BENZODIAZEPINES, HEALTH SERVICES UTILIZATION, AND SUICIDE IN VETERANS WITH POSTTRAUMATIC STRESS DISORDER

by

Rishiraj Deka

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STATEMENT OF DISSERTATION APPROVAL

The dissertation of **Rishiraj Deka**

has been approved by the following supervisory committee members:

Vanessa Stevens	Co-Chair	**08/23/2017** Date Approved
Joanne Francoise LaFleur	Co-Chair	**08/18/2017** Date Approved
Craig Bryan	Member	**08/18/2017** Date Approved
Gary Oderda	Member	**08/23/2017** Date Approved
Abril S. Atherton	Member	**08/23/2017** Date Approved

and by **Daniel M. Witt**, Chair/Dean of the

Department/College/School of **Pharmacotherapy**

and by David B. Kieda, Dean of The Graduate School.

ABSTRACT

Posttraumatic stress disorder (PTSD) is a trauma and stressor-related disorder that occurs after exposure to a traumatic event. Veterans are at the greatest risk of developing PTSD. Although benzodiazepines are not recommended for the treatment of PTSD, they are still commonly prescribed to veterans.

The overall distribution of therapies in the 1,134,201 cohort with PTSD is similar to that outlined in the 2010 Veterans Affairs Posttraumatic Stress Disorder Clinical Practice Guidelines. However, after the first-line psychotherapies and selective serotonin reuptake inhibitors (SSRIs), the not recommended benzodiazepines (7.07%) and atypical antipsychotics (7.53%) have the highest prevalence. The third most frequent overlapping therapy includes benzodiazepines in conjunction with SSRIs, although this percentage is only 0.49.

In order to evaluate the association between benzodiazepines and health outcomes, 1:2 propensity score (PS) matching was employed to create a balanced cohort. Plots of standardized differences and distributions of propensity scores indicated that 1:2 PS matching eliminated observable differences (in confounders and risk factors) between benzodiazepines users and nonusers. The final cohort included a total of 81,831 benzodiazepine users and 161,662 nonusers for a total size of 242,493 veterans with PTSD.

Generalized linear models and Cox proportional hazards models were used to

assess health outcomes. Other than substance abuse outpatient visits (which was higher but statistically insignificant), benzodiazepine users had significantly higher incidence rate ratios for all health care visits. This includes hospitalizations (1.27), ED (1.16), general outpatient (1.18), total mental outpatient (1.37), and mental outpatient visits (1.48). With an outcome of suicide as cause of death, the statistically significant hazard ratio between benzodiazepine users and nonusers is 2.73, thus demonstrating significant elevation in the risk of suicide.

The overall evidence from this study reveals that benzodiazepines are not uncommonly prescribed for patients with PTSD and that they are associated with greater health care utilization and suicide outcomes. Most importantly, this study strengthens the evidence against the use of benzodiazepines in veterans with PTSD and that clinicians should consider the benefits and risks – especially the almost three-fold increase in suicide death – when ultimately prescribing this pharmacotherapy.

This dissertation is dedicated to all those who have supported me in my life story so far.

CONTENTS

LIST OF TABLES

Tables

LIST OF FIGURES

Figures

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CHAPTER I

INTRODUCTION

PTSD

Posttraumatic stress disorder (PTSD) was officially established as an anxiety disorder in 1980.[1] Since that time, PTSD has been reclassified as a trauma and stressor-related disorder after exposure to a traumatic event that includes a disturbance duration of at least one month and clinically significant distress or impairment in occupational, social, or other critical areas of functioning.[1] In 2013, PTSD diagnostic criteria were further revised in the DSM-5.[2] Overall, in order to be currently diagnosed with PTSD, an individual must be exposed to a traumatic event that results in a cluster of symptoms, have negative self-worth, and serious impairment in occupational, social, or other areas of functioning that stems from the traumatic experience. (Appendix A)

The criterion of postexposure fear, helplessness, or horror is no longer included because it has been shown that the absence or prevalence of these emotions had no effect on PTSD prevalence.[2] Furthermore, PTSD is no longer classified as an anxiety disorder but rather as a trauma and stressor-related disorder.[2] A traumatic event is defined as exposure to actual or threatened death, serious injury, or sexual violence in at least one of the four following ways[2]:

1. Directly experiencing the traumatic event.
2. Witnessing the event in person as it occurred to others.
3. Learning that the traumatic event occurred to a close family member or close friend.
4. Experiencing repeated or extreme exposure to aversive details of the traumatic event.

The second criterion concerns the presence of one of the following intrusion symptoms after the traumatic event[2]:

1. Recurrent, involuntary, and intrusive distressing memories of the traumatic event.
2. Recurrent distressing dreams in which the content of the dream are related to the traumatic event.
3. Dissociative reactions such as flashbacks in which the individual feels or acts as if the traumatic event is recurring.
4. Intense or prolonged psychological distress at exposure to cues that resemble or symbolize an aspect of the traumatic event.
5. Marked physiological reactions to cues that resemble or symbolize an aspect of the traumatic event.

The third criterion concerns the avoidance of stimuli associated with the traumatic event after the event occurs and includes at least one of the following[2]:

1. Avoidance of or efforts to avoid distressing memories, thoughts, or feelings about or closely associated with the traumatic event.
2. Avoidance of or efforts to avoid external reminders that evoke distressing

memories, thoughts, or feelings about or closely associated with the traumatic event. These external reminders can include people, places, conversations, activities, objects, and situations.

The fourth criterion concerns negative alterations in cognition and mood associated with the traumatic event after the event occurs and includes at least two of the following[2]:

1. Inability to remember an important aspect of the traumatic event.
2. Persistent negative beliefs and expectations about oneself, others, or the world.
3. Persistent, distorted cognitions about the cause or results of the traumatic event that lead the individual to blame himself/herself or others.
4. Persistent negative emotional state. This includes fear, horror, guilt, shame, or anger.
5. Distinctly diminished interest or participation in significant activities.
6. Feelings of estrangement or detachment from others.
7. Persistent inability to experience positive emotions. This includes satisfaction, happiness, or loving feelings.

The fifth criterion concerns alterations in arousal and reactivity associated with the traumatic event after the event occurs and includes at least two of the following[2]:

1. Angry outbursts and irritable behavior with little or no provocation.
2. Self-destructive or reckless behavior.
3. Hypervigilance.
4. Exaggerated startle response.
5. Problems with concentration.
6. Sleep disturbance that includes difficulty falling asleep, staying asleep, or

restless sleep.

The sixth criterion is a disturbance duration longer than one month.[2] The seventh is that the disturbance causes clinically significant distress or impairment in occupational, social, or other important areas of functioning.[2] The final criterion is that the disturbance must not be attributable to the physiological effects of a substance or another medical condition.[2]

Risk Factors

Risk factors for PTSD include psychosocial, genetic, and biological components.[1] There are a variety of psychosocial risk factors in the general population; there is evidence that female gender, younger age at the time of trauma exposure, minority racial/ethnic status, lower socioeconomic status, lower education, and lower intelligence all serve as risk factors for PTSD.[2,3,4] Crime, rape, combat, childhood abuse/neglect, sexual molestation, and physical assault are associated with a high probability of lifetime PTSD.[5] Approximately 30% of PTSD cases among men are attributable to combat while almost half of all cases among women are attributable to sexual violence.[5] Sudden unexpected death accounts for approximately 30% of all cases of PTSD.[5]

A meta-analysis examined psychosocial risk factors in the military population.[6] Gender, race, and education are pretrauma sociodemographic factors were all found to be associated with PTSD in military personnel and veterans.[7] Females, non-white military persons, and service members with lower levels of education are more likely to develop PTSD.[7] Military rank, branch of service, occupation, cumulative length of deployments, and number of deployments are important military characteristics that contribute the development of PTSD among combat soldiers who returned from Vietnam, the Persian

Gulf, Iraq, and Afghanistan.[8] Nonofficers, army service, combat specialization, high numbers of deployments, and longer cumulative length of deployment are associated with PTSD.[8] More adverse life events, prior trauma exposure, and prior psychological problems are also pretrauma factors that increased risk for PTSD in the military population.[9] A number of variables in the trauma period also increased the risk for PTSD. These include increased combat exposure, discharging a weapon, witnessing someone being wounded or killed, severe trauma, and deployment-related stressors.[10] Deployment related stressors include excessive heat or cold, concerns or problems with family members back home, problems with leadership, lack of privacy, and boredom.[10] Finally, with respect to post-trauma, a lack of postdeployment social support and unemployment increased the risk for PTSD among veterans who served in Iraq and Afghanistan from 2002-2007.[10]

Risk factors for PTSD also include genetic components. Family studies have shown that offspring of parents with PTSD are more likely to develop PTSD themselves when compared to offspring of parents without PTSD.[11,12,13] Twin studies of PTSD have shown that exposure to traumatic events is influenced by genetic factors; these studies have also shown that PTSD is inheritable.[14,15] In addition, both twin and family studies suggest that genetic influences on PTSD overlap with other mental disorders.[11,12,13,14,15] The majority of genes that affect risk for PTSD also influence risk for other psychiatric disorders and vice versa. For example, genetic influences common to panic disorder and generalized anxiety disorder symptoms account for about 60% of the genetic variance in PTSD.[1] No robust genetic predictors of PTSD have been identified using genetic association studies.[16,17,18] Serotonin transporter polymorphism, 5-HTTLPR, is one genetic variant that has been examined in multiple studies, but with conflicting results.[16,17,18]

Finally, there are a number of potential biological risk factors for PTSD.[19] These include increased amygdala sensitivity, volume loss in the anterior cingulate cortex, and low levels of cortisol.[19] However, whether these brain abnormalities are risk factors for PTSD or markers of the disorder is still uncertain.[19] The amygdala mediates both stress response and emotional learning. Studies show patients with PTSD have increased amygdala responses to stressful scripts, trauma reminders, and general emotional stimuli that are not trauma-related.[19] The amygdala is also sensitized to the presentation of subliminally threatening cues in patients with PTSD. A second potential biological risk factor involves the medial prefrontal cortex (PFC).[19] The medial PFC consists of the anterior cingulate cortex (ACC), subcallosal cortex, and the medial frontal gyrus.[19] Through its connection with the amygdala, the medial PFC mediates stress response, emotional reactivity, and extinction of conditioned fear.[19] Patients with PTSD exhibit decreased volumes of the frontal cortex, including reduced ACC volumes, which are a measure of brain size.[19] This reduction in volume has been associated with PTSD symptom severity.[19] Extinction of conditioned fear is also associated with reduced ACC volumes, which provides a biological correlate for imprinted traumatic memories in PTSD.[19] Finally, both civilian and combat-related PTSD are associated with low levels of cortisol, a glucocorticoid secreted by the hypothalamic-pituitary-adrenal HPA axis. This stems from abnormal regulation of the HPA axis. In turn, low levels of cortisol lead to abnormal stress reactivity and fear processing in general.[19] While it is well documented that individuals with PTSD have altered cortisol levels, the direction of impairment, high or low, remains inconclusive.[19]

Pathophysiology

The noradrenergic, serotonergic, endogenous cannabinoid, opioid systems, and hypothalamic-pituitary adrenal axis all play a role in the development of PTSD.[13,14] Alterations in noradrenergic receptor activity, serotonergic receptor density, and endocannabinoid (eCB) receptors are linked to specific PTSD symptoms.[6,20] Dynorphin opioid receptor signaling in response to stress can lead to anxious behaviors such as PTSD.[19] Finally, increased levels of stress result in increased levels of corticotropin-releasing factor and abnormalities of the hypothalamic-pituitary adrenal axis, both of which are present in PTSD patients.[20]

The noradrenergic system consists of adrenoreceptors (AR), a group of G protein-coupled receptors with alpha 1, alpha 2, and beta subtypes. The AR system stimulates central nervous system activity and sympathetic autonomic responses. The AR system plays a role in PTSD because it influences amygdala functioning and associated fear signaling.[20] Increased noradrenaline activity leads to impaired medial prefrontal cortex functioning and fear extinction.[20] This explains subsequent increases in anxiety and PTSD symptom severity. A potential noradrenaline target is the noradrenaline transporter (NET).[20] The NET is also part of the noradrenergic system.[20] The NET acts as a noradrenaline plasma membrane monoamine transporter, maintains presynaptic noradrenaline storage, and regulates dopamine uptake. As shown in Figure 1, the NET has high concentrations in the frontal cortex, hippocampus, amygdala, thalamus, and cerebellar cortex.[20] There is decreased NET availability in patients with PTSD.[6]

Serotonergic (5-HT) receptors are another neurobiological system involved in the pathophysiology of PTSD.[19] The serotonergic (5-HT) receptors are a group of G protein-

coupled receptors involved in cognition, emotional processing, and behavioral regulation.[20] Fear regulation and threat responsiveness have been linked to 5-HT signaling in the amygdala.[21] 5-HT receptors can selectively induce anxiety attacks and trauma-related flashbacks in individuals with PTSD. The 5-HT 1A and 5-HT 1B receptors have been specifically identified in the study of stress disorders.[21] 5-HT 1A receptors have the highest density in the raphe nuclei, hippocampal formation, hypothalamus, and insula, temporal, cingulate, and ventral prefrontal cortices (Figure 1). Neuropathological abnormalities exhibited in limbic and paralimbic cortical areas, such as reduced cortex volume, reduced synaptic proteins, may be attributed to impaired 5-HT 1A receptor functioning; this impairment induces increased anxiety and fear responses. The 5-HT 1B receptors have the highest density in striatum, pallidum, nucleus acumbens, substantia nigra, and the ventral tegmental area (Figure 1). Alterations in 5-HT 1B receptor density have been shown to be linked to specific PTSD symptoms such as increased re-experiencing, numbing, and anxious arousal symptoms.[20] The eCB, through the cannabinoid receptors CB 1 and CB 2, play an integral role in the development and function of the PTSD circuit, particularly in stress response.[20] The CB 1 receptors play a specific and primary role in the behavioral consequences of stress exposure.[6] CB 1 are found in high density throughout the forebrain limbic structures and modulate a plethora of behaviors, including mood, anxiety, stress, memory, learning, and extinction of fear. Alteration or disruption of CB 1 signaling results in heightened anxiety and depression.[20]

The opioid system is also implicated in the development of PTSD.[20] Opioid receptors are G protein-coupled receptors and are classified into the encephalin, dynorphin, and morphine subtypes. The dynorphin opioid receptors mediate anxiety and have high

density levels in a ventral medial, prefrontal, cortex-hippocampal-limbic circuit. Dynorphin opioid receptor signaling in response to stress can lead to persistent depressive and anxious behaviors, important components of PTSD.[1]

The HPA axis is a neurocircuit involved with stress response. The HPA axis ties the central nervous system to the endocrine system and aids with adaptation to stress, maintenance of homeostasis, and baseline functioning.[20] Corticotropin-releasing factor (CRF) is a neuronal signaling molecule produced by cells in the hypothalamus in response to stress. CRF receptors consist of the CRF-1 and CRF-2 subtypes. Increased levels of CRF activate the HPA axis and lead to increased levels of cortisol. These high levels of cortisol facilitate encoding of traumatic memory and enduring anxiety effects through these CRF receptors. PTSD patients exhibit higher cerebrospinal fluid levels of CRF along with abnormalities in the HPA axis system such as a dysregulation of the pituitary adenylate cyclase-activating peptide that broadly regulates stress response.[20]

Epidemiology

Estimates of the lifetime prevalence of PTSD have been consistent since the advent of the Diagnostic and Statistical Manual of Mental Disorders-III-R (PTSD diagnosis in 1987).[1] In the United States, several studies have yielded a lifetime DSM-III-R prevalence ranging from approximately 8.0% to 12.0%.[22,23,24] Prevalence differs by gender as well. For men, DSM-III-R prevalence ranged from 5.0% to 6.0% while for women this prevalence ranged from 10.0% to 11.0%.[22,23,24] The most recent data in the United States are from the National Comorbidity Replication Survey (NCS-R), which was conducted on over 9200 adults between February 2001 and April 2003. The lifetime

prevalence of DSM-IV PTSD among adult Americans is 6.8%.[24] The lifetime prevalence of PTSD among adult men is 3.6% and among adult women is 9.7%.[24] In a recent survey of 27 countries, the highest lifetime prevalence of PTSD outside the United States was in Ukraine (4.8%) and New Zealand (6.1%).[1] Furthermore, high rates of lifetime PTSD have been found in many postconflict settings. This includes PTSD rates of 16% in Ethiopia, 18% in Gaza, 28% in Cambodia, and 37% in Algeria.[1] Among Operation Enduring Freedom/Operation Iraqi Freedom veterans, those with PTSD were three times more likely to report hopelessness or suicidal ideation than those without PTSD.[25] Expressions of hopelessness and thoughts of committing suicide are often used as behavioral markers for increased suicide risk.[26]

Chronic PTSD is an episode of PTSD that lasts one year or longer and is not currently recognized as a distinct clinical diagnosis in the DSM-V.[1] PTSD fails to remit even after many years for more than one-third of individuals who develop it.[22] The Detroit Area Survey of Trauma in young adults showed that after trauma exposure, 22% of women developed chronic PTSD compared to 6% of men.[27] Past-year prevalence is prevalence of PTSD within the past 12 months.[1] In 2005, the past-year prevalence of DSM-IV PTSD was 3.5% in the United States, higher than in any other country.[22] Past-year prevalence estimates were less than 1% in many other countries, including Mexico, Nigeria, Germany, Italy, Spain, Israel, China, and Japan.[1] Twelve month prevalence rates have also been shown to decline with age, ranging from 4.7% in those aged 55-64 to 0.6% in those aged 65-74 to 0.1% in those aged 75-84.[1]

The conditional risk of PTSD is defined as the probability of developing PTSD given exposure to a traumatic event.[1] In the NCS-R, 20% of exposed women and 8% of

exposed men developed DSM-IV PTSD.[24] In a DSM-V field trial, the conditional risk of PTSD ranged from 10.3% to 11.7%.[28] Conditional risk for PTSD may decline with age. For childhood events, lifetime conditional rates are approximately 35% for women and 10% for men.[28] For adulthood events, conditional rates are approximately 25% for women and 15% for men.[28]

The prevalence of PTSD is much higher in veterans compared to other subpopulations.[1] This is because veterans are at an elevated risk for exposure to trauma.[1] The 2001 Veterans Affairs (VA) National Survey of Veterans was a nationally representative survey of over 20,000 veterans enrolled in Veterans Health Administration (VHA) system.[29] Across wars and eras, 39% of VHA users (41% of men and 12% of women) reported exposure to combat and 36% reported exposure to the dead, dying, or wounded.[29] During the wars in Afghanistan and Iraq, with a prevalence of 50% among VHA users, the most frequent type of exposure was having a friend wounded or killed, with 50% of VHA users experiencing that.[29] Other types of exposure included seeing dead or seriously injured noncombatants (45%), witnessing an accident resulting in serious injury or death (45%), smelling decomposing bodies (37%), being physically moved or knocked over by an explosion (23%), having a blow to the head (18%), engaging in hand-to-hand combat (10%), and being responsible for the death of a civilian (5%).[29]

One study investigated the prevalence of PTSD in a sample of Army service members three to fourth months postdeployment; approximately 12% of those returning from Afghanistan and 18% of those returning from Iraq met the criteria for PTSD using the VA PTSD Checklist (PCL).[30] The PCL is a self-report measure that assesses the

symptoms of PTSD.[30] It is one of the most commonly-used self-report measures of PTSD but is not consistently used throughout the VA.[31] There are two versions of the PCL; the PCL-M is specific to PTSD caused by military experiences and the PCL-C is applied generally to any traumatic event.[31] The PCL consists of 17 items that correspond to DSM-IV PTSD symptoms. Respondents are asked to rate the degree [(1 (not at all) to 5 (extremely)] to which they were bothered by symptoms in the past month.[31] The PCL is both valid and reliable.[31] Another study found that 5% of Army and Marine service members returning from Iraq and 10% of Army and Marine service members returning from Afghanistan screened positive for PTSD 2 weeks after deployment.[30] The Primary Care PTSD Screen (PC-PTSD), a four-item screen, was used to identify veterans with PTSD.[30] The PC-PTSD consists of four yes/no questions on nightmare, avoidance, hyperarousal, and numbing symptoms. The results of the PC-PTSD are considered positive if a patient answers yes to any three items.[30] In a RAND survey of almost 2000 individuals who served in Afghanistan and Iraq, approximately 14% of all veterans met criteria for PTSD in the past 30 days using the PCL Checklist.[32] Finally, in a VA national sample of over 100,000 veterans who served in Afghanistan and Iraq, approximately 13% of veterans were diagnosed with PTSD.[33] PTSD was diagnosed using ICD-9 codes, and the majority of mental health diagnoses (60%) occurred in nonmental health settings, particularly in primary care (42%).[33] Finally, as will be described in further detail, pharmacotherapies for PTSD can be seen in Table 1.

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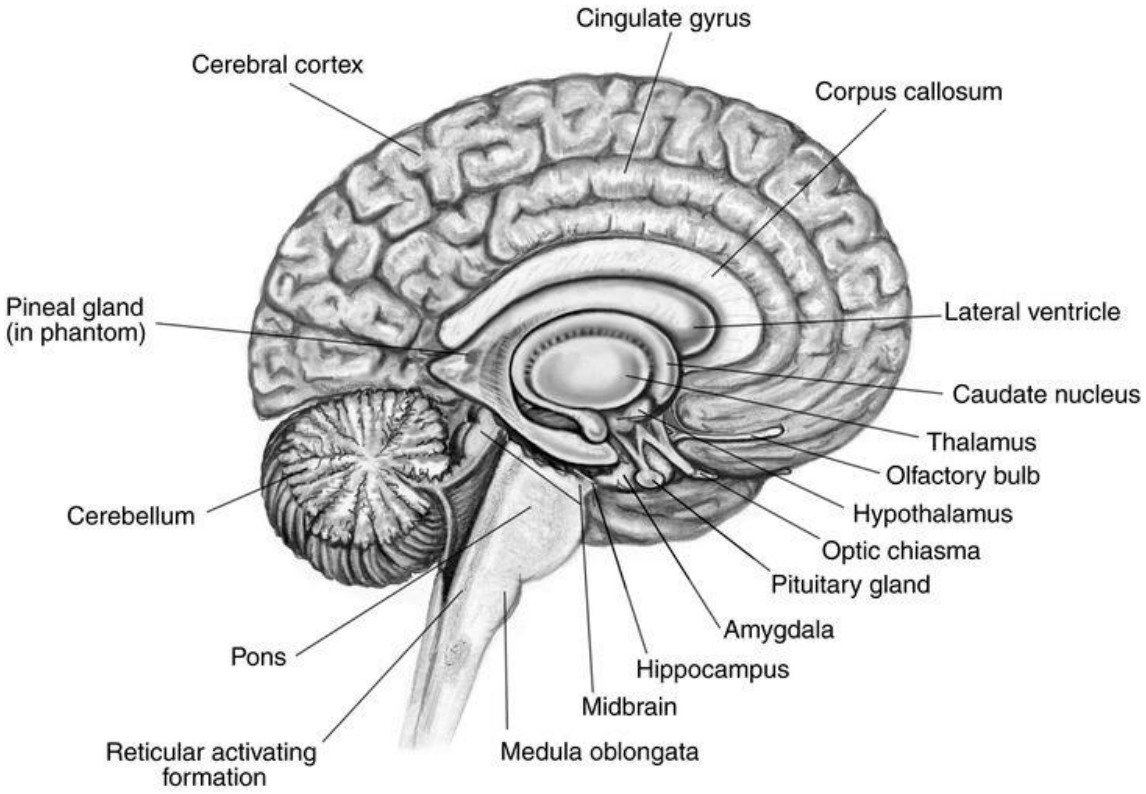

Figure 1. The Human Brain

Table 1. Pharmacotherapies Used for Treatment of PTSD[1,21,36]

Class	Generic	Recommendation
SSRIs	Sertraline Paroxetine Fluoxetine Citalopram Fluvoxamine	Recommended
SNRI	Venlafaxine	Recommended
Antiadrenergic Agent	Prazosin	Recommended
Tetracyclic Antidepressant	Mirtazapine	Recommended
Serotonergic Antidepressant	Nefazodone	Recommended
Tricyclic Antidepressant	Imipramine Amitriptyline	Recommended
Benzodiazepines	Lorazepam Clonazepam Alprazolam Diazepam Temazepam Chlordiazepoxide HCL	Not Recommended
Opioids	Acetaminophen Buprenorphine Codeine Fentanyl Hydrocodone Hydromorphone Methadone Morphine Oxycodone Suboxone	Not Recommended (but not contraindicated for patients with chronic pain)
Atypical Antipsychotics	Risperidone Olanzapine Quetiapine	Not Recommended
Conventional Antipsychotics	Thioridazine Chlorpromazine Haloperidol	Not Recommended

CHAPTER II

TREATMENTS AND OBJECTIVES

Psychotherapies

Cognitive behavioral therapy (CBT) is the most effective treatment for PTSD.[34] CBT involves talking with a therapist once a week, typically for up to four months.[34] The two different types of CBT that are recommended for the treatment of PTSD include cognitive processing therapy (CPT) and prolonged exposure (PE).[34] CPT focuses on examining distressing thoughts and memories of a traumatic event.[34] CPT allows individuals to develop skills to handle these distressing thoughts.[34] Through examining, challenging, and changing thoughts, individuals can change the way they feel about the traumatic event.[34] CPT has four components:[35]

1. Learning about PTSD symptoms and how treatment can be of assistance.
2. Becoming aware of thoughts and feelings.
3. Cognitive restructuring that involves learning skills to challenge an individual's thoughts and feelings.
4. Understanding common changes in beliefs that occur after going through a traumatic event.

