF**	**Estimate**	**Standard Error**	**Wald Chi-Square**	**Pr > ChiSq**
Intercept		1	-2.9090	0.1735	281.0948	<.0001
dud1	**1**	1	0.9299	0.0578	259.2799	<.0001
AGE		1	-0.0332	0.00266	155.2759	<.0001
REGION	**1**	1	0.0187	0.1315	0.0202	0.8871
REGION	**2**	1	-0.0578	0.1013	0.3259	0.5681
REGION	**4**	1	0.1361	0.1130	1.4517	0.2283
REGION	**5**	1	-0.0908	0.3062	0.0879	0.7668
unioncat	**2**	1	-0.2094	0.0540	15.0311	0.0001
unioncat	**3**	1	-0.0752	0.0615	1.4963	0.2212
insom1	**1**	1	0.3684	0.0986	13.9437	0.0002

Odds Ratio Estimates

Effect	Point Estimate	95% Wald Confidence Limits	
dud1 1 vs 0	6.423	5.122	8.055
AGE	0.967	0.962	0.972
REGION 1 vs 3	1.025	0.775	1.356
REGION 2 vs 3	0.950	0.790	1.141
REGION 4 vs 3	1.153	0.935	1.422
REGION 5 vs 3	0.919	0.433	1.951
unioncat 2 vs 1	0.610	0.507	0.735
unioncat 3 vs 1	0.698	0.565	0.862
insom1 1 vs 0	2.089	1.419	3.075

Association of Predicted Probabilities and Observed Responses			
Percent Concordant	47.4	**Somers' D**	0.294
Percent Discordant	18.0	**Gamma**	0.450
Percent Tied	34.7	**Tau-a**	0.002
Pairs	186263868	**c**	0.647

A7.25. Anxiety disorder, adjusting for demographics and insomnia

Model Fit Statistics		
Criterion	**Intercept Only**	**Intercept and Covariates**
AIC	10794.198	10562.551
SC	10804.545	10666.018
-2 Log L	10792.198	10542.551

Testing Global Null Hypothesis: BETA=0			
Test	**Chi-Square**	**DF**	**Pr > ChiSq**
Likelihood Ratio	249.6472	9	<.0001
Score	299.7858	9	<.0001
Wald	286.9657	9	<.0001

Type 3 Analysis of Effects			
Effect	**DF**	**Wald Chi-Square**	**Pr > ChiSq**
anx1	1	78.5930	<.0001
AGE	1	147.2039	<.0001
REGION	4	2.8462	0.5839
unioncat	2	33.7111	<.0001
insom1	1	13.4395	0.0002

Analysis of Maximum Likelihood Estimates						
Parameter		**DF**	**Estimate**	**Standard Error**	**Wald Chi-Square**	**Pr > ChiSq**
Intercept		1	-3.4592	0.1696	416.1012	<.0001
anx1	**1**	1	0.4298	0.0485	78.5930	<.0001
AGE		1	-0.0324	0.00267	147.2039	<.0001
REGION	**1**	1	-0.0192	0.1314	0.0213	0.8841
REGION	**2**	1	-0.0404	0.1008	0.1606	0.6886
REGION	**4**	1	0.1494	0.1126	1.7616	0.1844
REGION	**5**	1	-0.0911	0.3060	0.0886	0.7660
unioncat	**2**	1	-0.2350	0.0537	19.1172	<.0001
unioncat	**3**	1	-0.0734	0.0611	1.4446	0.2294
insom1	**1**	1	0.3612	0.0985	13.4395	0.0002

Odds Ratio Estimates

Effect	Point Estimate	95% Wald Confidence Limits	
anx1 1 vs 0	2.362	1.954	2.857
AGE	0.968	0.963	0.973
REGION 1 vs 3	0.980	0.741	1.296
REGION 2 vs 3	0.959	0.799	1.152
REGION 4 vs 3	1.160	0.941	1.429
REGION 5 vs 3	0.912	0.430	1.935
unioncat 2 vs 1	0.581	0.483	0.699
unioncat 3 vs 1	0.683	0.554	0.842
insom1 1 vs 0	2.059	1.400	3.030

Association of Predicted Probabilities and Observed Responses			
Percent Concordant	47.1	**Somers' D**	0.273
Percent Discordant	19.9	**Gamma**	0.407
Percent Tied	33.0	**Tau-a**	0.002
Pairs	186263868	**c**	0.636

A7.26. Mood disorder, adjusting for demographics and insomnia

Model Fit Statistics		
Criterion	**Intercept Only**	**Intercept and Covariates**
AIC	10794.198	10224.395
SC	10804.545	10327.862
-2 Log L	10792.198	10204.395