CPT is widely supported in treatment guidelines.[12,15-17, 36-37] In a randomized controlled a trial of veterans with chronic military-related PTSD, veterans who received CPT showed

better improvements in PTSD and comorbid symptoms than the waitlist control group.[19] Another randomized controlled trial showed that active duty military personnel treated with CPT experienced a greater reduction in PTSD symptom severity compared to those who used group present-centered therapy; only veterans treated with CPT experienced a reduction in depression.[36] Furthermore, a second randomized controlled trial conducted in active-duty service members showed that veterans treated with either individual or group CPT significantly improved in PTSD severity, depression, and suicidal ideation.[37]

While CPT focuses on examining distressing thoughts and feelings, PE helps individuals with PTSD via habituation to fear and anxiety.[34] Prolonged exposure to thoughts, feelings, and situations that an individual has been avoiding helps him or her learn that reminders of the trauma do not have to be avoided.[34] In PE, an individual identifies situations he or she has been avoiding and repeatedly confronts them until distress decreases.[34] The focus of PE is on the management of reactions to stressful memories.[16] Similar to CPT, PE has four components[34]:

1. Learning about PTSD symptoms and how treatment can be of assistance.
2. Breathing training to help an individual relax and manage distress.
3. Real world exposure to fear- or anxiety-provoking situations to reduce distress that contributes to avoidance of these situations.
4. Repeatedly reliving the trauma via imaginal exposure to reduce distress that contributes to avoidance of memories about the trauma.

There is strong evidence for exposure therapy, of which PE has received the most attention.[7-12] In a multisite randomized controlled trial, veterans and activity duty personnel who received PE experienced a greater reduction of PTSD symptoms relative

to those who received present-centered therapy.[13] In addition, in a randomized controlled trial of female assault survivors, PE alone and PE plus cognitive restructuring reduced PTSD and depression relative to a waitlist control (individuals who were waitlisted to treatment but did not receive either) in both intention-to-treat and completer samples.[11]

Pharmacotherapies

Trauma-focused psychotherapy is the recommended first-line treatment for PTSD and includes CPT and PE.[34] While psychotherapy is the preferred, first-line treatment for PTSD, pharmacotherapy is also an important treatment option.[38] The selective serotonin reuptake inhibitors (SSRIs) sertraline and paroxetine are approved by the FDA for the treatment of PTSD.[38] A 2008 meta-analysis included fourteen randomized clinical trials that investigated different SSRIs - sertraline, fluoxetine, paroxetine, and citalopram[39]; seven demonstrated a positive outcome benefit while seven demonstrated no benefit in the Clinician-Administered PTSD scale (CAPS) score, which measures the frequency and intensity of PTSD symptoms.[40-53] Two large randomized controlled trials investigated the serotonin-norepinephrine reuptake inhibitors (SNRI) venlafaxine.[43,54] Both studies had dropout rates exceeding 30% and showed very small, albeit statistically significant changes in CAPS.[43,54] The alpha-adrenergic blocker prazosin was effective for combat-related nightmares and sleep disturbance in veterans in two small studies.[55,56]

A 2013 meta-analysis found a number of effective treatments which reduced total PTSD symptom and severity scores, measured by CAPS.[57] Effective pharmacotherapies included sertraline, paroxetine, fluoxetine, venlafaxine, and risperidone.[40,43,46,52,58] CAPS-5 is the gold standard in PTSD assessment. In addition to assessing the 20 DSM-5 PTSD

symptoms, questions cover onset and duration of symptoms, subjective distress, impact of symptoms on social and role functioning, and overall PTSD severity.[59,60] The CAPS-5 total severity score is calculated by summing up the individual item severity scores for symptoms corresponding to given cluster.[59,60] Item scores range from 0-4 and total scores range from 0-80.[57,58] A 2014 Cochrane review found that of all the medication classes, evidence of treatment efficacy was most convincing for SSRIs.[59,60] Paroxetine, fluoxetine, and sertraline appear relatively fast acting, with improvements compared to placebo CAPS scores within 2-12 weeks.[61]

While benzodiazepines may be effective symptomatic treatments for insomnia, anxiety, and irritability associated with PTSD and helpful for treatment-resistant patients with severe symptoms, they have been shown to not effectively prevent PTSD or reduce core PTSD symptoms.[62,63,64,65] Furthermore, benzodiazepines interfere with PE therapy because they suppress fear extinction.[66,67] High doses of benzodiazepines taken in combination with opioids or alcohol can result in overdose and increase the risk of death.[66,67] A 2013 meta-analysis found that benzodiazepines did not significantly reduce total PTSD symptom and severity scores (as measured by CAPS) compared to placebo.[57]

Clinical Practice Guidelines

For clinical practice, first-line recommended pharmacotherapies include the SSRIs sertraline, paroxetine, fluoxetine, citalopram, and fluvoxamine and the SNRI venlafaxine.[38] If a patient has received maximally tolerated dosages of the first-line agent and an adequate duration of treatment, then it is advisable to switch to another agent within the SSRI or SNRI group to address specific symptoms that are still present.[38] If

none of these first-line agents are effective, a second-line agent is the next step of treatment.[38] Although prazosin is recommended for nightmares not relieved by first-line medications, a recent randomized clinical trial in the VA found no significant improvement in the frequency and severity of nightmares in veterans treated with prazosin compared to those who received placebo.[36,68] Other second-line agents include mirtazapine, nefazodone, and tricyclic antidepressants (imipramine, amitriptyline).[38] However, evidence for the effectiveness of second-line agents is not as strong as that for first-line medications because the latter agents effect the serotonergic receptors in the amygdala and other parts of the fear circuitry.[38] Furthermore, many of these second-line medications have serious adverse effects, including hypotension, weight gain, and liver failure, and carry the risk of toxicity if taken in an overdose; for the SSRI or SNRI groups, the only main adverse effect is sexual dysfunction, most commonly delayed orgasm.[38]

Benzodiazepines, opioids, atypical antipsychotics, and conventional antipsychotics are not recommended for the treatment of PTSD.[21,38] Veterans with PTSD who were prescribed opioids were significantly more likely to experience opioid-related accidents and overdose, alcohol and nonopioid drug-related accidents and overdose, self-inflected injuries (suicide attempt), and violence-related injuries (gunshot wounds).[69] Atypical antipsychotics have serious side effects that include weight gain, tardive dyskinesia, anxiety, and metabolic syndromes such as hyperglycemia, diabetes, and heart disease.[1] Table 1 shows some of the pharmacotherapies used to treat PTSD.

Benzodiazepines

Benzodiazepines are estimated to be prescribed to 30% to 74% of patients with PTSD.[21] However, of all the pharmacotherapies prescribed to patients with PTSD, benzodiazepines (along with opioids) are a potentially addictive group of medications.[37] Benzodiazepines may be effective symptomatic treatments for insomnia, anxiety, and irritability associated with PTSD; they may be helpful for treatment-resistant patients with severe symptoms.[21] Furthermore, benzodiazepines may reduce subjective anxiety in the short-term.[37] One of the most common inhibitory neurotransmitters in the central nervous system is gamma aminobutyric acid (GABA).[70] A GABA receptor complex contains sites for binding GABA as well as sites for binding other molecules that modulate GABA's activity. The GABA receptor complex contains a central core permeable to chloride and other ions. When GABA binds with this complex, it induces conformational change, which increases the permeability of chloride ions.[70] The resulting increase in the concentration of chloride ions in the postsynaptic neuron results in hyperpolarization, reducing the excitability of the neurons and producing an inhibitory effect in neuronal activities. Benzodiazepines increase the frequency with which the chlorine channel opens when GABA binds to its own site on the receptor complex.[70] Thus, benzodiazepines increase the efficiency of GABA and allow it to produce a larger inhibitory effect. However, benzodiazepines may be ineffective for PTSD because the pathophysiology of PTSD differs from that of other anxiety disorders for which benzodiazepines have some efficacy.[21] Locus ceruleus (brain stem) dysregulation is implicated in both panic disorder and PTSD; the hippocampus and amygdala are also implicated in PTSD.[21] In addition, benzodiazepines indiscriminately depress global brain function.[21] This includes structures

such as the prefrontal cortex that are already hypoactive in PTSD and which, when functioning properly, allow for various cognitive processes and modulation of the amygdala.[21] Thus, anxiety in PTSD may be different from anxiety in other disorders and may require different treatments.

Consistent evidence shows a lack of efficacy for the four core symptom clusters of PTSD, depression, and psychotherapy augmentation.[21] Benzodiazepines have shown no significant improvement compared to placebo in treating PTSD.[57] Furthermore, benzodiazepines are associated with specific problems in patients with PTSD. This includes worse overall PTSD symptom severity, psychotherapy outcomes, anxiety, aggression, substance abuse, and social functioning.[21,57,62,63,70,71] For example, benzodiazepines interfere with psychotherapy because they suppress fear extinction.[57] High doses of benzodiazepines taken in combination with opioids or alcohol can result in overdose and increase the risk of death.[66,67]

Benzodiazepines have been known to cause or worsen depression, dysphoria (dissatisfaction with life), and suicidal thoughts and behavior.[21] These are all risk factors for increased suicide behavior. This is especially problematic because veterans are already at an elevated risk for suicide and depression is comorbid in 30-50% of patients with PTSD.[72] Furthermore, benzodiazepine-induced depressive disorder can occur in individuals without a history of depression.[73,74] Another major issue of benzodiazepines is that benzodiazepine dependence is a distinct problem in patients with PTSD; this is because most patients have PTSD symptoms that last for longer than three months.[75] Discontinuing benzodiazepines in patients with benzodiazepine dependence results in decreased inhibition from GABA and hyperactive excitation from glutamate, which can cause

withdrawal symptoms that mimic and worsen PTSD symptoms (including anxiety, insomnia, agitation, perpetual disturbances, autonomic hyperactivity). Overall, although the therapeutic effects of benzodiazepines decrease with dependence, depression and impulsivity with high suicidal risk commonly persist.[76]

The relationship between PTSD and suicide behavior can also be conceptualized through a behavioral avoidance model.[77] This model represents a set of behaviors an individual undertakes to avoid or escape from unwanted emotional experiences.[75] PTSD results in traumatic memories, dreams, and symptoms that are uncomfortable, which drives avoidance behavior; this includes suicide, which an individual will undertake in order to avoid the emotions caused by PTSD.[77] Benzodiazepines serve the same function by allowing an individual to avoid/escape from emotional distress and pain.[21] On the other hand, psychotherapies disrupt the avoidance process via exposure-based interventions; thus, because benzodiazepines function as avoidance, they can affect behavioral conditions, such as suicide, in veterans with PTSD.

Potential explanations for benzodiazepines worsening PTSD outcomes include discontinuation symptoms, disruption of normal stress responses, avoidance of cognitive and emotional processing of trauma, and worsening of underlying PTSD pathophysiology.[21]

Overall, benzodiazepines are ineffective for PTSD prevention and treatment, actually worsen overall PTSD, encourage dependence side effects, and worsen risk factors for suicide behavior.[72] Thus, benzodiazepines should not be prescribed to patients with PTSD.[21]

Gaps in Research and Public Health Impact

Little is known about the comparative distribution of therapies veterans with PTSD receive in the VA and whether their symptoms improve as a result.[33,35,71] Health care utilization is higher for veterans with PTSD compared to veterans without PTSD.[78,79] However, it is unclear how resource utilization differs between those who receive benzodiazepines versus no benzodiazepines.[21,38,80,81] This is important to investigate because benzodiazepines are not effective for the treatment of PTSD and can worsen symptoms, causing veterans to seek more health care.[21] Suicide behavior is one of the leading causes of mortality among veterans.[81] While it is known that veterans with PTSD are more likely to have thoughts of hopelessness and suicidal ideation, it is unclear how suicide behavior differs between those who receive benzodiazepines versus no benzodiazepines.[21,82,83] This is important to investigate because benzodiazepines can worsen depression, dysphoria, and suicidal thoughts, leading to an increased risk in suicide behavior.[21,84-90]

Overall, despite the recommendation against their use, benzodiazepines are still prescribed for veterans in the VA. Thus, there remains a significant gap between research and actual clinical care. The findings of this large study will significantly strengthen the empirical evidence against benzodiazepines for the treatment of PTSD. The ultimate public health impact is to steer veterans away from benzodiazepines.

Objectives

1. Describe utilization of psychotherapies and pharmacotherapies, including benzodiazepines, for veterans with PTSD.

2. Evaluate the association between benzodiazepines and inpatient, outpatient, and emergency department (ED) utilization.

   Hypothesis: Benzodiazepines are associated with an increase in health care utilization.

3. Evaluate the risk of benzodiazepines and suicide behavior.

   Hypothesis: Benzodiazepines are associated with greater risk of suicide behavior.

Innovation

This is the first study to analyze a nationwide cohort of veterans with PTSD, with exposure being benzodiazepines versus no benzodiazepines use for PTSD. Furthermore, it is unclear how health care resource utilization and suicide behavior differs between benzodiazepine and nonbenzodiazepine treatments. By analyzing the outcomes of health care resource utilization and suicide behavior, this study investigates the difference in resource utilization and suicide behavior between these two treatment groups.

CHAPTER III

METHODS

Study Design

Randomized clinical trials (RCTs) are the gold standard study designs for estimating treatment effects.[90] This is because random assignment to treatment theoretically balances observed and unobserved characteristics between both treatment and comparison groups. Patients who take different treatments are exchangeable; other than the intervention that is evaluated, their characteristics are the same.[91] Thus, because these observed and unobserved variables are similar, the effect of treatment on outcomes can be estimated directly between the treatment and comparison groups. Unfortunately, RCTs are not always feasible due to ethical or practical reasons. Furthermore, RCTs are conducted in controlled circumstances, which limits the generalizability of results to day-to-day clinical practice.[92] On the other hand, an observational study design aims to represent the real clinical situation.[93]

However, in observational data, treatment assignment is not random.[90] This leads to confounding bias, where measured and unmeasured characteristics of individuals are associated with the outcome and with the probability of receiving treatment. Thus, statistical methods must be employed to reduce confounding inherent in observational studies.[91] While traditional regression models do not completely adjust for confounding,

propensity scores provide a way to balance measured covariates across treatment and comparison groups.[90] This will be a retrospective observational analysis of a cohort of veterans diagnosed with PTSD between January 1, 2001 and December 31, 2014, followed until December 31, 2015. Veterans will be followed from time of benzodiazepine initiation in the VHA.

Propensity Scores

In observational studies, propensity scores are unknown and must be estimated from the data.[91] The propensity score is the probability of receiving treatment conditional on baseline covariates.[90] Consider the following for each subject *i*: a binary treatment indicator variable T_i, equal to 1 if a subject receives treatment and 0 if a subject does not receive treatment; a vector of observed baseline covariates X_i; and the outcome of interest Y_i.[94,95] The propensity score, (P_i), for each subject *i* can be represented as the following:

$$P_i = Pr\,(T_i = 1 \mid X_i) \quad (1)$$

A logistic regression model is commonly used with treatment as the outcome and potential confounders, variables associated with outcome and exposure, as baseline covariates.[90]

Propensity Score Assumptions

The propensity score is a balancing score with two major assumptions:

1. $(Y_{1i}, Y_{0i}) \perp T_i \mid X_i$
2. $0 < Pr\,(T_i = 1 \mid X_i) < 1$

The first assumption states that there exists a vector of covariates, X_i, such that after

controlling for this vector, the potential outcomes Y_{1i} and Y_{0i} are independent of treatment status.[96] The second one assumes that for each variable in the vector X_i, there is a positive probability of being both treated and untreated.[96]

Variable Selection Strategies for Propensity Scores

The omission of confounders from propensity scores results in effect estimates that are biased to the same degree and in the same direction as estimates obtained from omitting the same confounders in a conventional outcome model. The recommended variable selection strategy is to include all variables associated with an outcome in a propensity score regardless of their association with exposure.[97] If a variable is related to the outcome but not the exposure, including it in the propensity score may help to reduce bias.[90,98,99] On the other hand, controlling for variables that are associated with the exposure but not the outcome can increase the variance and bias of effect estimates; these variables should not be included in the propensity score.[98,100] Thus, the variables to choose in the propensity score include confounders and variables associated with the outcome.[98,100]

Propensity Score Methods

There are four methods for using the propensity score to estimate treatment effects.[101] These methods include stratification on the propensity score, covariate adjustment using the propensity score, matching on the propensity score, and weighting by the inverse probability of treatment (IPTW) using the propensity score. Stratification on the propensity score involves comparing outcomes between treated and untreated

subjects within strata defined by the propensity score.[94,,95,101] Five strata defined by the quintiles of the propensity score are commonly used. The effect of treatment on outcomes is estimated within each stratum. Propensity-score matching involves forming matched sets of treated and untreated subjects with similar values of the propensity score.[94,95,101] A common approach is nearest neighbor pair-matching without replacement within specified calipers of the propensity score, often 0.2. Covariate adjustment using the propensity score is the most widespread propensity-score methods in the medical field.[97] In covariate adjustment, the treatment effect is estimated by the regression of the outcome on an indicator variable denoting treatment assignment and the propensity score. IPTW using the propensity score is the fourth method used to adjust for confounding.[95] Inverse probability weights are calculated as the inverse conditional probability that a subject received the exposure he or she actually received. This is 1/(Propensity Score) for the exposed and 1/(1-Propensity Score) for the unexposed.[97] Weighting by this quantity creates a synthetic population in which treatment assignment is independent of measured baseline covariates.[97]

Propensity score matching has been shown to eliminate a greater portion of the systematic difference between the treated and untreated subjects compared with stratification on the propensity score and covariate adjustment using the propensity score.[101-105] Monte Carlo simulations have been used to compare the performance of different propensity score methods.[103] Matching on the propensity score and weighting using the inverse probability of treatment eliminated a greater degree of the systematic differences between treated and untreated subjects compared to stratification and covariate adjustment. In addition, propensity score matching tended to have either

comparable or marginally superior performance compared with propensity-score weighting.[103] Thus, this study will use propensity score matching to balance measured covariates between benzodiazepine users and non-benzodiazepine users.

Formation of Matched Sets

After estimating propensity scores, propensity score matched sets of treated and untreated subjects must be formed.[94,95,101] A matched set is a set of at least one treated subject and at least one untreated subject with similar propensity score values.[94,95,101] The most commonly used method for the formation of these pairs is greedy matching using calipers of a specified width. For a given treated subject, the closest untreated subject within the specified caliper distance is selected for matching to this treated subject, even if the untreated subject would better have served as a match for a different treated subject.[94,95,101] In this approach, a treated subject is randomly selected, and the untreated subject with the closest propensity score that lies within a fixed distance (the propensity score caliper) of the treated subject's propensity score is selected for matching.[94,95,101] In matching without replacement, once an untreated subject has been matched to a treated subject, that untreated subject is not available for consideration as a match for subsequent treated subjects.[92,93,99] Recent research has found that matching on the logit of the propensity score using calipers of width 0.2 of the standard deviation of the logit of the propensity score resulted in estimates of treatment effect with lower mean squared error compared to other methods that are commonly used in the medical literature.[94,95,101]

Standardized Differences

Once the propensity score matched sets of treated and untreated subjects have been created, the next step is to assess balance in baseline characteristics.[94,95,101] The distribution of baseline characteristics should be similar between treated and untreated subjects within stratum matched on the true propensity score.[94,95,101] The standardized difference is used to assess balance between treatment groups in the propensity score matched sample; it is the absolute difference in sample means divided by an estimate of the pooled standard deviation of the variable.[94,95,101] The standardized difference represents the difference in means between the two comparison groups in units of standard deviation.[94,95,101] The standardized difference does not depend on the unit of measurement nor is it influenced by sample size; it can be used to compare the relative balance of variables measured in different units.[94,95,101] Thus, the standardized difference allows for the comparison of different treatment groups after the creation of propensity-matched pairs.[92,93,99] Some authors have suggested that standardized differences of less than 0.10 (10%) likely denote a threshold of acceptable imbalance between treated and untreated subjects.[94,95,101] Furthermore, the use of side-by-side box plots and quantile-quintile plots can be used to compare the distribution of continuous baseline covariates between exposed and unexposed subjects.[94,95,101]

Estimation of Treatment Effect

Once the propensity score has been estimated, a propensity score matched cohort has been created, and the balance in measured baseline variables between treated and untreated subjects has been assessed and found to be acceptable, the estimation of

treatment effect is possible.[94,95,101] When a subject in the treatment group is matched to a corresponding subject in the control group with the same propensity score, the matched pair will have, in probability, the same value of covariate vector X_i. The average treatment effect (ATE) for the population is used to evaluate the expected effect on outcome if treatment assignment was random[106]:

$$ATE = E(Y_1 - Y_0) = E(Y_1) - E(Y_0) \quad (2)$$

$E(Y_1)$ is the expected value for all subjects in the treatment group and $E(Y_0)$ is the expected value for all subjects in the control group.[106] The ATE is an unbiased estimator of the treatment effect because the treatment group does not, on average, differ systematically from the control group on the covariate vector X_i. The ATE is directly estimated in the propensity-score matched cohort through a regression of outcome Y_i on binary treatment indicator T_i.[106]

Data Sources

The data sources were the National Veterans Health Administration (VHA) Database and the VA/Department of Defense (DOD) Suicide Data Repository (SDR). The VHA database contains electronic health records of over 20 million veterans from the years 2000-2015; these veterans have sought health care at the 1400 VA facilities and 152 medical centers throughout the United States.[107] The VHA database includes the Corporate Data Warehouse (CDW) and MEDSAS datasets.[107] As shown in Table 2, diagnosis, psychotherapies, pharmacotherapies, health care visits, and suicide behavior were all queried from different datasets within the CDW; demographics, confounders, and risk factors were queried from the CDW and MEDSAS. [107,108,109] The other major

database analyzed in this study was the VA/DOD SDR. This database includes the National Death Index Plus, which contains all-cause mortality for all service members who separated from active duty between the years 1979-2014; it also contains a current mortality archive on all users of VHA services from 2000-2014.[110] All-cause mortality and suicide mortality were queried in the SDR. Scrambled social security numbers were used to link veterans in the different databases.[110] The objectives of this study were addressed through an analysis of these databases.

Study Population and Criteria

The study population consisted of veterans with PTSD who are new users of benzodiazepines and treated at VA facilities throughout the United States. This study was an analysis of veterans diagnosed with PTSD between January 1, 2001 and December 31, 2014 .[111] Veterans are at a high risk for mental disorders and PTSD is the most commonly diagnosed mental disorder.[111] A recent analysis of over 200,000 returning Operation Enduring Freedom/Operation Iraqi Freedom veterans found that rates of PTSD and other mental health disorders were increasing over time.[110] Veterans with a diagnosis prior to January 1, 2001 were excluded. DSM-5 diagnostic criteria is currently used to diagnose PTSD.[1] However, this diagnostic criteria is not easily identified in a structured data field. The International Classification of Diseases, Ninth Revision Clinical Modification (ICD-9-CM) codes was used to identify veterans with PTSD. The overall positive predictive value is 75% for at least one PTSD diagnosis (outpatient or inpatient) and 82% for at least two PTSD diagnoses (outpatient or inpatient) in VA databases.[112] Therefore, 75% of the individuals with at least one PTSD diagnosis in the VA databases

truly have PTSD. Veterans with one ICD-9 code of 309.81 in any inpatient or outpatient encounter during the study time period were classified as having PTSD.[112]

The creation of the cohort consisted of three distinct steps. The first step consisted of the cohort defining diagnosis, which will consist of one ICD-9 code for PTSD during the between January 1, 2001 and December 31, 2014. The second step involved inclusion of new users of benzodiazepines. A veteran was considered to be a new user of benzodiazepines if 1) he or she had one 30-day prescription of benzodiazepines in any health care encounter within 365 days after PTSD diagnosis, and 2) he or she had not used benzodiazepines at least six months prior to PTSD diagnosis. The third step in creating the cohort consisted of identifying VA utilizers and active VA users. A veteran was considered to be a VA utilizer if he or she had at least six months of VA care in any inpatient or outpatient setting at any point in time during the study period. In order to ensure veterans were active users of the VA, those without an encounter in any inpatient or outpatient setting within 12 priors prior to PTSD diagnosis were excluded from the cohort. The final eligible population consists of veterans diagnosed with PTSD between January 1, 2001 and December 31, 2014 who had at least six months of care and one VA encounter within twelve months prior to PTSD diagnosis.

Sample Size and Power

Sample size and power calculations were estimated with PS: Power and Sample Size software and based on the outcome of suicide behavior. With an outcome that can result in death, small effects are clinically relevant; a 10% difference in suicide is a very meaningful difference.[111] The national suicide prevention plan has set as a goal a 20%

reduction in suicide within the next decade.[111] Thus, in calculating sample size, the effect estimates were varied, including a 10% and 20% increase in risk for suicide behavior for veterans who are given benzodiazepines.[111] The significance level was 0.05 and the power was 0.8. Because 30% to 74% of patients are estimated to receive benzodiazepines[21], this range was varied in sample size calculations, including 30%, 52%, and 74%. Furthermore, while there was no data on suicide behavior for veterans who are not given benzodiazepines, approximately 13% to 21% of all veterans exhibit suicide behavior.[112, 113] Overall, as Table 3 reveals, the total required sample sizes ranged from 2,350 to 28,669 depending on the estimates for percent of veterans with suicide behavior, difference in suicide behavior, and prevalence of benzodiazepines among veterans.

Ultimately, the sample size was large and consequently, the study sufficiently powered. A study on the utilization of VA nonmental health services among returning Afghanistan and Iraq veterans included 53,728 veterans diagnosed with PTSD between October 7, 2001 and March 31, 2007.[111] Table 4 shows counts for VA patients diagnosed with PTSD, notes that include suicide in the title, and pharmacotherapies used to treat PTSD from 2000-2015.

During the time period from 2000-2015, 2,096,018 patients were diagnosed with PTSD. Using parameter estimates of 13%, 17%, and 21% for percent of veterans with suicide behavior, a 10% and 20% increase in risk for suicide behavior for veterans who are given benzodiazepines, 30%, 52%, and 74% for veterans who are given benzodiazepines, and a significance level of 0.05, the estimated power asymptotically approaches 1.

Data Collection and Measures

Exposure

The exposure consisted of two different treatment groups for veterans with PTSD, those who receive benzodiazepines versus those who do not. Patients were considered exposed for the entire study period if they were new users of benzodiazepines in the initial one-year period after diagnosis. An intention to treat (ITT) analysis in which exposure status as assumed throughout follow-up reflects the real-world clinical scenario because it admitted noncompliance and protocol deviations. Furthermore, ITT gave an unbiased estimate of the treatment effect because exclusion of noncompliant subjects and dropouts might create significant prognostic differences between the two treatment groups. This type of analysis also minimized type I error (false positive) due to its cautious approach and allowed for the greatest generalizability. However, the estimate of the treatment effect is generally conservative in ITT and thus more susceptible to type II error (false negative).[116,118]

Medications were grouped by drug class. The no benzodiazepines group consists of a number of treatments, which includes psychotherapy, SSRIs, SNRI, antiadrenergic agent, tetracyclic antidepressant, serotonergic antidepressant, tricyclic antidepressant, opioids, atypical antipsychotics, and conventional antipsychotics. Other medications were similarly classified in order to adjust for them in models (psychotherapy users versus no psychotherapy users, SSRI users versus no SSRI users). The VA CDW contains data that includes treatments.[108,109] Drug classes and names were used to identify medications in the outpatient drug and inpatient BCMA dispensed drug data sets; CPT codes were used to identify psychotherapy.[108,109]

Outcomes

The outcomes were health care utilization and suicide behavior. Health care utilization included mental health and nonmental health inpatient, outpatient, and ED visits. Stop codes and VA clinic codes with a diagnosis of PTSD were used to differentiate between nonmental and mental health visits. Visits were identified in the CDW in the outpatient and inpatient visit datasets. A stop code of 130 was used to differentiate between outpatient and ED visits. Suicide behavior was the other major outcome and included suicide completers, suicide attempters, and suicidal thoughts/ideation. Suicide behavior was identified multiple ways. One method was the presence of an Electronic Health Record note title with the term "suicide consult, event, attempt, flag, alert, warning, or report" in the VA CDW because these refer to current suicidal events while "suicide history" and "suicide follow-up" refer to suicidal events in the past.[108,109] ICD-9 codes in the VA CDW was a second method used to identify suicide behavior. Table 5 shows these ICD-9 codes.[118] The VA/DoD SDR contained data on suicide among veterans and was the third method used to identify completed suicides, with cause of death as outcome.[110]

Covariates

Comorbidities were considered in this study. Traumatic brain injury, anxiety disorder, bipolar disorder, depression, alcohol abuse, opioid abuse, chronic pain, homelessness, smoking, and illicit drug use are other comorbid conditions commonly found in patients with PTSD.[31,119-122] ICD-9 codes were used to identify comorbid conditions. Table 6 shows the ICD-9 codes for comorbidities.[123,124] Additional covariates

such as age, gender, socioeconomic status, service percentage disabilities, race, and military sexual trauma were directly identified in the VHA. Age was categorized to 0-29, 30-39, 40-49, 50-59, and 60+; gender to male and female; socioeconomic status to lowest, low, medium, and high; race to white, black or African-American, and other race. Service disabilities referred to disabilities that were incurred or aggravated during active military service; disability ratings were categorized to low percentage (0-29), medium percentage (30-59), and high percentage (60-100).

Finally, it was not possible to differentiate between the two types of psychotherapy, CBT and PE, using CPT codes. Thus, single measures were used to capture both groups. Table 7 shows the CPT codes for psychotherapy.[125,126] It should also be noted that these CPT codes are also unable to differentiate between CBT and other therapies, including supportive counseling and/or nonspecific therapies that are not expected to work for PTSD.

Specific Variables Included in Propensity Score Model

Figure 2 is a directed cyclic graph (DAG) that identifies which variables should be assessed for inclusion in the propensity score model in the relationship between benzodiazepines and the health utilization and suicide behavior outcomes. The DAG demonstrated that anxiety disorder, bipolar disorder, depression, opioid abuse, alcohol abuse, chronic pain, antidepressants, and prazosin could be associated with the exposure, benzodiazepine treatment, and could also be associated with all of the outcomes.[1,34,35, 70, 118-119, 122,126-136] Thus, these comorbidities and medications were potential confounders and needed to be adjusted for in the propensity score model.[90,94.95] Furthermore, risk factors for

the outcomes included traumatic brain injury, gender, marital status, opioids, atypical antipsychotics, conventional antipsychotics, race, socioeconomic status, service percentage disabilities, age, military sexual trauma, smoking status, illicit drug use, homelessness, education, and employment; all but the last two were adjusted for in the propensity score model.[1,33,36,57,90, 94,95, 137] There was no structured VA data on the risk factors of education and employment; thus, these two variables were not be adjusted for since more proximal risk factors were used.

Statistical and Outcome Analysis

Descriptive statistics were used to describe the different treatments for PTSD.[137] This includes patients who received a treatment (n, %), treatments per patient by class (n, median, IQR), fills per patient by class (n, median, IQR), median duration for oral and nonoral pharmacotherapies, median quantity for oral pharmacotherapies, patients who received an inpatient pharmacotherapy treatment (n, %), median duration for inpatient pharmacotherapy, patients who received a first or second (within thirty days of their first therapy) psychotherapy/pharmacotherapy (n, %), and most frequent overlapping therapies (n, %) .

The impact of benzodiazepine use in veterans with PTSD was assessed in the matched cohort using regression models. Models included the treatment group as the primary independent variable and any additional variables that remained imbalanced between the groups in the matched sample.[90,94,95] This doubly robust estimation combines a form of outcome regression with a model for exposure, the propensity score.[138] When used individually to estimate association, both outcome regression and propensity score

methods are unbiased only if the statistical model is correctly specified.[138] The doubly robust estimator combines these two approaches such that only 1 of the 2 models needs to be correctly specified in order to obtain an unbiased effect estimate.[138] Incidence rate ratios, rate differences, and hazard ratios were used to estimate the treatment effect. The incidence rate ratio is the ratio of the number of new cases per population at risk in given time period between two groups.[139] The rate difference is the difference between the number of new cases per population at risk between two groups.[139] The hazard ratio is the ratio of the hazard rates at any point in time between two groups.[139]

Health care utilization (mental and nonmental health outpatient visits, inpatient hospitalizations, and ER visits) was analyzed with generalized linear models (GLM), which consists of the following components[140]:

1. A random component specifying the conditional distribution of the response variable y_i given the values of the explanatory variables
    a. Distribution is a member of an exponential family
        i. Poisson, Binomial, Gaussian, Inverse Gaussian, Gamma
2. A linear predictor
    a. Linear function of regressors
        i. $n_i = a + b_1x_{i1} + b_2x_{i2} + ... + b_kx_{ik}$ (3)
3. A link function g(.)
    a. Transforms the expectation of the response variable, $u_i = E(Y_i)$, to the linear predictor
        i. $g(u_i) = n_i = a + b_1x_{i1} + b_2x_{i2} + ... + b_kx_{ik}$ (4)

However, in order to use GLM model, a number of assumptions must be assessed. GLM assumptions include[140]:

1. Dependent variable assumes a distribution from an exponential family
    a. Modified Park Test will be used to identify the potential

distribution

2. Linear relationship between the transformed response in terms of the link function and the explanatory variables
    a. Scatter plot to see if nonlinearity is present
3. Homogeneity of variance of the residuals
    a. Residual is difference between observed value of the dependent variable, y_i, and the estimated value, $\hat{y}_i$
    b. Variance of residuals should be constant
        i. Graphically, plot of residuals against estimated values should show no pattern
        ii. Statistically, White Test of homogeneity
4. Normality of residuals
    a. Residuals should be normally distributed
        i. Graphically, plot of residuals against normal quantiles should lie along 45-degree line
        ii. Statistically, Shapiro-Wilk W-Test of normality

In addition, log-binomial or modified Poisson regression was used to directly estimate risk differences.[139] Log-binomial regression was used unless model convergence is an issue.[141] In that case, modified Poisson regression, which is Poisson regression with robust error variance, was used.[140] Modified Poisson regression has a major assumption that the variance equals the mean:

$$\text{Var}(y) = \varphi * E(y) = \varphi * \mu, \text{ where } \varphi = 1 \quad (5)$$

This assumption can be assessed statistically through the scale factor, the scaled deviance and the scaled Pearson.[140] If either scale factor is greater than one, then a negative binomial model was used to account for this over-dispersion where the variance is not equal to the mean.[140]

Because it was a time to event outcome, suicide-related outcomes were estimated through hazard ratios from a Cox Proportional Hazards regression model.[140] The major assumption of a Cox model is that of proportional hazards.[140] This means that the survival curves for two groups must have hazard functions that are proportional over time.[140] Proportionality was assessed though a plot of the residuals against time by exposure group (benzodiazepine users vs. nonbenzodiazepine users). Median survival times in all of the suicide outcomes were also reported and differences in overall survival between the two groups were assessed through log-rank tests. All statistical analyses were performed using SAS V9.3 (Cary, NC) and Stata 13 (College Station, TX), assuming a two-sided alpha of 0.05.

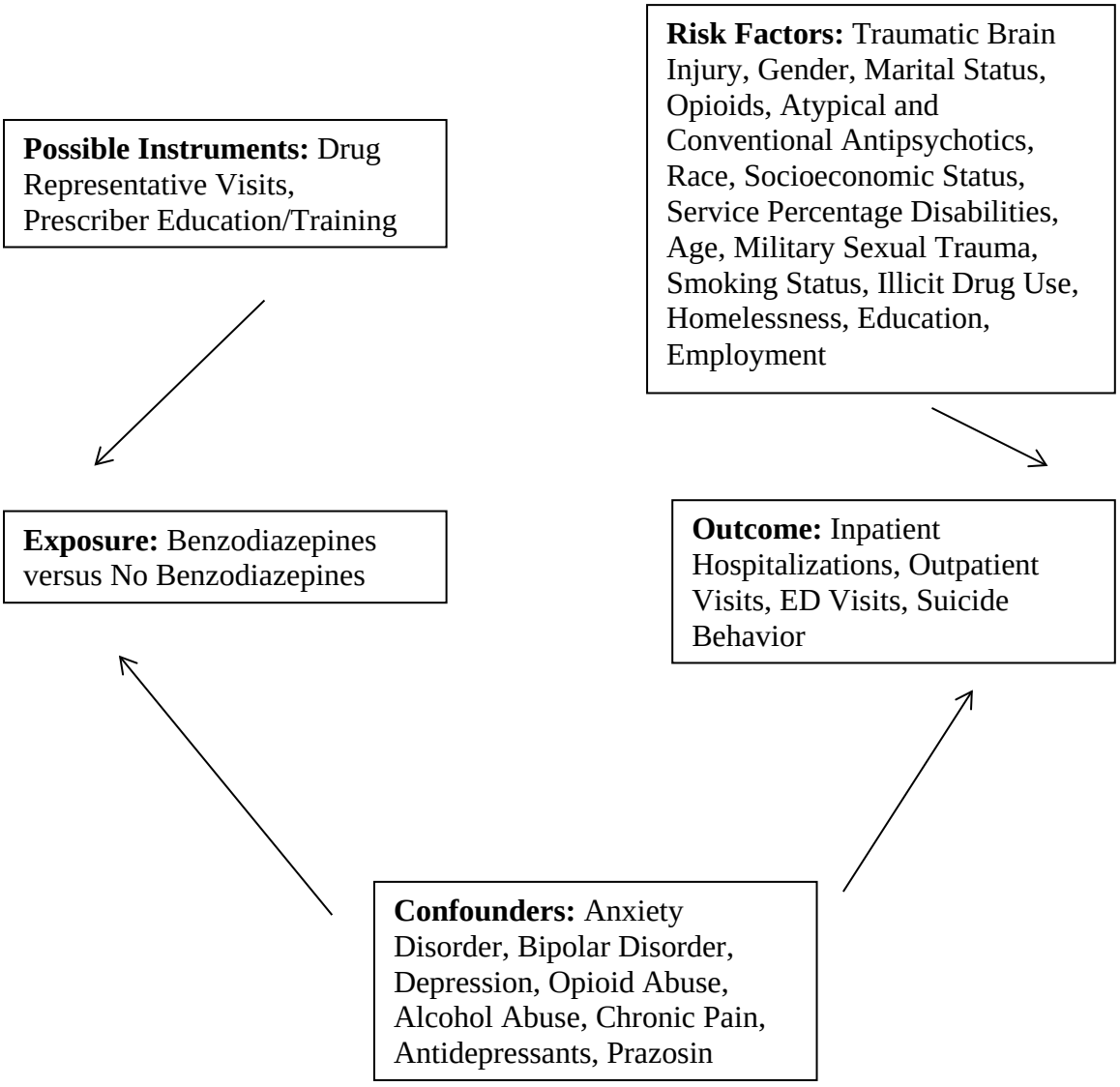

Figure 2. Directed Acyclic Graph for Health Care Utilization and Suicide Behavior

Table 2. Data Sources for Variables

Variable	Data Source
Diagnosis	Outpatient Diagnosis, Inpatient Diagnosis
Psychotherapies	Outpatient Procedure, Inpatient CPT Procedure
Pharmacotherapies	Outpatient Prescription Fill, Bar Code Medication Administration, Dispensed Drug
Demographics, Confounders, and Risk Factors	Patient Demographics, Outpatient Diagnosis, Inpatient Diagnosis
Health Care Visits	Outpatient Visits, Inpatient Visits
Suicide Behavior	Outpatient Diagnosis, Inpatient Diagnosis
Mortality, Including All-Cause and Suicide	Suicide Data Repository

Table 3. Sample Size Estimates

Percent of Veterans with Suicide Behavior	**Difference in Suicide Behavior**	**Percent of Veterans Given Benzodiazepines**	**Number of Veterans with Benzodiazepines**	**Number of Veterans with No Benzodiazepines**	**Total Sample Size**
13%	10%	30%	7, 770	18,130	25,900
13%	10%	52%	11,413	10,535	21,952
13%	10%	74%	21,215	7,454	28,669
13%	20%	30%	2,007	4,683	6,690
13%	20%	52%	2,967	2,739	5,706
13%	20%	74%	5,548	1,950	7,498
17%	10%	30%	5,655	13,194	18,849
17%	10%	52%	8,303	7,664	15,967
17%	10%	74%	14,437	5,419	19,856
17%	20%	30%	1,457	3,400	4,857
17%	20%	52%	2,152	1,987	2,350
17%	20%	74%	4,023	1,412	5,435
21%	10%	30%	4,346	10,141	14,487
21%	10%	52%	6,377	5,886	12,263
21%	10%	74%	11,850	4,160	16,010
21%	20%	30%	1,117	2,606	3,723
21%	20%	52%	1,647	1,521	3,168
21%	20%	74%	3,076	1,080	4,156

Table 4. Counts for VA Patients with PTSD, Notes with Suicide in Title, and Pharmacotherapies

	Counts
Patients with PTSD	2,096,018
Suicide in TIU note	591,676
SSRI	1,294,778
SNRI	318,794
Antiadrenergic Agent	416,169
Tetracyclic Antidepressant	397,908
Serotonergic Antidepressant	60,185
Tricyclic Antidepressant	227,918
Benzodiazepines	882,351
Opioids	1,063,824
Atypical Antipsychotics	537,288

Table 5. Suicide Behavior with ICD-9 Codes[118]

Suicide Behavior	ICD-9
Suicide and Self-Inflicted Poisoning by Solid or Liquid Substances	E950.0-E950.9
Suicide and Self-Inflicted Poisoning by Gases in Domestic Use	E951.0-E951.1, E951.8
Suicide and Self-Inflicted Poisoning by Other Gases and Vapors	E952.0-E952.1, E952.8-E952.9
Suicide and Self-Inflicted Injury by Hanging, Strangulation, and Suffocation	E953.0-E953.1, E953.8-E953.9
Suicide and Self-Inflicted Injury by Submersion	E954
Suicide and Self-Inflicted Injury by Firearms, Air Guns, and Explosives	E955.0-E955.7, E955.9
Suicide and Self-Inflicted Injury by Cutting and Piercing Instrument	E956
Suicide and Self-Inflicted Injury by Jumping From High Place	E957.0-E957.2, E957.9
Suicide and Self-Inflicted Injury by Other and Unspecified Means	E958.0-E958.9
Late Effects of Self-Inflicted Injury	E959
Suicidal Ideation	V62.84

Table 6. Comorbidities with ICD-9 Codes[123,124]

Comorbidity	**ICD-9**
Traumatic Brain Injury	850.0-850.5, 850.9, 851.0-851.9, 852.0-852.5, 853.0, 853.1, 854.0, 854.1
Anxiety Disorder	300.00, 300.01, 300.02, 300.09
Bipolar Disorder	296.00-296.06, 296.40-296.46, 296.50-296.56, 296.60-296.66, 296.7, 296.80
Depression	296.20-296.26, 296.30-296.36, 296.82, 311
Alcohol Abuse	305.00, 305.01, 305.02, 305.03
Opioid Abuse	305.50, 305.51, 305.52, 305.53
Chronic Pain	338.21, 338.22, 338.28, 338.29
Homelessness	V60.0
Smoking Status	V15.82, 305.1
Illicit Drug Use	305.90

Table 7. Psychotherapy with CPT Codes[125,126]

Psychotherapy	**CPT Code Before 2013**	**CPT Code 2013+**
Talk Therapy for 30 Minutes	90804/90810	90832
Talk Therapy for 45 Minutes	90806/90812	90834
Talk Therapy for 60 Minutes	90806/90814	90837
Crisis, for 60 Minutes	NA	90839
Group Therapy	90857	90853

CHAPTER IV

RESULTS

Objective 1 Results

The results of this section report the size of the cohort with PTSD, the distribution of therapies (including duration, number, and fills) for this cohort, inpatient exposure, and the most frequent overlapping therapies.

The number of veterans with one ICD-9 code for PTSD between January 1, 2001 and December 31, 2014 was 1,445,934 (Figure 3). The next step involved excluding 121,000 patients who used benzodiazepines within six months prior to PTSD diagnosis; this resulted in a cohort of 1,324,934. Afterwards, 7,589 patients who did not have 6+ months of VA care in any inpatient or outpatient setting at any point in time during the study were excluded, reducing the cohort to 1,317,345. The final step involved excluding 183,144 patients who did not have an encounter in any inpatient or outpatient setting within 12 months prior to PTSD diagnosis. As shown in Figure 3, removing these non-active VA users resulted in a final cohort of 1,134,201 veterans. Of these, 80,832 patients were users of benzodiazepines - at least a 30-day supply, no use within six months prior to PTSD diagnosis, and use of benzodiazepines within 365 days after diagnosis.

Baseline Characteristics

Baseline characteristics were captured 12 months prior to PTSD diagnosis (Table 8). In the cohort with PTSD (1,134,201), the median age was 53.12 with an IQR of 23.69. 90.60% of veterans were male and 66.90% were white. Regarding comorbidities, 13.41% of veterans had anxiety disorder, 12.64% had diabetes, 10.04% were smokers, 8.85% had depression, 7.98% had chronic pulmonary disease, and 5.95% had alcohol abuse. The prevalence of depression for the entire cohort with no time restrictions was 32.87% (372,866). 47.33% of veterans were married, 20.47% were divorced, 18.60% were single, and 2.28% were widowed. The most common periods of service were the Vietnam Era, Persian Gulf Era, and post-Vietnam, with respective percentages of 43.87, 39.43, and 8.46. Post-Vietnam refers to veterans with a first service entry date after the Vietnam Era ended, ie May 7, 1975. 59.56% of veterans had low service percentage disabilities, 17.18% had high service percentage disabilities, and 14.04% had low service percentage disabilities. The most common age categories were 60+, 50-59, 0-29, and 40-49, with respective percentages of 28.38%, 25.82%, 13.77%, and 13.06%. Lastly, socioeconomic status was evenly spread throughout the veteran population, with 24.21% being of lowest status, 20.56% being low status, 17.33% being medium status, and 17.31% being high status.

Distribution of Psychotherapies and Pharmacotherapies

All psychotherapies and pharmacotherapies were captured one year after PTSD diagnosis (Figure 4). Annualized duration and quantity were also captured one year after PTSD diagnosis. Oral treatment consisted of tablets, capsules, oral solution and oral

concentrate. Nonoral treatment consisted of injection, intravenous, suppository, syringe, gel, and solution. Because solution can refer to oral or injectable drugs, a conservative approach of grouping solution with nonoral pharmacotherapies was taken.

For the distribution on the use of recommended psychotherapies and pharmacotherapies in the cohort with PTSD, 46.76% of veterans received psychotherapy, 26.78% received SSRIs, 6.75% received prazosin, 6.07% received mirtazapine, and 4.31% received venlafaxine (Table 9). The median number of psychotherapy sessions was 5, ranging from 1 for 60 min crisis to 7 for group therapy (Figure 5). The median number of distinct SSRI treatments was 1; the median number of fills was 7. The median number of fills for all pharmacotherapies ranged from 4 to 8 (Figure 6). The median duration for oral and nonoral SSRIs was 90 days, with a large variation (respective interquartile ranges are 210 and 150); the median duration for all other pharmacotherapy classes, both oral and nonoral, was equal or shorter compared to SSRIs (with the exception of nonoral prazosin) (Figure 7). The median quantity for oral SSRIs was 45, which was less than or equal to all other pharmacotherapies except mirtazapine, which had a quantity of 30 (Figure 8).