Testing Global Null Hypothesis: BETA=0			
Test	**Chi-Square**	**DF**	**Pr > ChiSq**
Likelihood Ratio	587.8027	9	<.0001
Score	798.9578	9	<.0001
Wald	671.4523	9	<.0001

Type 3 Analysis of Effects			
Effect	**DF**	**Wald Chi-Square**	**Pr > ChiSq**
moo1	1	467.9825	<.0001
AGE	1	141.1469	<.0001
REGION	4	3.3866	0.4953
unioncat	2	24.9089	<.0001
insom1	1	10.0956	0.0015

Analysis of Maximum Likelihood Estimates						
Parameter		**DF**	**Estimate**	**Standard Error**	**Wald Chi-Square**	**Pr > ChiSq**
Intercept		1	-3.4642	0.1706	412.1491	<.0001
moo1	**1**	1	0.7751	0.0358	467.9825	<.0001
AGE		1	-0.0325	0.00273	141.1469	<.0001
REGION	**1**	1	-0.00750	0.1316	0.0033	0.9545
REGION	**2**	1	-0.0793	0.1014	0.6119	0.4341
REGION	**4**	1	0.1396	0.1132	1.5212	0.2174
REGION	**5**	1	-0.0739	0.3064	0.0581	0.8095
unioncat	**2**	1	-0.1943	0.0540	12.9571	0.0003
unioncat	**3**	1	-0.0782	0.0617	1.6023	0.2056
insom1	**1**	1	0.3139	0.0988	10.0956	0.0015

Odds Ratio Estimates			
Effect	**Point Estimate**	**95% Wald Confidence Limits**	
moo1 1 vs 0	4.713	4.095	5.423
AGE	0.968	0.963	0.973
REGION 1 vs 3	0.972	0.734	1.286
REGION 2 vs 3	0.904	0.752	1.087
REGION 4 vs 3	1.126	0.913	1.389
REGION 5 vs 3	0.909	0.428	1.931
unioncat 2 vs 1	0.627	0.521	0.755
unioncat 3 vs 1	0.704	0.570	0.870
insom1 1 vs 0	1.874	1.272	2.760

Association of Predicted Probabilities and Observed Responses			
Percent Concordant	60.8	**Somers' D**	0.426
Percent Discordant	18.2	**Gamma**	0.539
Percent Tied	21.0	**Tau-a**	0.003
Pairs	186263868	**c**	0.713

A7.27. Alcohol, Drug, Mood and anxiety disorders in one model also adjusting for demographics and insomnia

Model Fit Statistics		
Criterion	**Intercept Only**	**Intercept and Covariates**
AIC	10794.198	10045.283
SC	10804.545	10179.790
-2 Log L	10792.198	10019.283

Testing Global Null Hypothesis: BETA=0			
Test	**Chi-Square**	**DF**	**Pr > ChiSq**
Likelihood Ratio	772.9148	12	<.0001
Score	1361.5279	12	<.0001
Wald	1012.3694	12	<.0001

Type 3 Analysis of Effects			
Effect	**DF**	**Wald Chi-Square**	**Pr > ChiSq**
aud1	1	48.8795	<.0001
dud1	1	83.9023	<.0001
anx1	1	34.6796	<.0001
moo1	1	354.5113	<.0001
AGE	1	126.3104	<.0001
REGION	4	3.3860	0.4954
unioncat	2	20.8662	<.0001
insom1	1	7.9063	0.0049

Analysis of Maximum Likelihood Estimates						
Parameter		**DF**	**Estimate**	**Standard Error**	**Wald Chi-Square**	**Pr > ChiSq**
Intercept		1	-2.1951	0.1905	132.7888	<.0001
aud1	**1**	1	0.6424	0.0919	48.8795	<.0001
dud1	**1**	1	0.5998	0.0655	83.9023	<.0001
anx1	**1**	1	0.2909	0.0494	34.6796	<.0001
moo1	**1**	1	0.6952	0.0369	354.5113	<.0001
AGE		1	-0.0312	0.00278	126.3104	<.0001

Analysis of Maximum Likelihood Estimates						
Parameter		**DF**	**Estimate**	**Standard Error**	**Wald Chi-Square**	**Pr > ChiSq**
REGION	**1**	1	-0.00717	0.1318	0.0030	0.9566
REGION	**2**	1	-0.0970	0.1018	0.9091	0.3404
REGION	**4**	1	0.1116	0.1139	0.9608	0.3270
REGION	**5**	1	-0.0470	0.3066	0.0235	0.8782
unioncat	**2**	1	-0.1703	0.0543	9.8340	0.0017
unioncat	**3**	1	-0.0858	0.0624	1.8919	0.1690
insom1	**1**	1	0.2793	0.0993	7.9063	0.0049