For the distribution on the use of not recommended pharmacotherapies in the cohort with PTSD, 7.53% of veterans received atypical antipsychotics, 7.07% received benzodiazepines, 6.95% received opioids, and 0.34% received conventional antipsychotics; the respective median number of distinct treatments for all classes was 1 (Table 10). In Figure 6, the median number of fills for benzodiazepines was 9; the respective median number of fills for conventional antipsychotics, atypical antipsychotics, and opioids was 7, 8, and 13. In Figure 7, the median duration for oral and nonoral benzodiazepines was 90 days, with a large variation (respective interquartile range is both

150). The median duration for all other pharmacotherapy classes, both oral and nonoral, was equal or shorter compared to benzodiazepines. As shown in Figure 8, the median quantity for benzodiazepines was 60, which was greater than or equal to all other pharmacotherapies except opioids, which had a quantity of 100.

Inpatient Pharmacotherapy Exposure

A total of 306,166 veterans with PTSD had at least one inpatient encounter, with a median length of 4 days and an IQR of 6 (Table 11). As shown in Figure 9, the total number of veterans who received benzodiazepines for at least 30 days was 15,260 (1.34% of total cohort); the median duration of benzodiazepine exposure is 55 days. The overall distribution of inpatient treatment percentages ranged from 0.027% (nefazodone) to 2.64% (opioids); median duration ranged from 49 days (tricyclic antidepressants) to 61 days (atypical antipsychotics).

Distribution of First or Second Therapies in Cohort with PTSD

In the cohort of veterans with PTSD, 63.41% received a first or second psychotherapy/pharmacotherapy within one year after PTSD diagnosis (Table 12, Figure 10). In this group, 37.32% of veterans received psychotherapy, 17.08% received SSRIs, 6.16% received opioids, 4.14% received atypical antipsychotics, and 4.01% received benzodiazepines.

Approximately 49.6% of veterans received either only one psychotherapy or pharmacotherapy and nothing else within 30 days of their first therapy (Table 13). In this subgroup, 25.84% of veterans received psychotherapy, 11.44% received SSRIs, 4.50%

received opioids, 2.53% received benzodiazepines, and 2.48% received atypical antipsychotics.

Approximately 13.77% of veterans received a second (overlapping) psychotherapy/pharmacotherapy within 30 days of their first therapy (Table 14). In this subgroup, 11.48% of veterans received psychotherapy, 5.63% received SSRIs, 1.67% received opioids, 1.66% received atypical antipsychotics, and 1.47% received benzodiazepines.

Most Frequent Overlapping Therapies in Cohort with PTSD

The most frequent overlapping therapies in the cohort with PTSD included psychotherapies, psychotherapy/SSRI, SSRI/prazosin, SSRI/atypical antipsychotics, and SSRI/benzodiazepines; the percentage of veterans who received these respective combinations are 4.39%, 3.11%, 0.64%, 0.52%, and 0.49% (Table 15, Figure 11). The majority of combinations include two psychotherapies and all combinations included either one psychotherapy or one SSRI.

Objective 2 Results

The results of this section describe the cohort with PTSD before and after propensity score matching and the models used to analyze health care utilization. The health care utilization incidence rate ratios and incidence rate differences between benzodiazepine users and nonbenzodiazepine users are then reported.

Propensity Score Matching

Before propensity score matching, there were 80,832 benzodiazepine users and 1,053,369 nonbenzodiazepine users (Figure 12). After 1:2 matching, 891,705 patients have been excluded; the final propensity score matched cohort consists of 242,493 veterans, with 80,831 benzodiazepine users and 161,662 non-benzodiazepine users. In the propensity score model, all variables were represented through dummy coding (0 or 1).

A histogram of the distribution of the propensity scores before and after matching shows that the mean (0.0796), median (0.0695), mode (0.080), and maximum (0.287) are now the same (Figure 13, Figure 14). As shown in Table 16, before propensity score matching, chi-square tests for confounders and risk factors between the benzodiazepine and non-benzodiazepine users indicated significant differences in almost all of these variables. However, after matching, in Table 17, the number of variables with a statistically significant difference between them has decreased; although the chi-square test results indicate that some differences remain, none of these differences are clinically meaningful. Furthermore, as shown in Table 18, all of the standardized differences have decreased after propensity score matching. Before matching, the (dummy) variables male, divorced, single, separated, widowed/widower, unknown marital status, white, medium service percentage disabilities, high service percentage disabilities, age 0-29, age 30-39, age 50-59, age 60+, and homeless all had standardized differences greater than 0.1. A plot of the standardized differences (Figure 15) before matching reveals that three variables have a very high standardized difference: medium service percentage disabilities (0.337), high service percentage disabilities (0.432), and homeless (0.294). In Figure 16, after matching, the standardized differences for all of the variables have

decreased, approaching zero for all of them.

Model Selection

The health care utilization outcomes are hospitalizations, emergency department (ED) visits, general outpatient visits, mental health outpatient visits, substance abuse outpatient visits, and total mental health outpatient visits (sum of mental health outpatient visits and substance abuse outpatient visits). Modified Park test coefficients indicated that the suggested distributions are either Poisson or Gamma (Table 19). The histogram for ED visits is skewed to the right due to the large proportion of zeroes (62.4%). Thus, a Gamma distribution was be used to model this outcome; it was modeled with a Poisson regression. However, as shown in Table 20, the scaled Deviance and scaled Pearson values for ED visits are 5.40 and 12.40. Thus, in order to account for this overdispersion (variance>mean), a negative binomial model was used for ED visits.

There is overdispersion present in general outpatient, mental health outpatient, substance abuse outpatient, and total mental health outpatient visits because the respective scaled Deviance and scaled Pearson values are 23.75, 35.43; 40.87, 163.99; 23.59, 148.88; 52.94, 182.31 (Table 20). Thus, a negative binomial model was used for these distributions. Finally, a Poisson model was used to model hospitalizations because overdispersion is not present in that distribution; the scaled Deviance and scaled Pearson values are 0.21 and 2.08.

Due to the presence of a large number of zeroes in all of the outcomes, a Vuong test was run to determine whether a zero-inflated negative binomial/Poisson or standard negative binomial/Poisson model is preferred (Table 21). The significant p-values

indicate that a zero-inflated negative binomial model should be used for general outpatient, mental health outpatient, substance abuse outpatient, and total mental health outpatient visits while a nonsignificant p-value indicates that a standard negative binomial model should be used for ED visits; a significant p-value indicates that a zero-inflated Poisson model should be used for hospitalizations (Table 22).

IRRs and IRDs for Health Care Visits

The health care utilization incidence rate ratios (IRR) and incidence rate differences (IRD) are all statistically significant between veterans who receive benzodiazepines and those who do not receive benzodiazepines except for substance abuse outpatient visits (Table 23, Figure 17). The IRRs are all higher for benzodiazepine users; this includes inpatient hospitalizations (1.27), ED visits (1.16), general nonmental health outpatient visits (1.18), total mental health outpatient visits (1.37), and mental health outpatient visits (1.48). An IRR of 1.2718 means that benzodiazepine users have 27.18% more hospitalizations than nonbenzodiazepine users over a six-year time period. The respective IRDs are all higher for benzodiazepine users; this includes inpatient hospitalizations (0.02), ED visits (0.27), general outpatient visits (3.48), total mental health outpatient visits (5.75), and mental health outpatient visits (5.47). An IRD of 0.0271 means that benzodiazepine users have on average 0.0271 additional hospitalizations than nonbenzodiazepine users over a six-year time period. Although the IRR (1.07) and IRD (0.27) are higher for benzodiazepine users, the p-values are not significant for either (respective values of 0.074 and 0.069). Thus, there is not a statistically significant difference between veterans who receive benzodiazepines and

those who not receive benzodiazepines for substance abuse outpatient visits.

Objective 3 Results

The results of this section report counts and hazard ratios for the suicide behavior outcomes using ICD-9 codes, note titles, and the Suicide Data Repository. The suicide outcomes were analyzed through the Suicide Data Repository, ICD-9 codes, and Suicide Note Titles. Cox proportional hazards regression was used to analyze the various suicide outcomes. As shown in Figures 18, 19, 20, 21, 22, 23, 24, and 25, plots of the Schoenfeld residuals against time indicate that residuals for the benzodiazepine group and non-benzodiazepine group are parallel and do not cross for almost all of the suicide outcomes. Thus, the proportional hazards assumption of the Cox model is not violated. For suicide and self-inflicted injury using note titles, the Schoenfeld residuals for the two groups only cross at the very end; furthermore, it the number of suicide events are low, 24 for veterans who receive benzodiazepines and 22 for patients who do not receive benzodiazepines. A Cox model will still be used to model this suicide outcome. The hazard rate ratios and 95% confidence intervals for all of the suicide outcomes are presented in Figure 26.

Suicide Defined Through the Suicide Data Repository

Using the Suicide Data Repository, there were all-cause death counts for 26,841 (11.06%) patients in the entire cohort (Table 24). The all-cause mortality hazard ratio between benzodiazepine users and non-benzodiazepine users is 1.86 (Table 25). The suicide mortality counts for benzodiazepine users are 456 (3.68%) and for

nonbenzodiazepine users are 349 (2.41%) (Table 24). The suicide mortality hazard ratio is 2.73 (Table 25). The VA Clinical Practice Guidelines for PTSD were implemented in 2010. The percentage of benzodiazepine users who had suicide as cause of death before and after 2010 is 1.70% and 1.97%; the respective percentages for non-benzodiazepine users are 0.81% and 1.60% (Table 24). As shown in Table 25, in the Cox model adjusted for 2010, the suicide mortality hazard ratio is now 2.33.

Suicide Behavior Defined Through ICD-9 Codes

As shown in Table 26, using ICD-9 codes, 6.45% of veterans who received benzodiazepines and 4.45% of veterans who do not receive benzodiazepines exhibited suicide behavior. Of patients who received benzodiazepines, 5.65% exhibited suicidal thoughts or ideation, and 1.74% had a self-inflicted injury or attempted suicide; of patients who did not receive benzodiazepines, 4.05% exhibited suicidal thoughts or ideation, and 0.99% had a self-inflicted injury or attempted suicide (Table 26). The hazard ratio between benzodiazepine users and non-benzodiazepine users is 1.56 for suicide behavior, 1.51 for suicide thoughts/ideation, and 1.84 for suicide/self-inflicted injury (Table 27).

Suicide Behavior Defined Through Note Titles

As shown in Table 28, using note titles, 2.17% of benzodiazepine users and 1.13% of nonbenzodiazepine users exhibited suicide behavior. Of patients who received benzodiazepines, 2.14% exhibited suicidal thoughts or ideation, and 0.03% had a self-inflicted injury or attempted suicide; of patients who did not receive benzodiazepines,

1.12% exhibited suicidal thoughts or ideation, and 0.01% had a self-inflicted injury or attempted suicide (Table 28). The hazard ratio between benzodiazepine users and non-benzodiazepine users is 1.97 for suicide behavior, 1.96 for suicide thoughts/ideation, and 2.27 for suicide/self-inflicted injury (Table 29).

In 2008, suicide behavior note titles began to be implemented as "Suicide Behavior Reports." However, this was not consistently implemented at many VA facilities because notes with other titles are still used. As shown in Table 30, 0.64% of benzodiazepine users and 0.47% of nonbenzodiazepine users had a note title for suicide behavior before 2008. Of patients who received benzodiazepines, 0.63% exhibited suicidal thoughts or ideation, and 0.01% had a self-inflicted injury or attempted suicide; of patients who did not receive benzodiazepines, 0.46% exhibited suicidal thoughts or ideation, and 0.01% had a self-inflicted injury or attempted suicide (Table 30). Approximately 1.53% of benzodiazepine users and 0.67% of nonbenzodiazepine users had a note title for suicide behavior after 2008. Of patients who received benzodiazepines, 1.51% exhibited suicidal thoughts or ideation, and 0.02% had a self-inflicted injury or attempted suicide; of patients who did not receive benzodiazepines, 0.66% exhibited suicidal thoughts or ideation, and 0.01% had a self-inflicted injury or attempted suicide (Table 30). As shown in Table 31, in the Cox model adjusted for 2008, the respective the hazard ratio between benzodiazepine users and nonbenzodiazepine users is 1.84 for suicide behavior, 1.83 for suicide thoughts/ideation, and 2.10 for suicide/self-inflicted injury (Table 31). Median survival times are presented in Table 32 for benzodiazepine users and nonbenzodiazepine users for all of the suicide outcomes. All median survival times were significantly lower for benzodiazepine users than non-

users (log-rank test p-value<0.0001).

ICD-9 Codes or Note Titles

Kappa statistics were used to evaluate agreement between ICD-9 codes and note titles. The kappa statistic is 0.2069 for suicide behavior, 0.1967 for suicide thoughts and ideation, and 0.0042 for suicide and self-inflicted injury. The kappa values indicated only slight agreement between the ICD-9 codes and note titles. Thus, ICD-9 codes and note titles were not combined into a composite outcome.

As shown in Table 33, using ICD-9 codes or note titles, 7.51% of benzodiazepine users and 5.03% of nonbenzodiazepine users exhibited suicide behavior. Of patients who received benzodiazepines, 6.82% exhibited suicidal thoughts or ideation, and 1.77% had a self-inflicted injury or attempted suicide; of patients who did not receive benzodiazepines, 4.69% exhibited suicidal thoughts or ideation, and 1.01% had a self-inflicted injury or attempted suicide (Table 33). The hazard ratio between benzodiazepine users and non-benzodiazepine users is 1.60 for suicide behavior, 1.57 for suicide thoughts/ideation, and 1.85 for suicide/self-inflicted injury (Table 34).

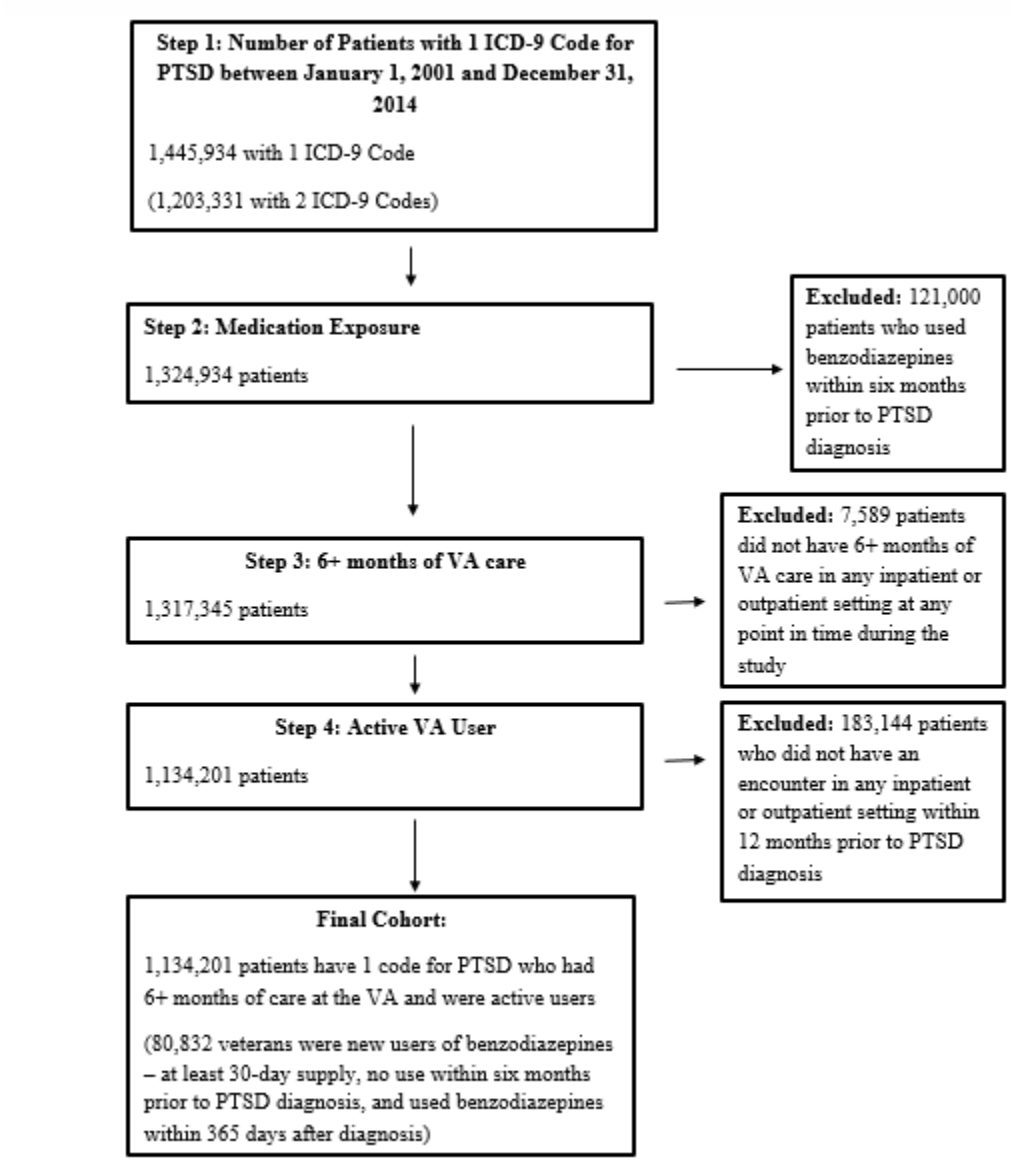

Figure 3. PTSD Cohort Flow Chart

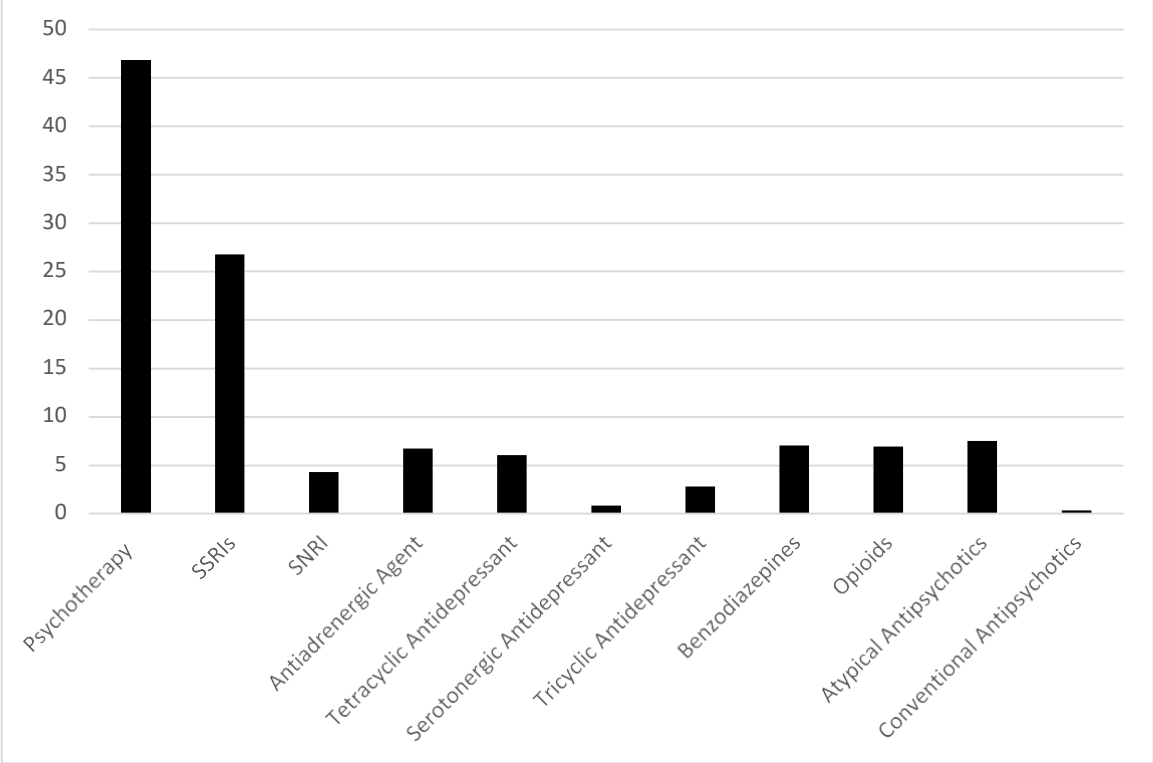

Figure 4. Percentage Overall Use of Psychotherapies and Pharmacotherapies for Veterans with PTSD (*n*=1,134,201)

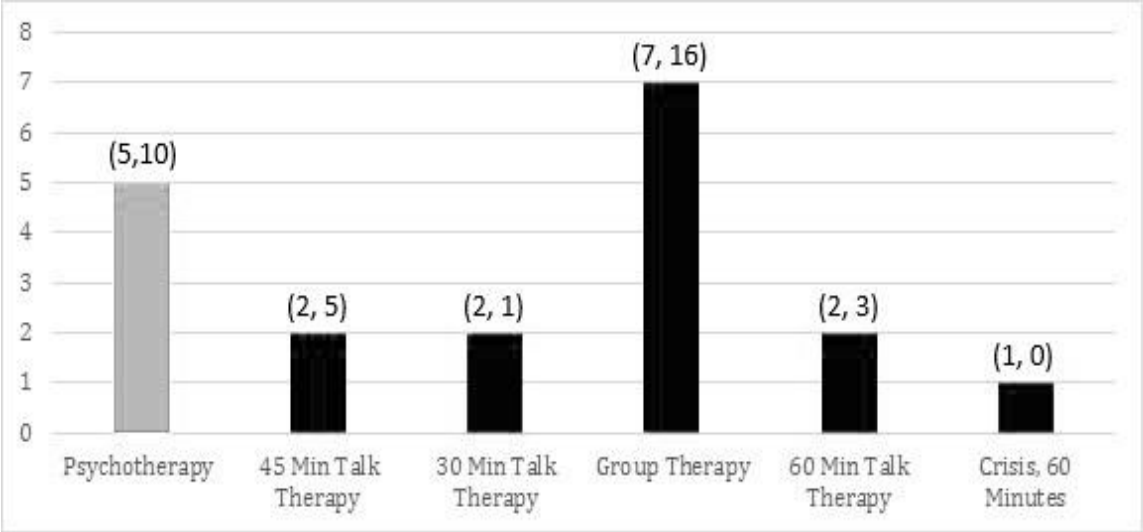

Figure 5. Median Number and IQR of Behavioral Health Sessions for Veterans with PTSD

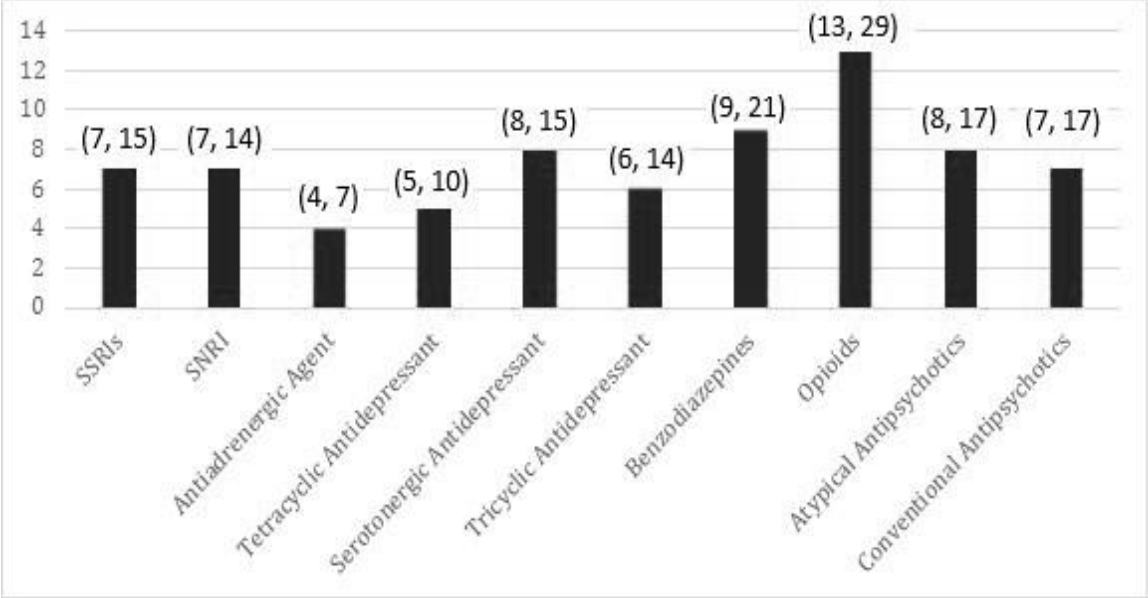

Figure 6. Median Number and IQR of Pharmacotherapy Treatment Fills Used for Veterans with PTSD

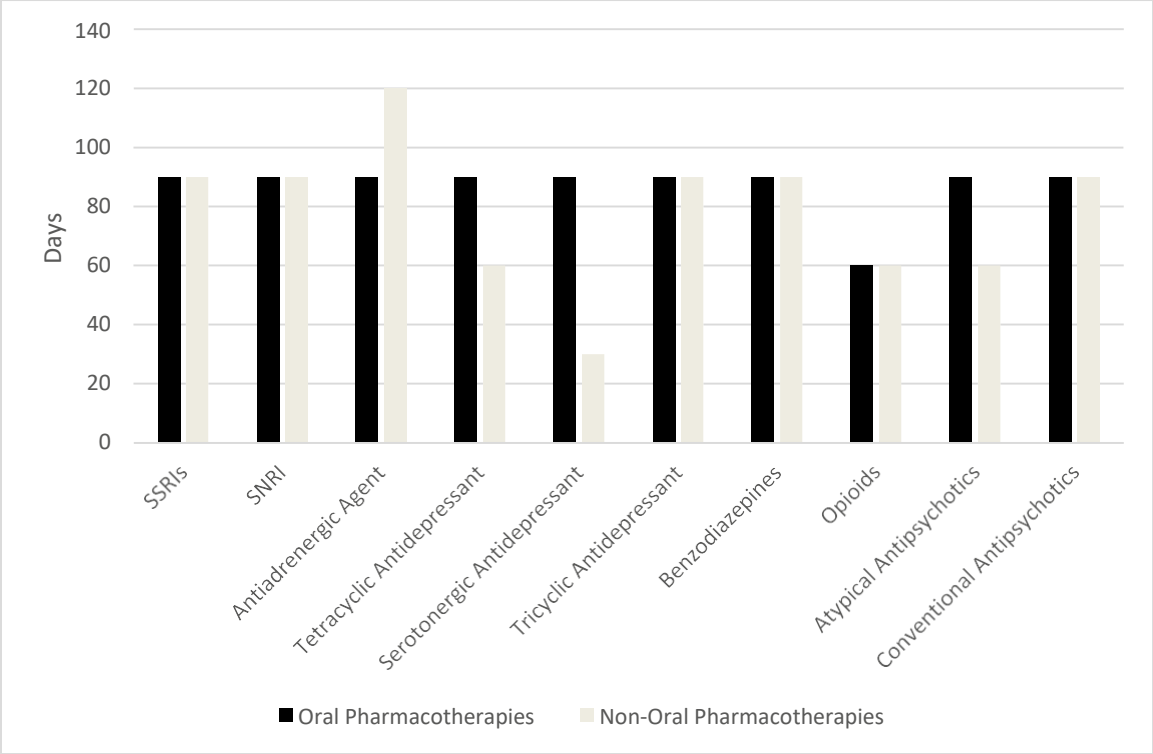

Figure 7. Median Duration for Oral and Nonoral Pharmacotherapies

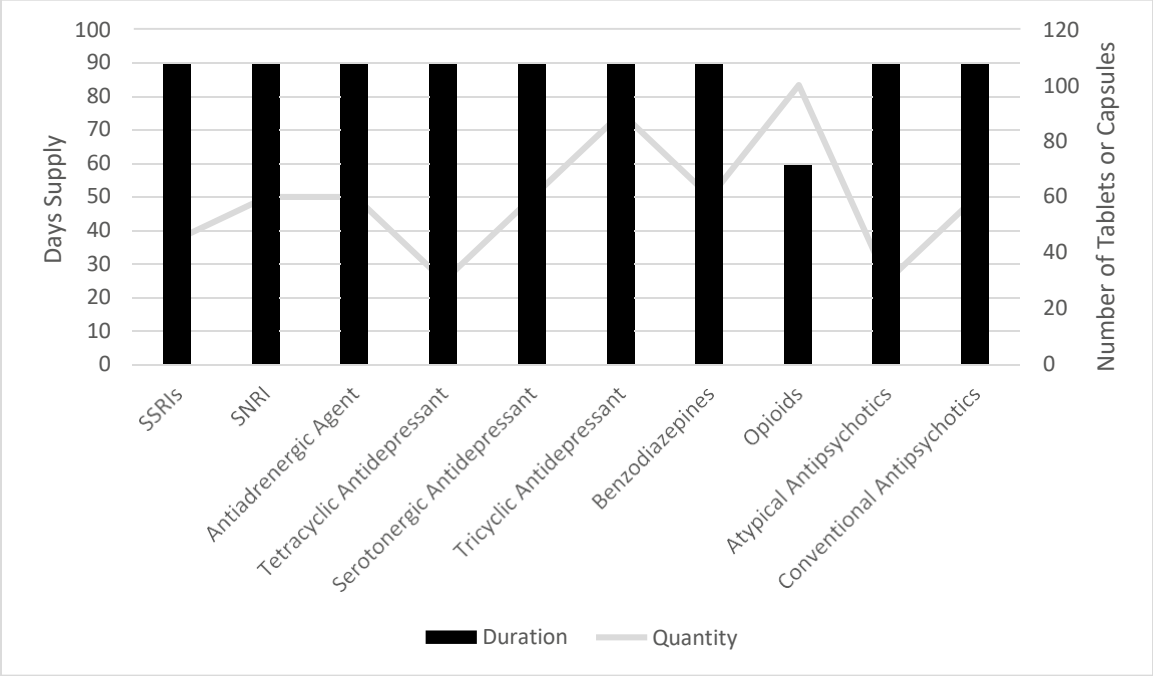

Figure 8. Median Duration and Quantity for Oral Pharmacotherapies

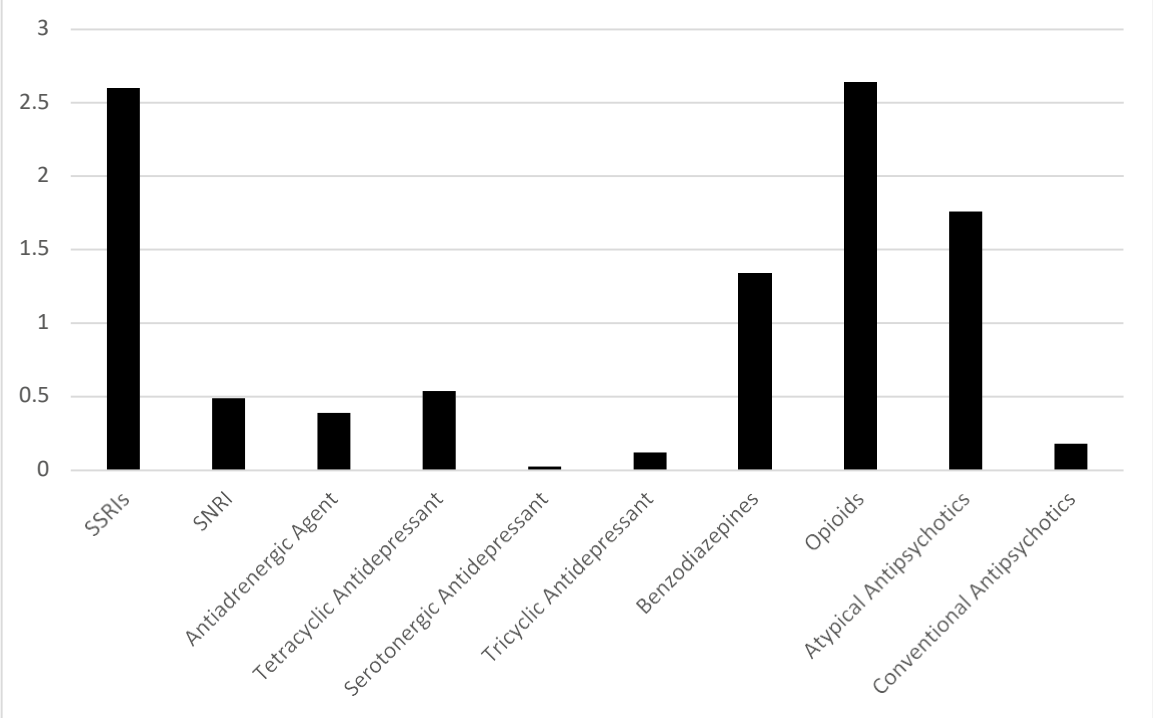

Figure 9. Percentage Use of Pharmacotherapies in the Inpatient Setting for Veterans with PTSD

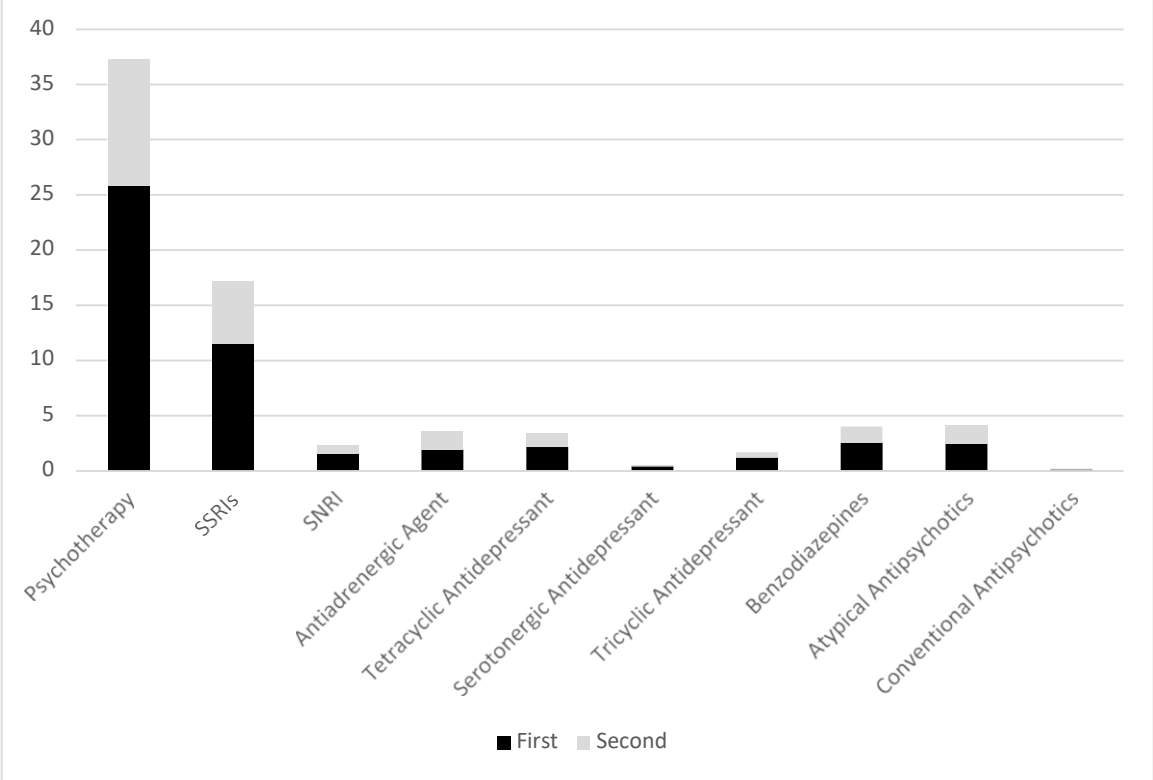

Figure 10. Percentage Use of First or Second (Overlapping) Psychotherapies and Pharmacotherapies for Veterans with PTSD (63.41%)

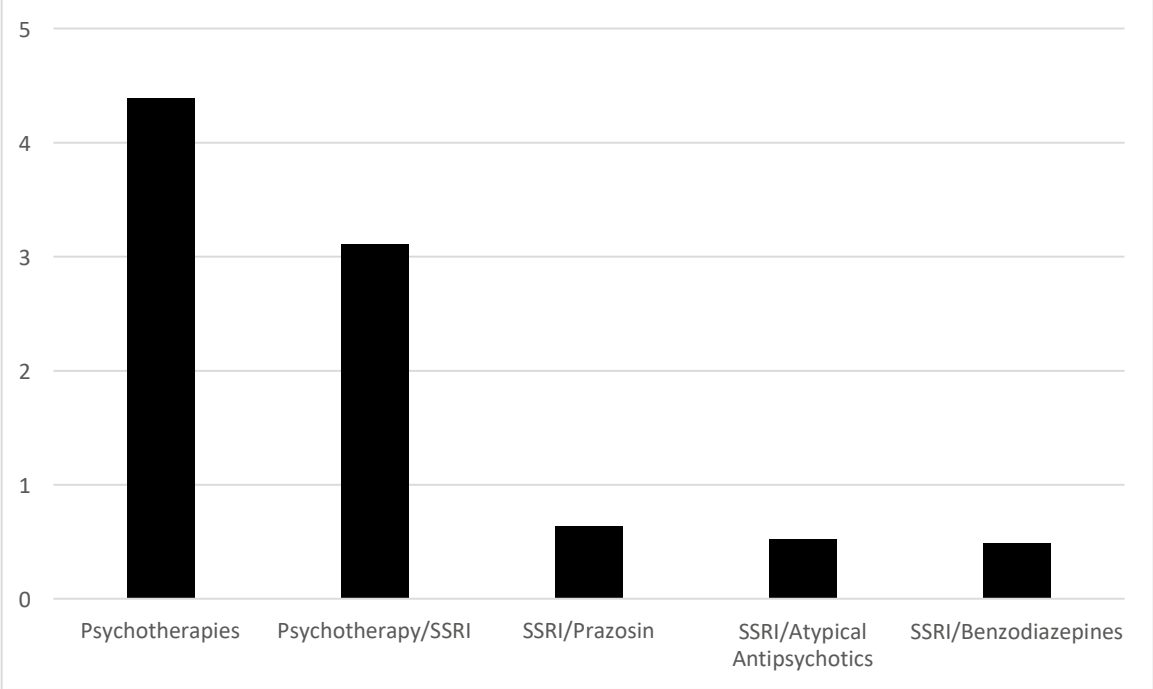

Figure 11. Percentage Use of Most Frequent Overlapping Psychotherapies and Pharmacotherapies for Veterans with PTSD (9.18%)

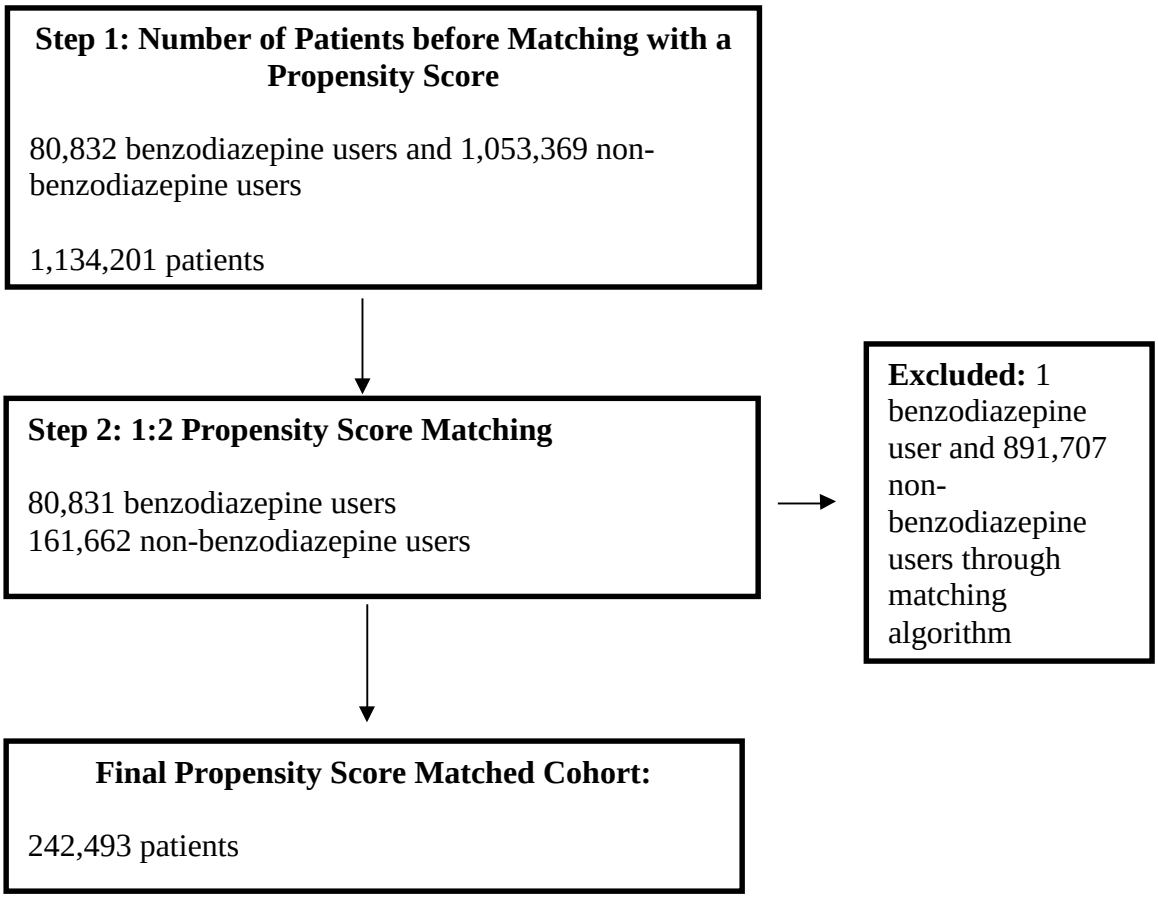

Figure 12. Propensity Score Matched Cohort Flow Chart

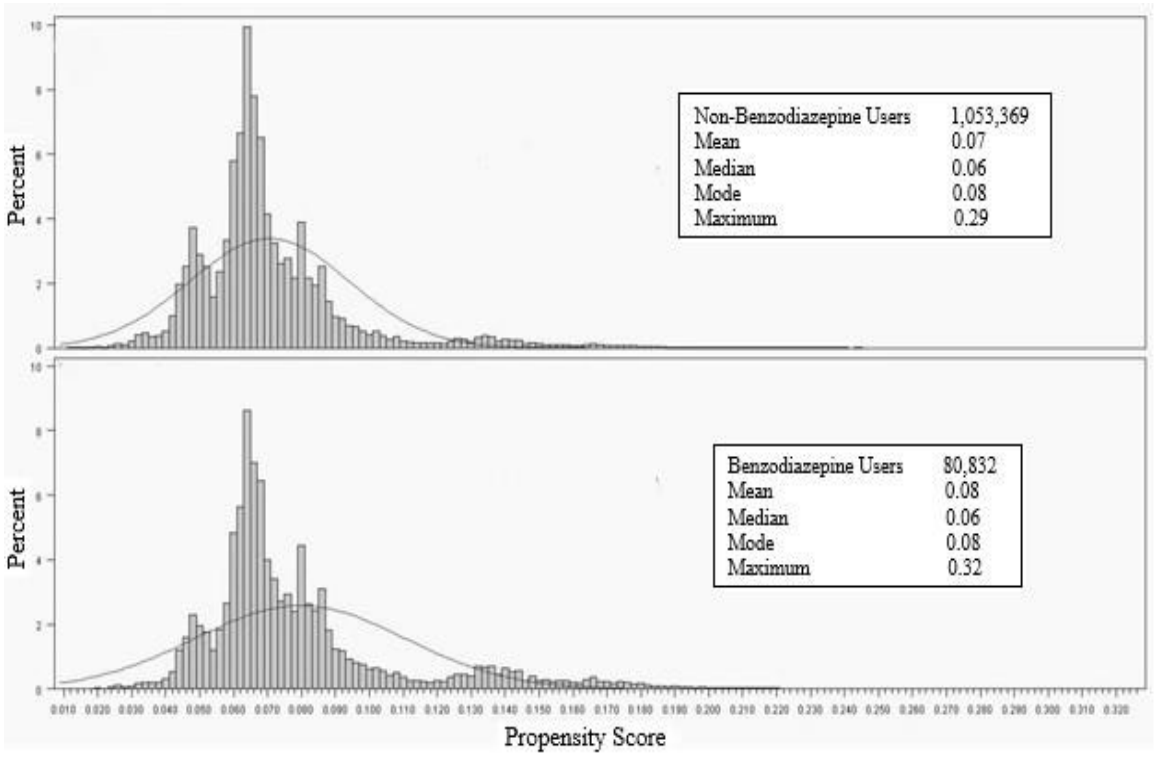

Figure 13. Distribution of Propensity Scores Before Matching

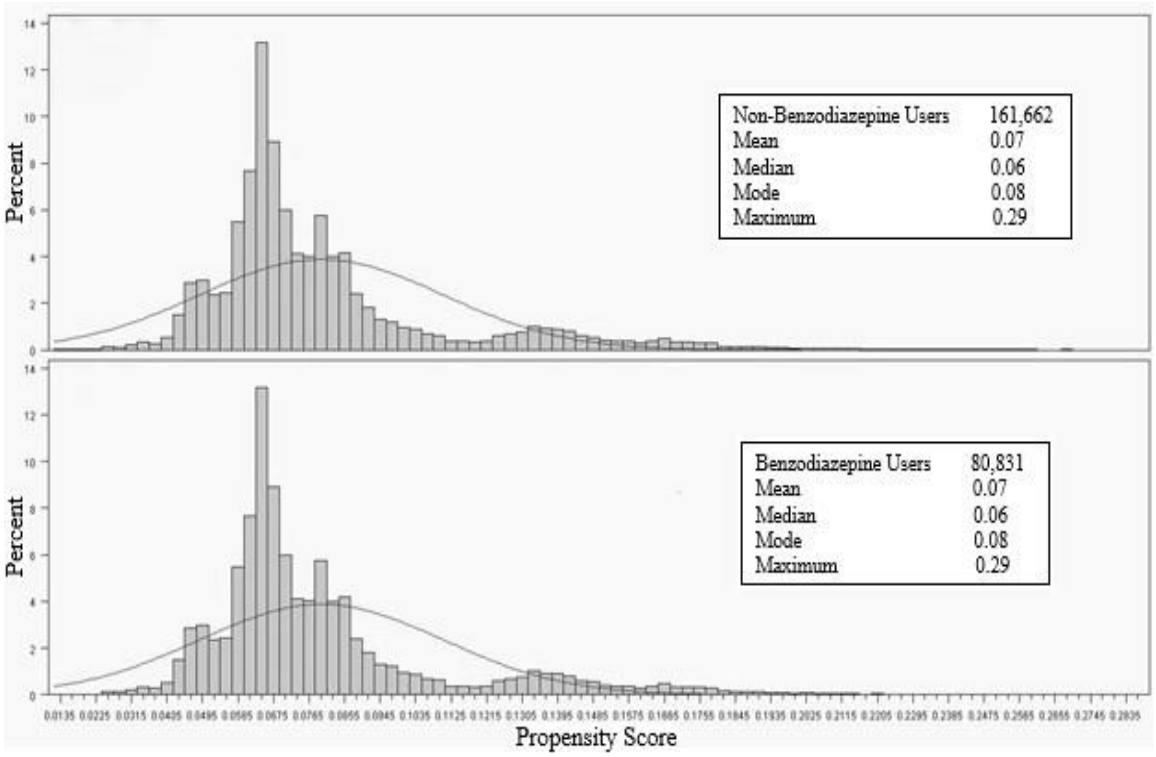

Figure 14. Distribution of Propensity Scores After Matching

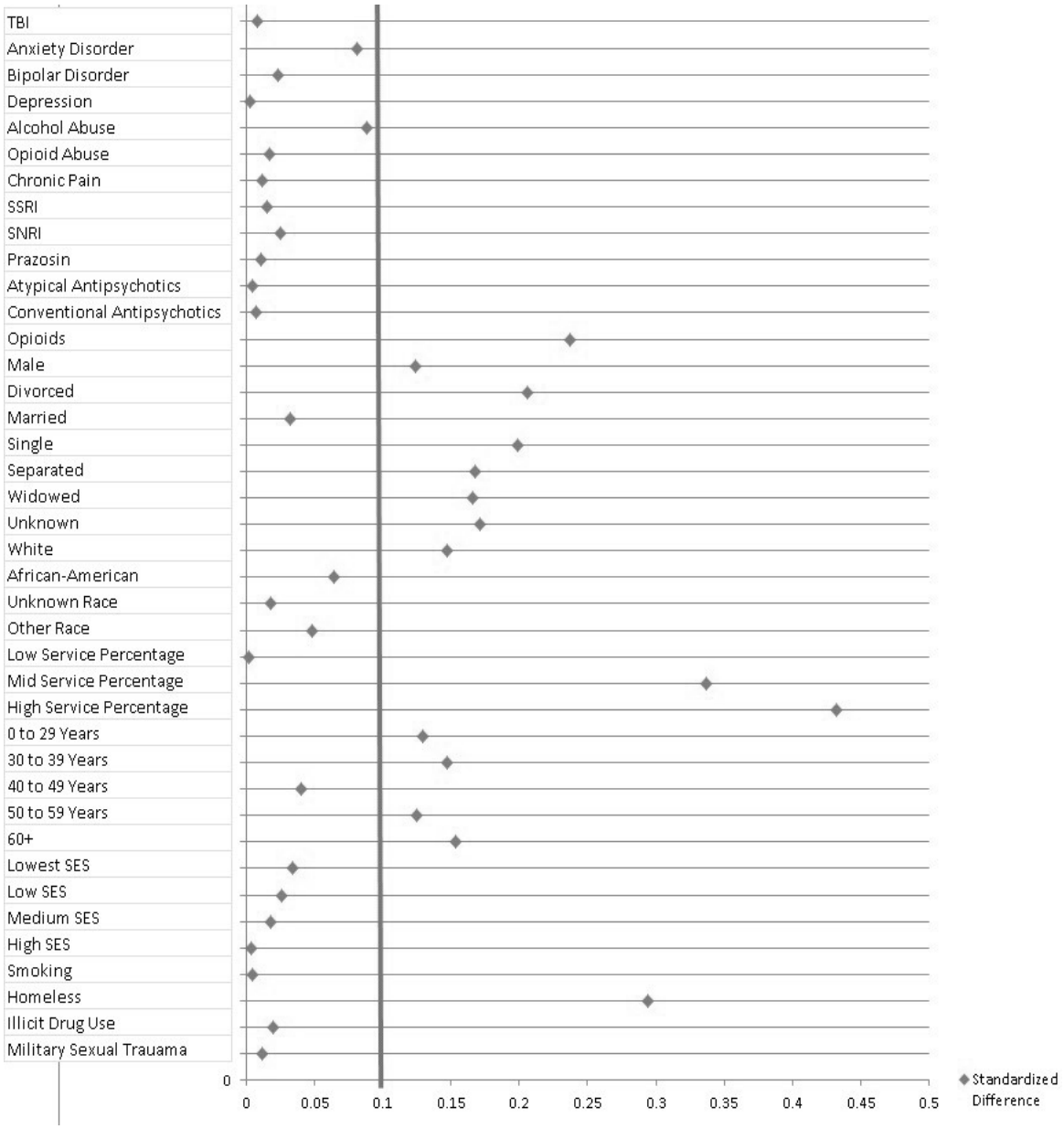

Figure 15. Standardized Differences in Confounders and Risk Factors Before Matching