Odds Ratio Estimates			
Effect	**Point Estimate**	**95% Wald Confidence Limits**	
aud1 1 vs 0	3.614	2.521	5.181
dud1 1 vs 0	3.319	2.567	4.290
anx1 1 vs 0	1.789	1.474	2.171
moo1 1 vs 0	4.016	3.475	4.642
AGE	0.969	0.964	0.975
REGION 1 vs 3	0.954	0.721	1.264
REGION 2 vs 3	0.872	0.725	1.050
REGION 4 vs 3	1.075	0.870	1.328
REGION 5 vs 3	0.917	0.432	1.948
unioncat 2 vs 1	0.653	0.541	0.787
unioncat 3 vs 1	0.710	0.573	0.880
insom1 1 vs 0	1.748	1.184	2.580

Association of Predicted Probabilities and Observed Responses			
Percent Concordant	65.2	**Somers' D**	0.484
Percent Discordant	16.8	**Gamma**	0.590
Percent Tied	18.0	**Tau-a**	0.003
Pairs	186263868	**c**	0.742

A7.28. Alcohol, Drug, Mood and anxiety disorders in one model also adjusting for demographics, insomnia and benzodiazepine prescription history

Model Fit Statistics		
Criterion	**Intercept Only**	**Intercept and Covariates**
AIC	10794.198	9925.647
SC	10804.545	10070.501
-2 Log L	10792.198	9897.647

Testing Global Null Hypothesis: BETA=0			
Test	**Chi-Square**	**DF**	**Pr > ChiSq**
Likelihood Ratio	894.5506	13	<.0001
Score	1468.6975	13	<.0001
Wald	1102.7918	13	<.0001

Type 3 Analysis of Effects			
Effect	**DF**	**Wald Chi-Square**	**Pr > ChiSq**
aud1	1	51.7659	<.0001
dud1	1	81.8131	<.0001
anx1	1	22.0790	<.0001
moo1	1	289.1679	<.0001
AGE	1	181.7306	<.0001
REGION	4	3.3811	0.4962
unioncat	2	18.7347	<.0001
insom1	1	6.2847	0.0122
benzo_bl1	1	112.0715	<.0001

Analysis of Maximum Likelihood Estimates						
Parameter		**DF**	**Estimate**	**Standard Error**	**Wald Chi-Square**	**Pr > ChiSq**
Intercept		1	-2.0014	0.1914	109.3067	<.0001
aud1	**1**	1	0.6627	0.0921	51.7659	<.0001
dud1	**1**	1	0.5926	0.0655	81.8131	<.0001
anx1	**1**	1	0.2332	0.0496	22.0790	<.0001
moo1	**1**	1	0.6325	0.0372	289.1679	<.0001
AGE		1	-0.0392	0.00291	181.7306	<.0001
REGION	**1**	1	0.00948	0.1318	0.0052	0.9427

Analysis of Maximum Likelihood Estimates						
Parameter		**DF**	**Estimate**	**Standard Error**	**Wald Chi-Square**	**Pr > ChiSq**
REGION	**2**	1	-0.1011	0.1018	0.9871	0.3204
REGION	**4**	1	0.1181	0.1139	1.0743	0.3000
REGION	**5**	1	-0.0339	0.3067	0.0122	0.9121
unioncat	**2**	1	-0.1667	0.0544	9.4020	0.0022
unioncat	**3**	1	-0.0732	0.0624	1.3759	0.2408
insom1	**1**	1	0.2494	0.0995	6.2847	0.0122
benzo_bl1	**1**	1	0.4301	0.0406	112.0715	<.0001

Odds Ratio Estimates			
Effect	**Point Estimate**	**95% Wald Confidence Limits**	
aud1 1 vs 0	3.764	2.623	5.400
dud1 1 vs 0	3.271	2.530	4.229
anx1 1 vs 0	1.594	1.312	1.937
moo1 1 vs 0	3.543	3.063	4.099
AGE	0.962	0.956	0.967
REGION 1 vs 3	1.002	0.757	1.327
REGION 2 vs 3	0.897	0.745	1.080
REGION 4 vs 3	1.117	0.904	1.381
REGION 5 vs 3	0.960	0.451	2.039
unioncat 2 vs 1	0.666	0.552	0.803
unioncat 3 vs 1	0.731	0.590	0.906
insom1 1 vs 0	1.647	1.115	2.432
benzo_bl1 1 vs 0	2.364	2.016	2.772

Association of Predicted Probabilities and Observed Responses			
Percent Concordant	67.6	**Somers' D**	0.516
Percent Discordant	15.9	**Gamma**	0.618
Percent Tied	16.5	**Tau-a**	0.004
Pairs	186263868	**c**	0.758