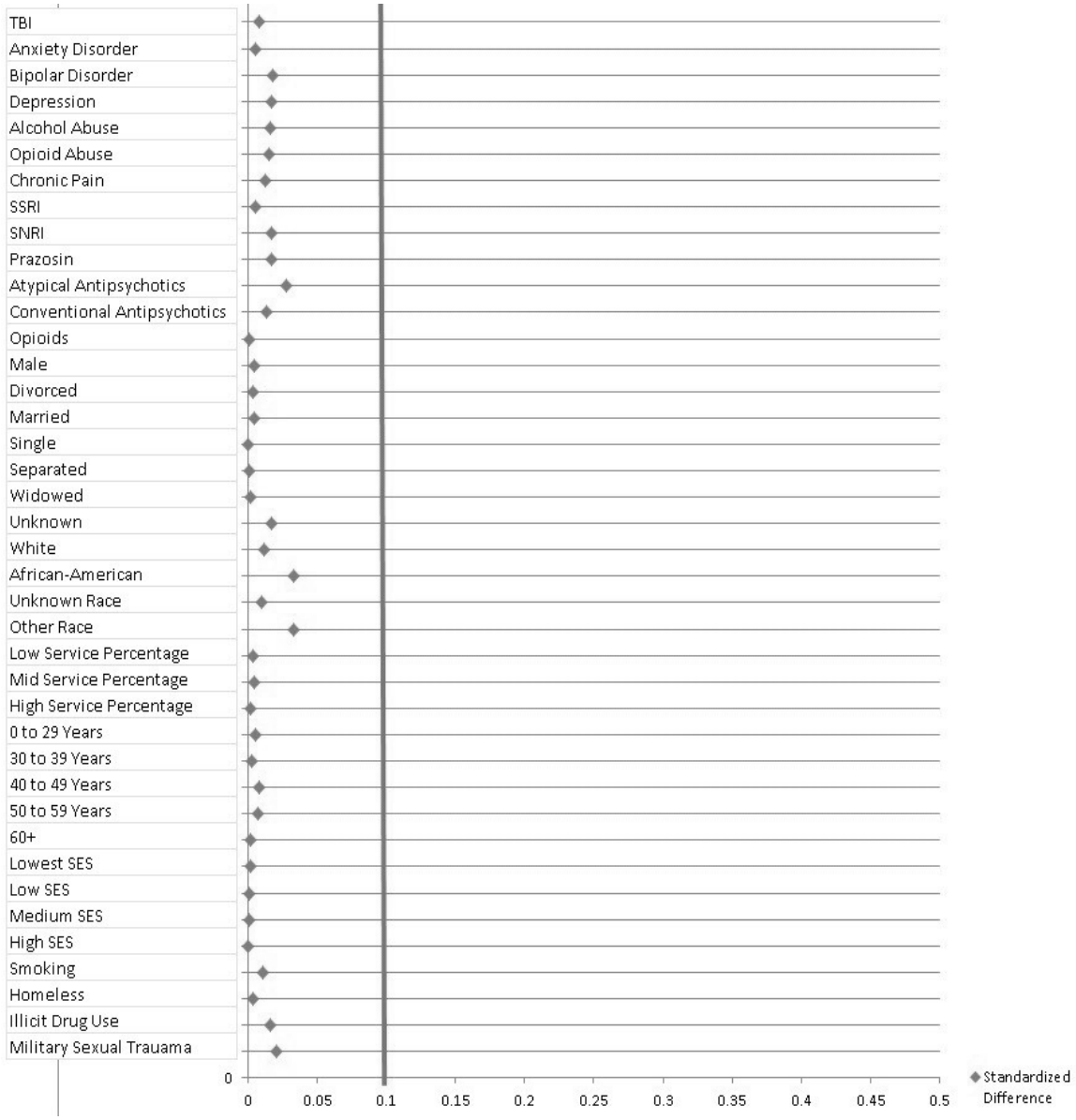

Figure 16. Standardized Differences in Confounders and Risk Factors After Matching

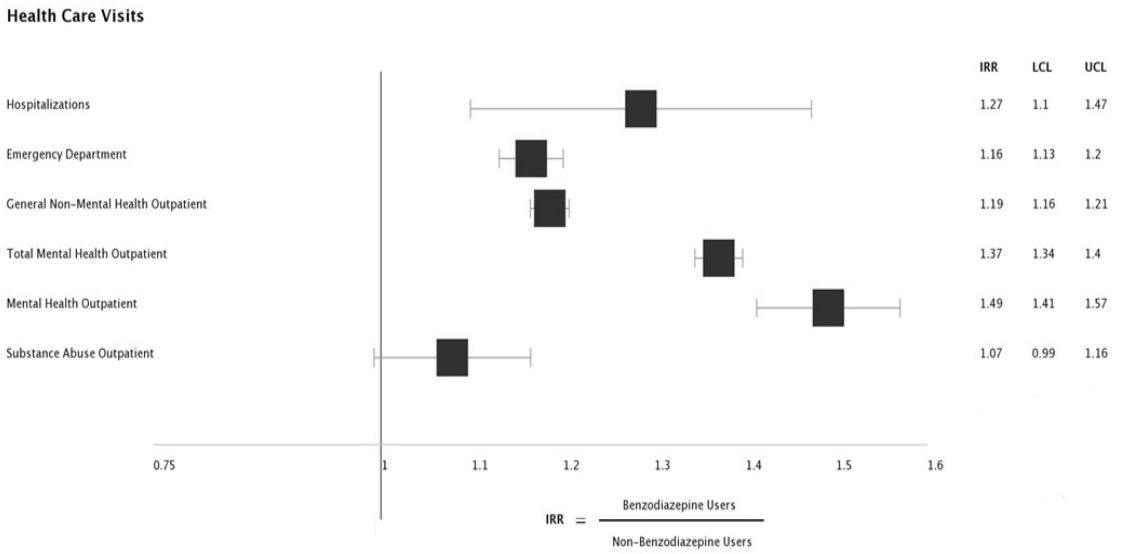

Figure 17. Health Care Utilization Incidence Rate Ratios

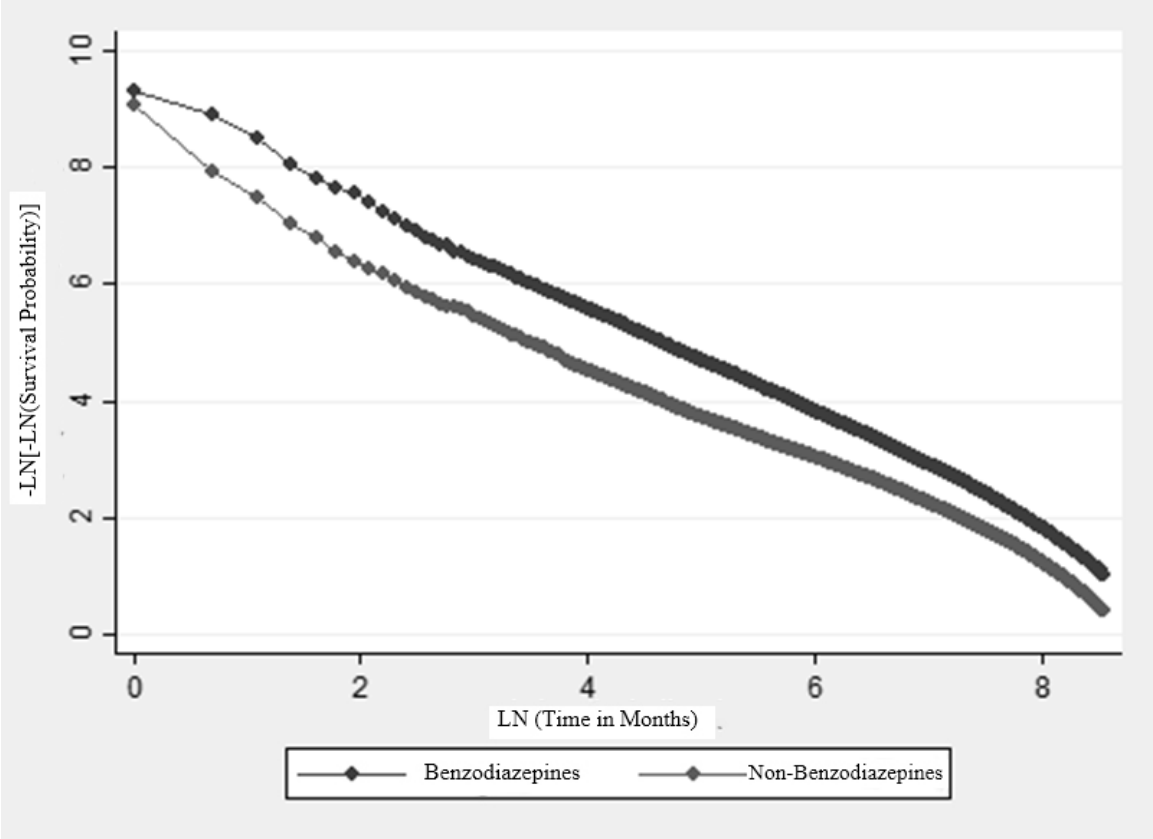

Figure 18. Schoenfeld Residuals for Overall Mortality Using the Suicide Data Repository

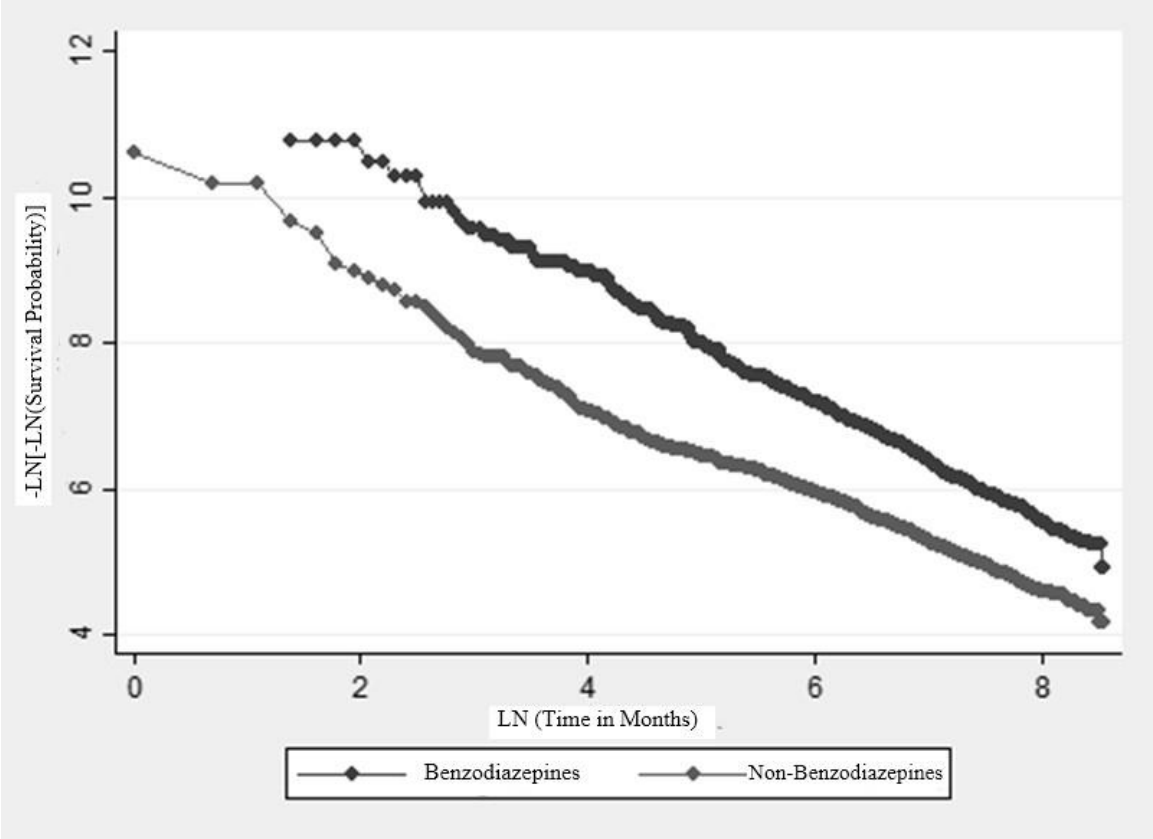

Figure 19. Schoenfeld Residuals for Suicide Mortality Using the Suicide Data Repository

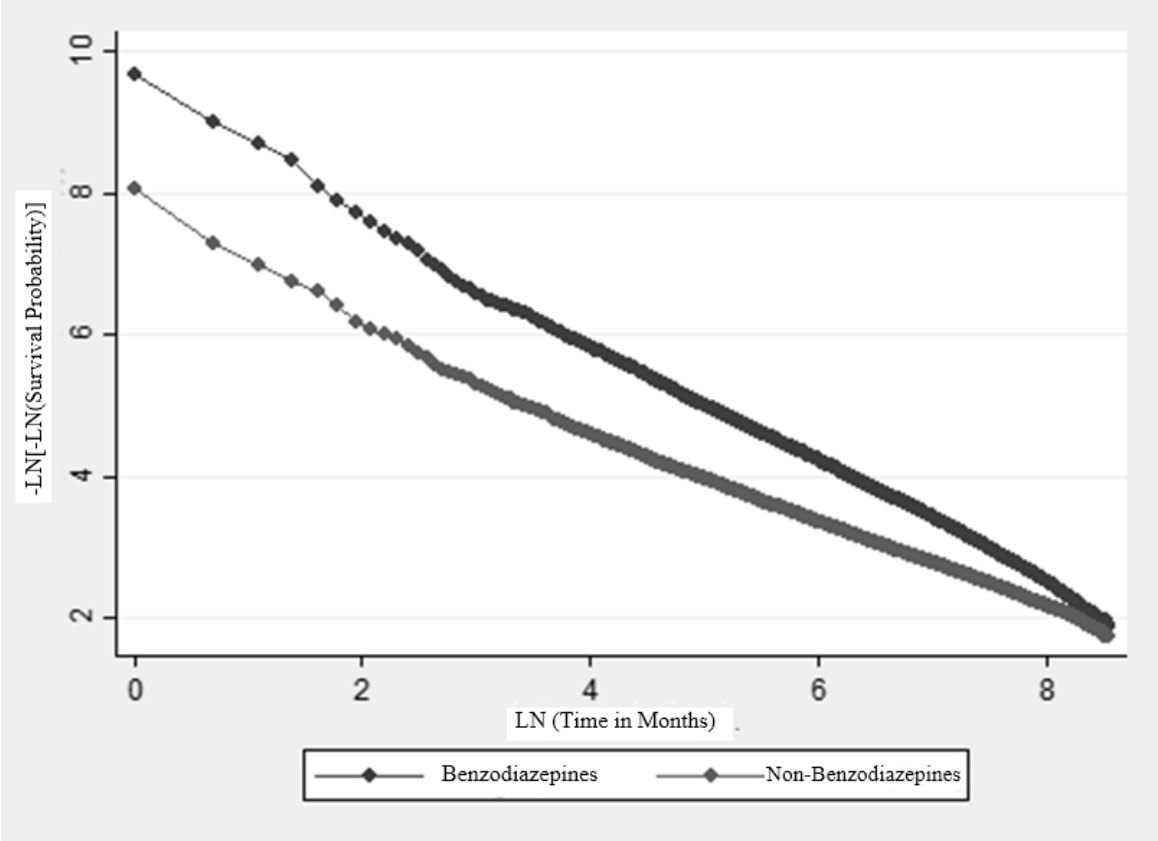

Figure 20. Schoenfeld Residuals for Suicide Behavior Using ICD-9 Codes

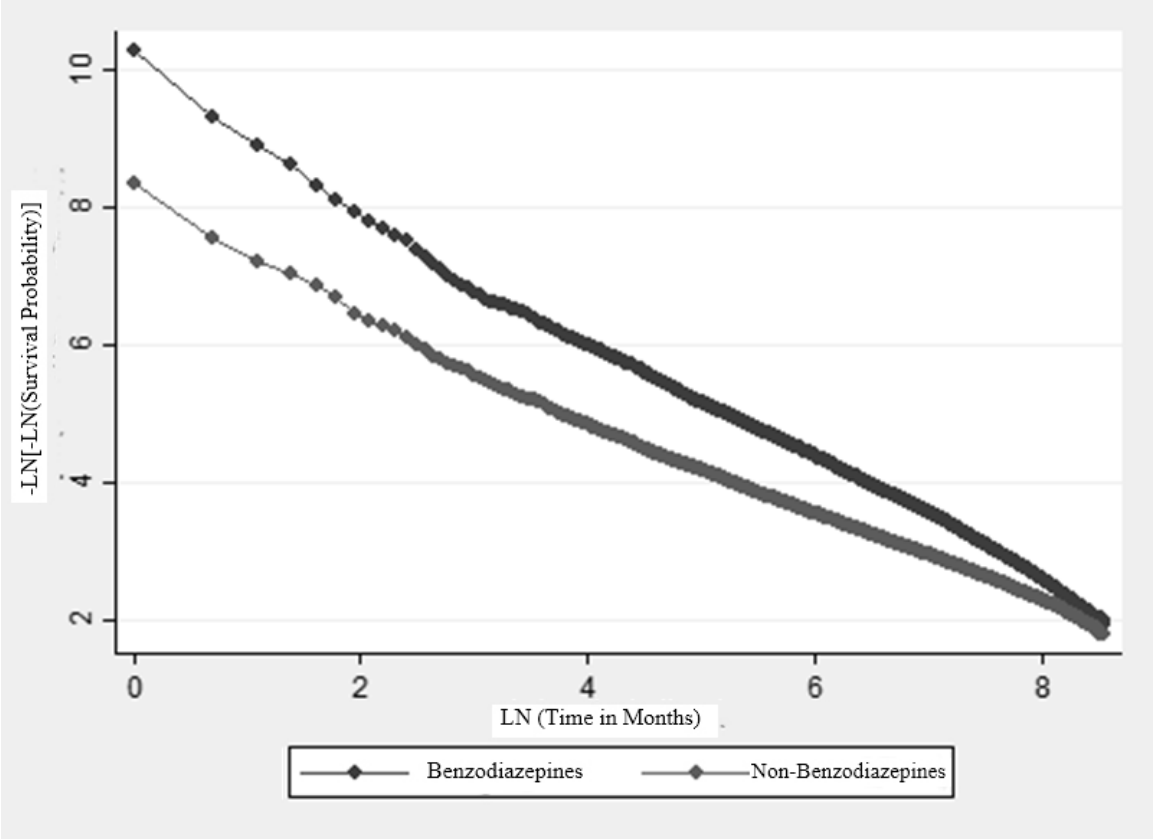

Figure 21. Schoenfeld Residuals for Suicide Thoughts Using ICD-9 Codes

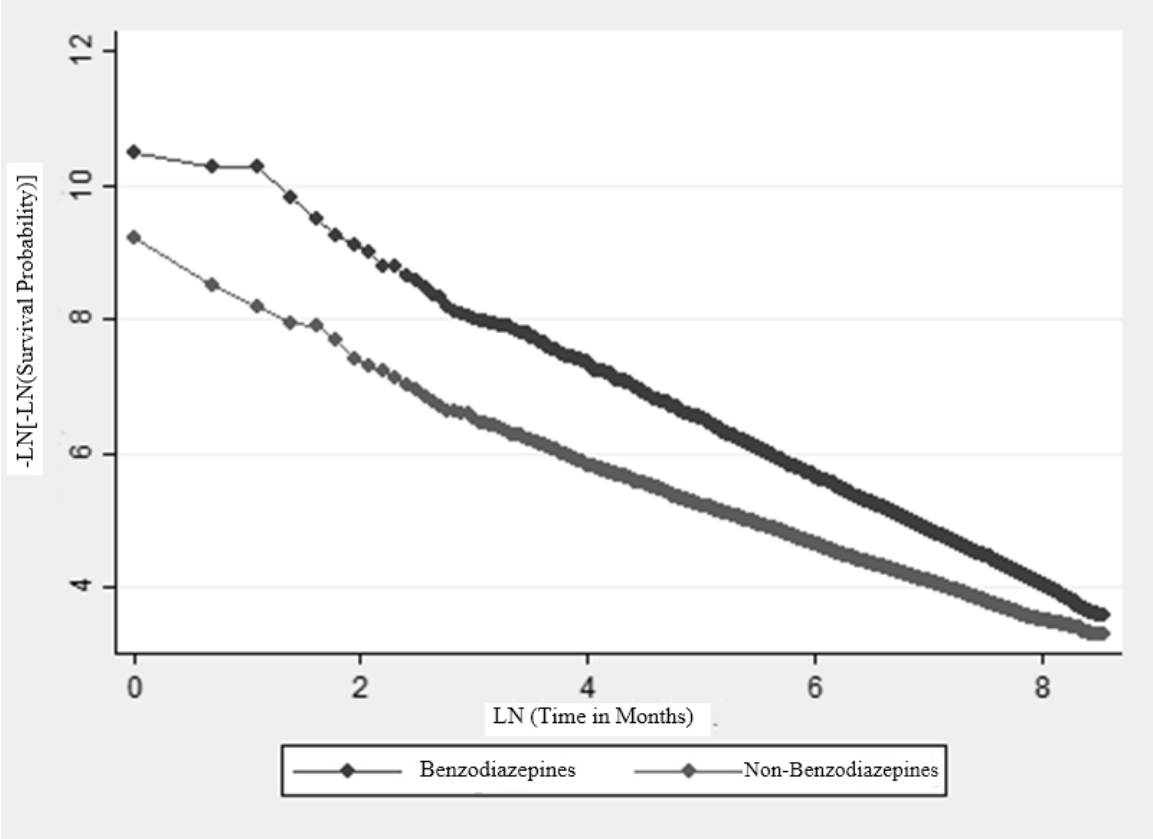

Figure 22. Schoenfeld Residuals for Suicide and Self-Inflicted Injury Using ICD-9 Codes

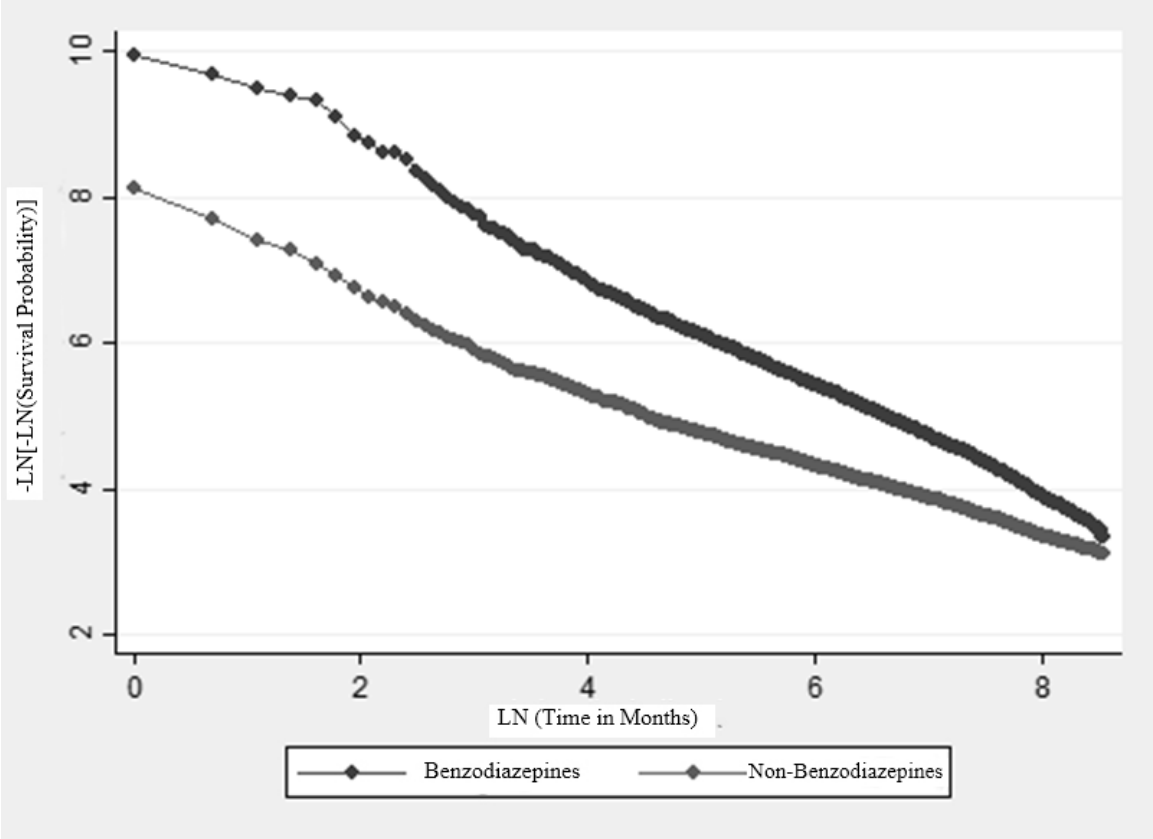

Figure 23. Schoenfeld Residuals for Suicide Behavior Using Note Titles

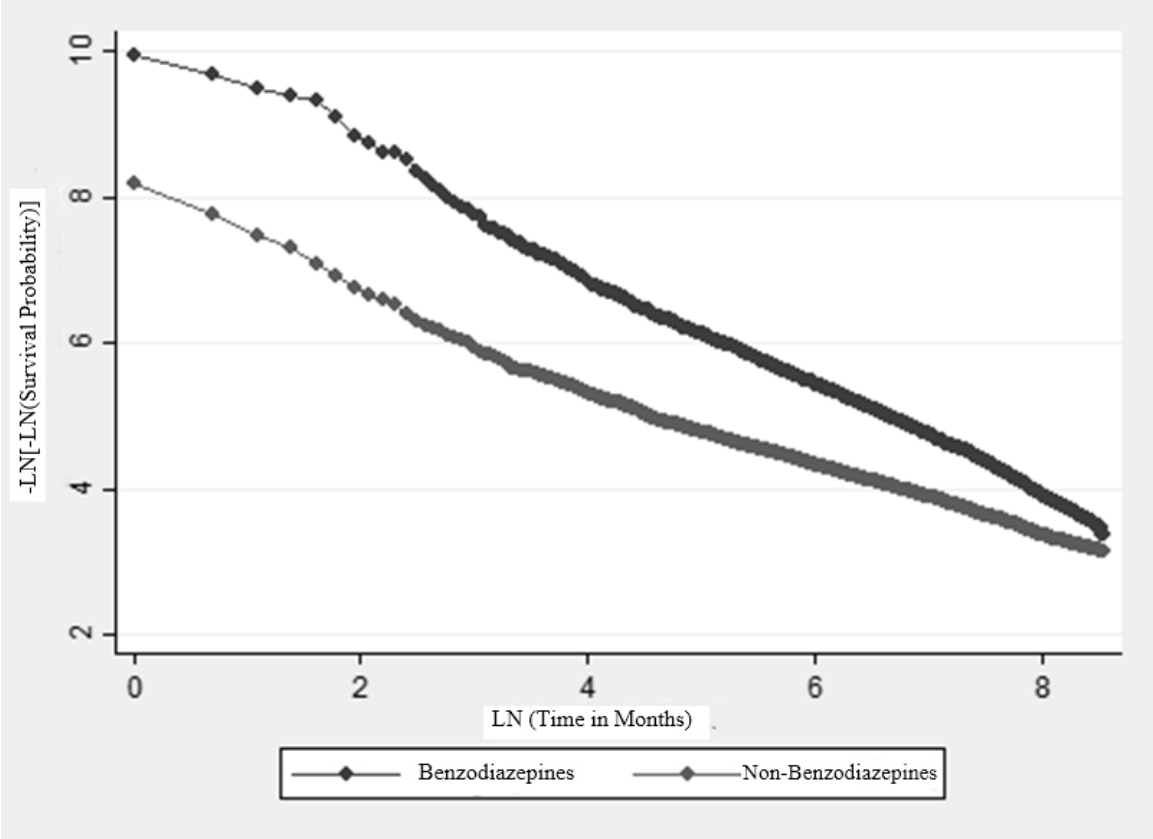

Figure 24. Schoenfeld Residuals for Suicide Thoughts Using Note Titles

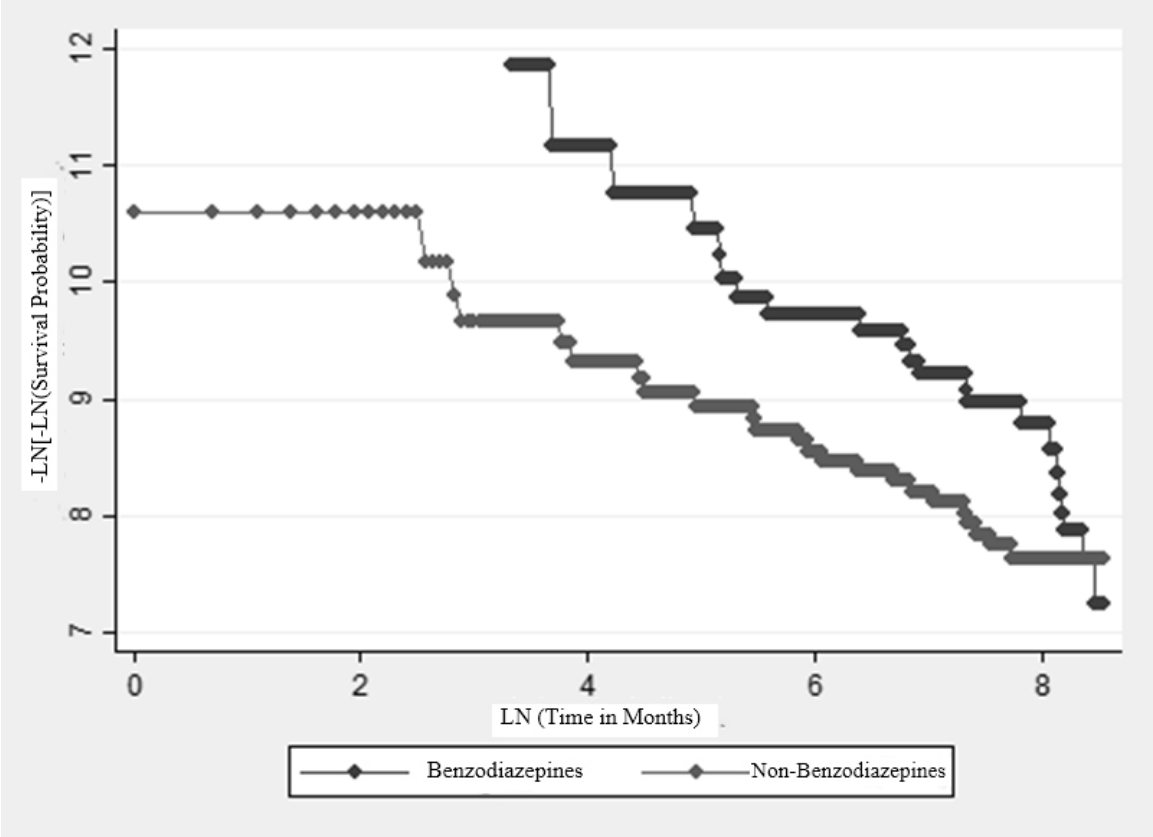

Figure 25. Schoenfeld Residuals for Suicide and Self-Inflicted Injury Using Note Titles

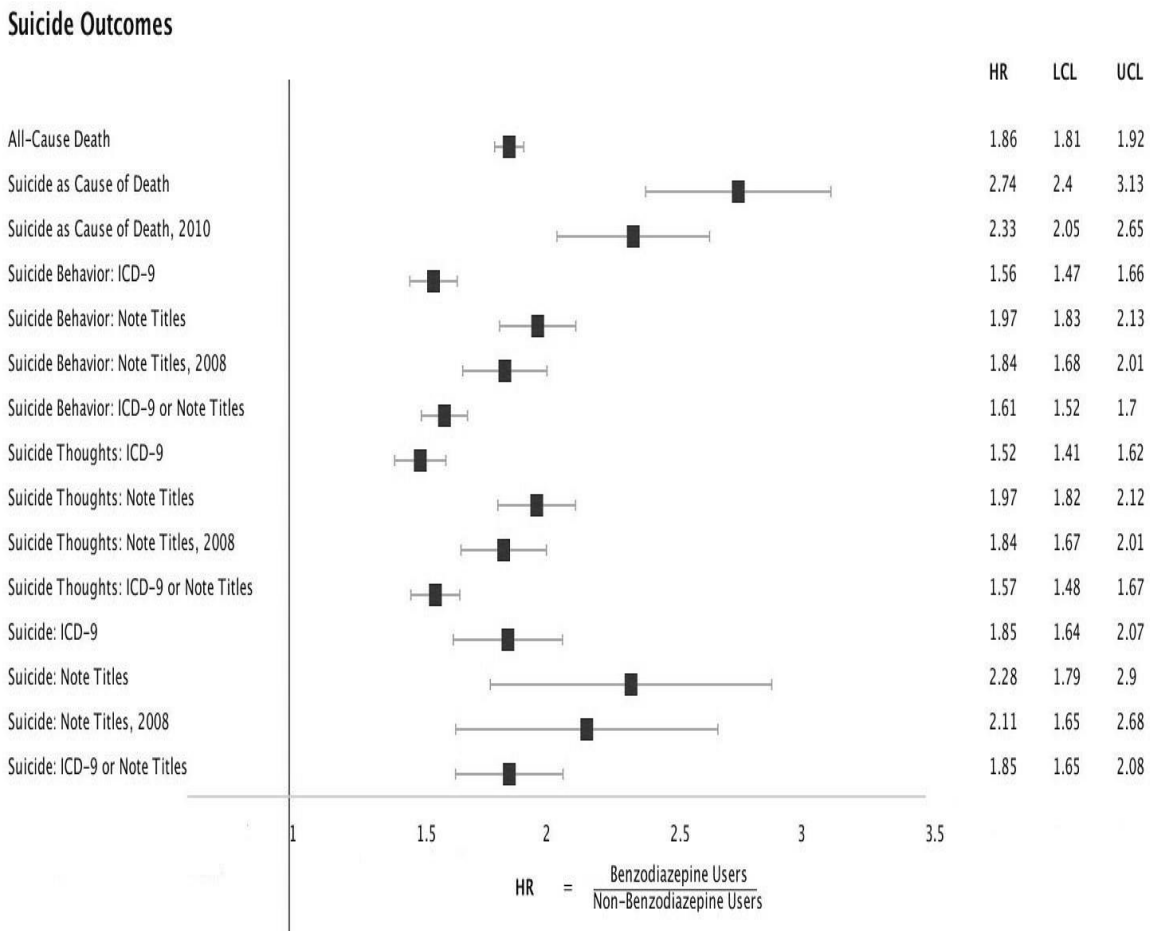

Figure 26. Suicide Outcomes Hazard Ratios

Table 8. Baseline Characteristics in Cohort with PTSD (*n*=1,134,201)*

Variable	Mean/N	SD/%
Age (Median, IQR)	53.12	23.69
Gender		
Male	1,027,908	90.60%
Female	102,660	9.05%
Unknown/Missing	3,633	0.32%
Race		
White	758,832	66.90%
Black or African-American	222,261	19.59%
Declined to Answer/Unknown/Missing	118,504	10.40%
Others	34,604	3.05%
Comorbidities		
Anxiety Disorder	152,181	13.41%
Smoking	113,904	10.04%
Depression†	100,463	8.85%
Alcohol Abuse	67,518	5.95%
Bipolar Disorder	32,719	2.89%
Chronic Pain	14,070	1.24%
Illicit Drug Use	11,415	1.01%
Military Sexual Trauma	9,525	0.83%
Homeless	7,107	0.63%
Traumatic Brain Injury	6,684	0.60%
Opioid Abuse	5,166	0.45%
Charlson Comorbidities		
Diabetes	143,474	12.64%
Chronic Pulmonary Disease	90,583	7.98%
Diabetes with Chronic Complications	28,359	2.50%
Cerebrovascular Disease	25,169	2.21%
Congestive Heart Failure	16,212	1.42%
Peptic Ulcer Disease	7,379	0.65%
Rheumatologic Disease	5,988	0.52%
Mild Liver Disease	5,675	0.50%
Peripheral Vascular Disease	4,882	0.43%
AIDS	3,883	0.34%
Dementia	3,143	0.27%
Hemiplegia or Paraplegia	2,234	0.19%
Myocardial Infarction	2,188	0.19%
Renal Disease	1,190	0.10%
Moderate or Severe Liver Disease	919	0.08%
Marital Status		
Married	536,841	47.33%
Divorced	232,277	20.47%
Single	210,988	18.60%
Unknown/Missing	128,161	11.29%
Widowed/Widower	25,913	2.28%
Separated	21	0.00%

Table 8. Continued

Period of Service		
Vietnam Era	497,665	43.87%
Persian Gulf	447,232	39.43%
Post-Vietnam	95,980	8.46%
Others	93,212	8.21%
Unknown/Missing	112	0.01%
Service Percentage Disabilities		
Low	675,604	59.56%
High	194,918	17.18%
Medium	159,254	14.04%
Unknown	104,425	9.21%
Age		
60+	321,891	28.38%
50-59	292,950	25.82%
0-29	156,728	13.77%
40-49	148,176	13.06%
30-39	126,674	11.16%
Unknown	465	0.04%
Socioeconomic Status		
Lowest	274,620	24.21%
Low	233,239	20.56%
Medium	196,597	17.33%
High	196,390	17.31%
Unknown	233,355	20.57%

*Captured 12 months prior to PTSD diagnosis

†Post-Vietnam refers to veterans with a first service entry date after the Vietnam Era ended, i.e. May 7, 1975 ‡Prevalence of depression for the entire cohort with no time restrictions is 372,866 veterans with depression (32.87%).

Table 9. Overall Use of Recommended Psychotherapies/Pharmacotherapies in Cohort with PTSD (*n*=1,134,201)

Recommended Treatments	**Total Number of Patients, N (% of Total Cohort)**	**Total Number of Treatments Per Patient by Class, N (Median, IQR)**	**Total Number of Fills Per Patient by Class, N (Median, IQR)**	**Median Duration for Oral in Days (IQR)‡**	**Median Duration for Non-Oral in Days (IQR) ‡**	**Median Quantity for Oral (IQR)‡**
Psychotherapy*	530,394 (46.76%)	7,267,678 (5,10)		NA	NA	NA
Talk Therapy for 45 Minutes	288,877 (25.46%)	1,803,175 (2,5)				
Talk Therapy for 30 Minutes	220,382 (19.43%)	848,699 (2, 1)				
Group Therapy	193,483 (17.05%)	4,136,962 (7,16)				
Talk Therapy for 60 Minutes	113,568 (10.01%)	476,036 (2,3)				
Crisis, for 60 Minutes	2,311 (0.20%)	2,806 (1,0)				
SSRIs	303,747 (26.78%)	474,836 (1,0)	2,565,993 (7, 15)	90 (210)	90 (150)	45 (45)
Citalopram	113,704 (10.02%)					
Sertraline	113,579 (10.01%)					
Fluoxetine	47,377 (4.17%)					
Paroxetine	28,794 (2.53%)					
Fluvoxamine	293 (0.03%)					
SNRI Venlafaxine	48,943 (4.31%)	81,875 (1,0)	357,226 (7, 14)	90 (150)	90 (125)	60 (60)
Antiadrenergic Agent Prazosin	76,622 (6.75%)	104,314 (1,0)	354,782 (4, 7)	90 (150)	120 (0)	60 (60)
Tetracyclic Antidepressant Mirtazapine	68,890 (6.07%)	84,912 (1,0)	350,096 (5, 10)	90 (150)	60 (150)	30 (15)
Serotonergic Antidepressant Nefazodone	9,840 (0.86%)	12,934 (1,0)	83,268 (8, 15)	90 (210)	30 (30)	60 (30)

Table 9. Continued

Tricyclic Antidepressant	32,111 (2.83%)	39,999 (1,0)	188,814 (6, 14)	90 (150)	90 (180)	90 (70)
Amitriptyline	30,580 (2.69%)					
Imipramine	1,531 (0.13%)					

*Psychotherapies are not mutually exclusive to each other
†All treatments captured one year after PTSD diagnosis; oral consists of tablets, capsules, oral solution, and oral concentrate; non-oral consists of injection, intravenous, suppository, syringe, gel, and solution (since "solution" can refer to oral or injectable drugs, it is safe to keep this grouped with non-oral)
‡Annualized duration and quantity captured one year after PTSD diagnosis

Table 10. Overall Use of Not Recommended Psychotherapies/Pharmacotherapies in Cohort with PTSD (*n*=1,134,201)

Not Recommended Treatments	**Total Number of Patients, N (% of Total Cohort)**	**Total Number of Treatments Per Patient by Class, N (Median, IQR)**	**Total Number of Fills Per Patient by Class, N (Median, IQR)**	**Median Duration for Oral in Days (IQR)†**	**Median Duration for Non-Oral in Days (IQR) †**	**Median Quantity for Oral (IQR)†**
Benzodiazepines	80,832 (7.07%)	115,098 (1,0)	702,201 (9, 21)	90 (150)	90 (150)	60 (60)
Clonazepam	27,233 (7.47%)					
Lorazepam	19,133 (6.08%)					
Temazepam	16,341 (4.74%)					
Alprazolam	10,812 (3.31%)					
Diazepam	6,188 (2.21%)					
Chlordiazepoxide HCL	1,125 (0.30%)					
Opioids	78,870 (6.95%)	205,607 (1,1)	1,254,847 (13, 29)	60 (180)	60 (120)	100 (40)
Acetaminophen Combination	63,589 (5.60%)					
Hydrocodone	42,515 (3.74%)					
Oxycodone	16,038 (1.41%)					
Codeine	12,453 (1.09%)					
Morphine	4,584 (0.40%)					
Methadone	1,842 (0.16%)					
Fentanyl	1,069 (0.09%)					
Buprenorphine	691 (0.06%)					
Hydromorphone	369 (0.03%)					

Table 10. Continued

Atypical Antipsychotics	85,432 (7.53%)	152,224 (1,0)	714,537 (8, 17)	90 (150)	60 (120)	30 (30)
Quetiapine	50,191 (4.42%)					
Risperidone	24,583 (2.16%)					
Olanzapine	10,658 (0.93%)					
Conventional Antipsychotics	3,894 (0.34%)	5,113 (1,0)	26,981 (7, 17)	90 (150)	90 (180)	60 (60)
Haloperidol	2,479 (0.21%)					
Chlorpromazine	1,105 (0.09%)					
Thioridazine	310 (0.03%)					

*Annualized duration and quantity captured one year after PTSD diagnosis; oral consists of tablets, capsules, oral solution, and oral concentrate; non-oral consists of injection, intravenous, suppository, syringe, gel, and solution (since "solution" can refer to oral or injectable drugs, it is safe to keep this grouped with non-oral)

Table 11. Inpatient Pharmacotherapy Exposure in Cohort with PTSD

Treatments*	Total Number of Patients, N (% of Total Cohort)	Median Duration in Days	Median Length of Inpatient Stay in Days, IQR (N=306,166)
			4 (6)
Recommended Treatments			
SSRIs	29,557 (2.60%)	57	
SNRI	5,629 (0.49%)	55	
Antiadrenergic Agent	4,429 (0.39%)	51	
Tetracyclic Antidepressant	6,194 (0.54%)	57	
Serotonergic Antidepressant	307 (0.027%)	52	
Tricyclic Antidepressant	1,457 (0.12%)	49	
Not Recommended Treatments			
Benzodiazepines	15,260 (1.34%)	55	
Opioids	29,964 (2.64%)	58	
Atypical Antipsychotics	20,035 (1.76%)	61	
Conventional Antipsychotics	2,097 (0.18%)	60	

*Annualized duration (at least thirty days) captured one year after PTSD diagnosis for oral, which consists of tablets, capsules, oral solution, and oral concentrate

Table 12. First or Second Psychotherapy/Pharmacotherapy in Cohort with PTSD

Recommended Treatments	Total Number of Patients, N (%)
Psychotherapy*	423,350 (37.32%)
Talk Therapy for 45 Minutes	172,100 (15.17%)
Talk Therapy for 30 Minutes	126,858 (11.18%)
Group Therapy	114,033 (10.05%)
Talk Therapy for 60 Minutes	58,860 (5.19%)
Crisis, for 60 Minutes	1,134 (0.09%)
SSRIs	193,757 (17.08%)
Citalopram	75,181 (6.62%)
Sertraline	70,221 (6.19%)
Fluoxetine	29,927 (2.63%)
Paroxetine	18,246 (1.60%)
Fluvoxamine	182 (0.01%)
SNRI	26,517 (2.33%)
Venlafaxine	
Antiadrenergic Agent	41,120 (3.62%)
Prazosin	
Tetracyclic Antidepressant	38,120 (3.36%)
Mirtazapine	
Serotonergic Antidepressant	6,297 (0.55%)
Nefazodone	
Tricyclic Antidepressant	19,083 (1.68%)
Amitriptyline	18,163 (1.60%)
Imipramine	920 (0.08%)
Not Recommended Treatments	
Benzodiazepines	45,547 (4.01%)
Clonazepam	14,792 (1.30%)
Lorazepam	10,952 (0.90%)
Temazepam	9,365 (0.80%)
Alprazolam	6,334 (0.55%)
Diazepam	3,424 (0.30%)
Chlordiazepoxide HCL	680 (0.06%)
Atypical Antipsychotics	47,030 (4.14%)
Quetiapine	27,236 (2.40%)
Risperidone	13,690 (1.20%)
Olanzapine	6,104 (0.53%)
Conventional Antipsychotics	2,134 (0.18%)
Haloperidol	1,357 (0.11%)
Chlorpromazine	570 (0.05%)
Thioridazine	207 (0.01%)

*Treatments captured one year after PTSD diagnosis

Table 13. First Psychotherapy or Pharmacotherapy in Cohort with PTSD

Recommended Treatments	Total Number of Patients, N (%)
Psychotherapy*	293,132 (25.84%)
Talk Therapy for 45 Minutes	111,629 (9.84%)
Talk Therapy for 30 Minutes	78,190 (6.89%)
Group Therapy	70,383 (6.20%)
Talk Therapy for 60 Minutes	32,480 (2.86%)
Crisis, for 60 Minutes	440 (0.04%)
SSRIs	129,863 (11.44%)
Citalopram	50,288 (4.43%)
Sertraline	46,777 (4.12%)
Fluoxetine	20,294 (1.79%)
Paroxetine	12,388 (1.09%)
Fluvoxamine	116 (0.01%)
SNRI Venlafaxine	17,265 (1.52%)
Antiadrenergic Agent Prazosin	21,837 (1.92%)
Tetracyclic Antidepressant Mirtazapine	24,451 (2.15%)
Serotonergic Antidepressant Nefazodone	4,744 (0.41%)
Tricyclic Antidepressant	13,369 (1.17%)
Amitriptyline	12,692 (1.11%)
Imipramine	677 (0.05%)
Not Recommended Treatments	
Benzodiazepines	28,769 (2.53%)
Clonazepam	8,942 (0.78%)
Lorazepam	6,766 (0.60%)
Temazepam	6,130 (0.54%)
Alprazolam	4,115 (0.36%)
Diazepam	2,327 (0.20%)
Chlordiazepoxide HCL	489 (0.04%)
Atypical Antipsychotics	28,198 (2.48%)
Quetiapine	16,027 (1.41%)
Risperidone	8,279 (0.73%)
Olanzapine	3,892 (0.34%)
Conventional Antipsychotics	1,423 (0.12%)
Haloperidol	903 (0.07%)
Chlorpromazine	367 (0.03%)
Thioridazine	153 (0.01%)

*Psychotherapies are not mutually exclusive to each other

Table 14. Second Psychotherapy or Pharmacotherapy in Cohort with PTSD

Recommended Treatments	Total Number of Patients, N (%)
Psychotherapy†	130,218 (11.48%)
Talk Therapy for 45 Minutes	60,471 (5.33%)
Talk Therapy for 30 Minutes	48,668 (4.29%)
Group Therapy	43,650 (3.84%)
Talk Therapy for 60 Minutes	27,380 (2.41%)
Crisis, for 60 Minutes	694 (0.06%)
SSRIs	63,894 (5.63%)
Sertraline	24,893 (2.19%)
Citalopram	23,444 (2.06%)
Fluoxetine	9,633 (0.84%)
Paroxetine	5,858 (0.51%)
Fluvoxamine	66 (0.01%)
SNRI Venlafaxine	9,252 (0.81%)
Antiadrenergic Agent Prazosin	19,283 (1.70%)
Tetracyclic Antidepressant Mirtazapine	13,669 (1.20%)
Serotonergic Antidepressant Nefazodone	1,553 (0.13%)
Tricyclic Antidepressant	5,714 (0.50%)
Amitriptyline	5,471 (0.48%)
Imipramine	243 (0.02%)
Not Recommended Treatments	
Benzodiazepines	16,778 (1.47%)
Clonazepam	5,850 (0.51%)
Lorazepam	4,186 (0.37%)
Temazepam	3,235 (0.28%)
Alprazolam	2,219 (0.19%)
Diazepam	1,097 (0.10%)
Chlordiazepoxide HCL	191 (0.01%)
Atypical Antipsychotics	18,832 (1.66%)
Quetiapine	11,209 (0.98%)
Risperidone	5,411 (0.47%)
Olanzapine	2,212 (0.19%)
Conventional Antipsychotics	711 (0.06%)
Haloperidol	454 (0.04%)
Chlorpromazine	203 (0.01%)
Thioridazine	54 (0.00%)

*Patients who received another treatment for PTSD within 30 days of their first treatment
†Psychotherapies are not mutually exclusive to each other

Table 15. Most Frequent Overlapping Therapies in Cohort with PTSD

Combination	N (%)
Psychotherapies	49,890 (4.39)
Psychotherapy/SSRI	35,386 (3.11)
SSRI/Prazosin	7,312 (0.64)
SSRI/Atypical Antipsychotics	6,001 (0.52)
SSRI/Benzodiazepines	5,603 (0.49)

Table 16. Comparison of Confounders and Risk Factors Before Matching

Variable	No Benzodiazepines (n=1,053,369)	Benzodiazepines (n=80,832)	P-Value*
Traumatic Brain Injury, N (%)			
No	1,047,115 (99.41%)	80,402 (99.47%)	
Yes	6,254 (0.59%)	430 (0.53%)	0.027
Anxiety Disorder, N (%)			
No	914,179 (86.79%)	67,841 (83.93%)	
Yes	139,190 (13.21%)	12,991 (16.07%)	<0.0001
Bipolar Disorder, N (%)			
No	1,023,278 (97.14%)	78,204 (96.75%)	
Yes	30,091 (2.86%)	2,628 (3.25%)	<0.0001
Depression, N (%)			
No	960,000 (91.14%)	73,738 (91.22%)	
Yes	93,369 (8.86%)	7,094 (8.78%)	**0.398**
Alcohol Abuse, N (%)			
No	989,214 (93.91%)	77,469 (95.84%)	
Yes	64,155 (6.09%)	3,363 (4.16%)	<0.0001
Opioid Abuse, N (%)			
No	1,048,489 (99.54%)	80,546 (99.65%)	
Yes	4,880 (0.46%)	286 (0.35%)	<0.0001
Chronic Pain, N (%)			
No	1,040,405 (98.77%)	79,726 (98.63%)	
Yes	12,964 (1.23%)	1,106 (1.37%)	0.0007
SSRI, N (%)			
No	854,565 (81.13%)	66,058 (81.72%)	
Yes	198,804 (18.87%)	14,774 (18.28%)	<0.0001
SNRI, N (%)			
No	1,031,000 (97.88%)	78,814 (97.50%)	
Yes	22,369 (2.12%)	2,018 (2.50%)	<0.0001
Prazosin, N (%)			
No	1,037,680 (98.51%)	79,733 (98.64%)	
Yes	15,689 (1.49%)	1,099 (1.36%)	0.003
Atypical Antipsychotics, N (%)			
No	1,006,868 (95.59%)	77,349 (95.69%)	
Yes	46,501 (4.41%)	3,483 (4.31%)	**0.159**

Table 16. Continued

Conventional Antipsychotics, N (%)			
No	1,050,386 (99.72%)	80,632 (99.75%)	
Yes	2,983 (0.23%)	200 (0.25%)	**0.064**
Opioids, N (%)			
No	985,405 (93.55%)	69,926 (86.51%)	
Yes	67,964 (6.45%)	10,906 (13.49%)	<0.0001
Gender, N (%)			
Female	92,661 (8.80%)	9,999 (12.37%)	
Male	957,345 (90.88%)	70,563 (87.30%)	
Unknown/Missing	3,363 (0.32%)	270 (0.33%)	<0.0001
Marital Status			
Divorced	216,331 (20.54%)	15,946 (19.73%)	
Married	497,949 (47.27%)	38,892 (48.11%)	
Single	196,479 (18.65%)	14,509 (17.95%)	
Separated	21 (0.01%)	0 (0.00%)	
Widowed	24,209 (2.30%)	1,704 (2.11%)	
Unknown/Missing	118,380 (11.24%)	9,781(12.10%)	<0.0001
Race			
White	700,444 (66.50%)	58,388 (72.23%)	
Black or African-American	210,727 (20.01%)	11,534 (14.27%)	
Others	32,295 (3.07%)	2,309 (2.86%)	
Declined to Answer /Unknown/Missing	110,173 (10.43%)	8,601 (10.64%)	<0.0001
Socioeconomic Status			
Lowest	256,181 (24.32%)	18,439 (22.81%)	
Low	216,197 (20.52%)	17,042 (21.08%)	
Medium	182,290 (17.31%)	14,307 (17.70%)	
High	182,643 (17.34%)	13,747 (17.01%)	
Unknown	216,058 (20.51%)	17,297 (21.40%)	<0.0001

Table 16. Continued

Service Percentage Disabilities			
Low	628,347 (59.65%)	47,257 (58.46%)	
Medium	148,805 (14.13%)	10,449 (12.93%)	
High	180,678 (17.15%)	14,240 (17.62%)	
Unknown	95,539 (9.07%)	8,886 (10.99%)	
			<0.0001
Age			
0-29	161,264 (15.31%)	15,364 (19.01%)	
30-39	128,362 (12.19%)	12,296 (15.21%)	
40-49	154,423 (14.66%)	12,503 (15.47%)	
50-59	306,544 (29.10%)	21,089 (26.09%)	
60+	302,328 (28.70%)	19,563 (24.20%)	
Unknown	448 (0.04%)	17 (0.02%)	
			<0.0001
Military Sexual Trauma, N (%)			
No	16,202 (1.54%)	1,508 (1.87%)	
Yes	8,733 (0.83%)	792 (0.98%)	
Unknown	1,028,434 (97.63%)	78,532 (97.15%)	
			<0.0001
Smoking Status, N (%)			
No	947,693 (89.87%)	72,604 (89.82%)	
Yes	105,676 (10.03%)	8,228 (10.18%)	
			0.180
Illicit Drug Use, N (%)			
No	1,042,924 (99.01%)	79,862 (98.80%)	
Yes	10,445 (0.99%)	970 (1.20%)	
			<0.0001
Homelessness, N (%)			
No	951,049 (90.29%)	71,620 (88.60%)	
Yes	6,781 (0.64%)	326 (0.40%)	
Unknown	95,539 (9.07%)	8,886 (10.99%)	
			<0.0001

***Chi-Square Test**

Table 17. Comparison of Confounders and Risk Factors After Matching

Variable	No Benzodiazepines (n=161,662)	Benzodiazepines (n=80,831)	P-Value*
Traumatic Brain Injury, N (%)			
No	160,889 (99.52%)	80,401 (99.47%)	
Yes	773 (0.48%)	430 (0.53%)	**0.075**
Anxiety Disorder, N (%)			
No	136,050 (84.16%)	67,841 (83.93%)	
Yes	25,612 (15.84%)	12,990 (16.07%)	**0.148**
Bipolar Disorder, N (%)			
No	156, 902 (97.06%)	78,204 (96.75%)	
Yes	4,760 (2.94%)	2,627 (3.25%)	<0.0001
Depression, N (%)			
No	148,259 (91.71%)	73,737 (91.22%)	
Yes	13,403 (8.29%)	7,094 (8.78%)	<0.0001
Alcohol Abuse, N (%)			
No	155,454 (96.16%)	77,468 (95.84%)	
Yes	6,208 (3.84%)	3,363 (4.16%)	0.0001
Opioid Abuse, N (%)			
No	161,224 (99.73%)	80,546 (99.65%)	
Yes	438 (0.27%)	286 (0.35%)	0.0004
Chronic Pain, N (%)			
No	159,684 (98.784%)	79,726 (98.63%)	
Yes	1,978 (1.22%)	1,105 (1.37%)	0.003
SSRI, N (%)			
No	132,489 (81.95%)	66,057 (81.72%)	
Yes	29,173 (18.27%)	14,774 (18.28%)	**0.162**
SNRI, N (%)			
No	158,036 (97.76%)	78,813 (97.50%)	
Yes	3,626 (2.24%)	2,018 (2.50%)	<0.0001
Prazosin, N (%)			
No	159,771 (98.83%)	79,732 (98.64%)	
Yes	1,891 (1.17%)	1,099 (1.36%)	<0.0001
Atypical Antipsychotics, N (%)			
No	155,574 (96.23%)	77,348 (95.69%)	
Yes	6,088 (3.77%)	3,483 (4.31%)	<0.0001

Table 17. Continued

Conventional Antipsychotics, N (%)			
No	161,364 (99.82%)	80,631 (99.75%)	
Yes	298 (0.18%)	200 (0.25%)	0.001
Opioids, N (%)			
No	139,813 (86.48%)	69,926 (86.51%)	
Yes	21,849 (13.52%)	10,905 (13.49%)	**0.867**
Gender, N (%)			
Female	19,394 (12.00%)	9,998 (12.37%)	
Male	141,788 (87.71%)	70,563 (87.30%)	
Unknown/Missing	480 (0.30%)	270 (0.33%)	0.008
Marital Status			
Divorced	31,765 (19.65%)	15,946 (19.73%)	
Married	78,140 (48.34%)	38,891 (48.11%)	
Single	29,095 (18.00%)	14,509 (17.95%)	
Separated	3,316 (2.05%)	1,704 (2.11%)	
Widowed	3,212 (1.99%)	1,708 (2.11%)	
Unknown/Missing	16,134 (9.98%)	8,073 (9.99%)	**0.320**
Race			
White	116,331 (71.96%)	58,387 (72.23%)	
Black or African-American	23,395 (14.47%)	11,534 (14.27%)	
Others	4,912 (3.04%)	2,309 (2.86%)	
Declined to Answer /Unknown/Missing	17,024 (10.53%)	8,601 (10.64%)	0.008
Socioeconomic Status			
Lowest	36,997 (22.89%)	18,438 (22.81%)	
Low	34,022 (21.05%)	17,042 (21.08%)	
Medium	28,557 (17.66%)	14,307 (17.70%)	
High	27,489 (17.00%)	13,747 (17.01%)	
Missing	34,597 (21.40%)	17,297 (21.40%)	**0.995**

Table 17. Continued

Service Percentage Disabilities			
Low	94,788 (58.63%)	47,256 (58.46%)	
Medium	20,900 (12.93%)	10,449 (12.93%)	
High	28,170 (17.43%)	14,240 (17.62%)	
Missing	17,804 (11.01%)	8,886 (10.99%)	**0.700**
Age			
0-29	30,100 (18.62%)	15,364 (19.01%)	
30-39	24,341 (15.06%)	12,295 (15.21%)	
40-49	24,844 (15.37%)	12,503 (15.47%)	
50-59	42,559 (26.33%)	21,089 (26.09%)	
60+	39,790 (24.61%)	19,563 (24.20%)	
Unknown	28 (0.02%)	17 (0.02%)	**0.060**
Military Sexual Trauma, N (%)			
No	2,728 (1.69%)	1,508 (1.87%)	
Yes	1,497 (0.93%)	792 (0.98%)	
Missing	157,437 (97.39%)	78,531 (97.15%)	0.003
Smoking Status, N (%)			
No	145,752 (90.16%)	72,603 (89.92%)	
Yes	15,910 (9.84%)	8,228 (10.18%)	0.008
Illicit Drug Use, N (%)			
No	160,002 (98.97%)	79,862 (98.80%)	
Yes	1,660 (1.03%)	969 (1.20%)	0.0001
Homelessness, N (%)			
No	143,154 (88.55%)	71,619 (88.60%)	
Yes	704 (0.44%)	326 (0.40%)	
Missing	17,804 (11.01%)	8,886 (10.99%)	**0.509**

***Chi-Square Test**

Table 18. Standardized Differences Before and After Propensity Score Matching

Variable	Standardized Difference in Cohort (n=1,134,201)	Standardized Difference in Matched Sample (n=242,493)
TBI	0.008	0.008
Anxiety Disorder	0.081	0.006
Bipolar Disorder	0.023	0.018
Depression	0.003	0.017
Alcohol Abuse	0.088	0.016
Opioid Abuse	0.017	0.015
Chronic Pain	0.012	0.013
SSRI	0.015	0.006
SNRI	0.025	0.017
Prazosin	0.011	0.017
Atypical Antipsychotics	0.005	0.028
Conventional Antipsychotics	0.007	0.014
Opioids	0.237	0.001
Male	0.124	0.005
Marital Status		
Divorced	0.206	0.004
Married	0.032	0.005
Single	0.199	0
Separated	0.168	0.001
Widowed/Widower	0.166	0.002
Unknown	0.171	0.017
Race		
White	0.147	0.012
Black or African-American	0.064	0.033
Others	0.048	0.033
Declined to Answer /Unknown	0.018	0.010
Service Percentage Disabilities		
Low	0.002	0.004
Medium	0.337	0.005
High	0.432	0.002
Age		
0-29	0.129	0.006
30-39	0.147	0.003
40-49	0.040	0.008
50-59	0.125	0.007
60+	0.153	0.002

Table 18. Continued

Socioeconomic Status		
Lowest	0.034	0.002
Low	0.026	0.001
Medium	0.018	0.001
High	0.004	0
Smoking	0.005	0.011
Homeless	0.294	0.004
Illicit Drug Use	0.020	0.016
Military Sexual Trauma	0.012	0.021

Table 19: Modified Park Test Results

Health Care Utilization Outcome	Modified Park Test Coefficient	Suggested Distribution	Proportion Zeroes
Hospitalizations	1.13	Poisson	237,884 (98.1%)
ED Visits	2.36	Gamma	151,300 (62.4%)
General Outpatient Visits	1.48	Poisson	36,494 (15.0%)
Mental Sum Outpatient Visits	1.03	Poisson	92,353 (38.1%)
Mental Outpatient Visits	1.07	Poisson	88,255 (36.4%)
Substance Abuse Outpatient Visits	1.04	Poisson	211,809 (87.3%)

Table 20. Scaled Deviance and Scaled Pearson Values

Health Care Utilization Outcome	Scaled Deviance	Scaled Pearson
Hospitalizations	0.21	2.08
ED Visits	5.40	12.40
General Outpatient Visits	23.75	35.43
Total Mental Outpatient Visits	52.94	182.31
Mental Outpatient Visits	40.87	163.99
Substance Abuse Outpatient Visits	23.59	148.88

Table 21. Vuong Test Results

Health Care Utilization Outcome	P-Value
Hospitalizations	0.000
ED Visits	0.424
General Outpatient Visits	0.000
Total Mental Outpatient Visits	0.000
Mental Outpatient Visits	0.000
Substance Abuse Outpatient Visits	0.000

Table 22. Model Used for Health Care Utilization Outcomes

Model	Outcome(s)
Zero-Inflated Poisson	Hospitalizations
Zero-Inflated Negative Binomial	General Outpatient, Mental, Substance Abuse, Mental Sum Outpatient Visits
Standard Negative Binomial	ED Visits

Table 23. Health Care Utilization Incidence Rate Ratios and Rate Differences

Health Care Utilization Outcome	Incidence Rate Ratio (IRR)	P-Value	Incidence Rate Difference (IRD)	P-Value
Hospitalizations	1.2718 (1.0982, 1.4729)	<0.0001	0.0249 (0.0199, 0.0300)	<0.0001
Emergency Department	1.1645 (1.1299, 1.2002)	<0.0001	0.2758 (0.2125, 0.3392)	<0.0001
General Outpatient	1.1853 (1.1641, 1.2068)	<0.0001	3.4800 (3.1473, 3.8126)	<0.0001
Total Mental Health Outpatient	1.3708 (1.3448, 1.3974)	<0.0001	5.7502 (4.6278, 6.8727)	<0.0001
Mental Health Outpatient	1.4895 (1.4128, 1.5703)	<0.0001	5.4729 (4.5468, 6.3990)	<0.0001
Substance Abuse Outpatient	1.0749 (0.9923, 1.1644)	0.074	0.2773 (-0.0232, 0.5778)	0.069

Table 24: Mortality Counts Using Suicide Data Repository

Outcome	Benzodiazepines, N (%)	No Benzodiazepines, N (%)	Total
All-Cause Death	12,387 (15.13%)	14,454 (8.94%)	26,841 (11.06%)
Suicide as Cause of Death	456 (3.68%)	349 (2.41%)	805 (2.99%)
Before 2010	211 (1.70%)	117 (0.81%)	328 (1.22%)
After 2010	245 (1.97%)	232 (1.60%)	477 (1.77%)

Table 25: Hazard Rate Ratios Using Suicide Data Repository

Suicide Outcome	Hazard Ratio (HR)	P-Value
All-Cause Death	1.8634 (1.8071, 1.9214)	<0.0001
Suicide as Cause of Death	2.7399 (2.4001, 3.1279)	<0.0001
Suicide as Cause of Death, Adjusted for 2010	2.3324 (2.0519, 2.6513)	<0.0001

Table 26: Suicide Behavior Counts Using ICD-9 Codes

Suicide Behavior Outcome	Benzodiazepines, N (%)	No Benzodiazepines, N (%)	Total, N (%)
Suicide Behavior*	5,286 (6.45%)	7,206 (4.45%)	12,492 (5.15%)
Suicide Thoughts and Ideation	4,628 (5.65%)	6,555 (4.05%)	11,183 (4.61%)
Suicide and Self-Inflicted Injury	1,432 (1.74%)	1,615 (0.99%)	3,047 (1.25%)

*****Suicide thoughts and ideation, suicide and self-inflicted injury are not mutually exclusive to each other within benzodiazepines and no benzodiazepines groups (patients can exhibit both ICD-9 codes)
Note: With no time restrictions, 6.90% of veterans in the cohort (16,740) have suicide behavior, 6.00% (14,550) have suicide thoughts/ideation, and 1.89% (4,591) have suicide/self-inflicted injury

Table 27: Hazard Rate Ratios Using ICD-9 Codes

Suicide Behavior Outcome	Hazard Ratio (HR)	P-Value
Suicide Behavior	1.5643 (1.4737, 1.6604)	<0.0001
Suicide Thoughts and Ideation	1.5177 (1.4144, 1.6156)	<0.0001
Suicide and Self-Inflicted Injury	1.8467 (1.6446, 2.0736)	<0.0001

Table 28: Suicide Behavior Counts Using Note Titles

Suicide Behavior Outcome	Benzodiazepines, N (%)	No Benzodiazepines, N (%)	Total, N (%)
Suicide Behavior	1,779 (2.17%)	1,837 (1.13%)	3,616 (1.49%)
Suicide Thoughts and Ideation	1,755 (2.14%)	1,815 (1.12%)	3,570 (1.47%)
Suicide and Self-Inflicted Injury	24 (0.03%)	22 (0.01%)	46 (0.02%)

Note: With no time restrictions, 2.01% of veterans in the cohort (4,896) have suicide behavior, 1.98% (4,808) have suicide thoughts/ideation, and 0.03% (88) have suicide/self-inflicted injury

Table 29: Hazard Rate Ratios Using Note Titles

Suicide Behavior Outcome	Hazard Ratio (HR)	P-Value
Suicide Behavior	1.9707 (1.8266, 2.1260)	<0.0001
Suicide Thoughts and Ideation	1.9664 (1.8199, 2.1247)	<0.0001
Suicide and Self-Inflicted Injury	2.2767 (1.7900, 2.8956)	<0.0001

Table 30: Suicide Behavior Counts Using Note Titles Before and After 2008

Suicide Behavior Outcome	Benzodiazepines, N (%)	No Benzodiazepines, N (%)	Total, N (%)
Suicide Behavior Before 2008	524 (0.64%)	759 (0.47%)	1,283 (0.52%)
Suicide Thoughts and Ideation	516 (0.63%)	748 (0.46%)	1,264 (0.51%)
Suicide and Self-Inflicted Injury	8 (0.01%)	11 (0.01%)	19 (0.01%)
Suicide Behavior After 2008	1,255 (1.53%)	1,078 (0.67%)	2,333 (0.95%)
Suicide Thoughts and Ideation	1,239 (1.51%)	1,067 (0.66%)	2,306 (0.94%)
Suicide and Self-Inflicted Injury	16 (0.02%)	11 (0.01%)	27 (0.01%)

Table 31: Hazard Rate Ratios Adjusted For 2008

Suicide Behavior Outcome	Hazard Ratio (HR)	P-Value
Suicide Behavior	1.8397 (1.6816, 2.0127)	<0.0001
Suicide Thoughts and Ideation	1.8351 (1.6749, 2.0105)	<0.0001
Suicide and Self-Inflicted Injury	2.1069 (1.6540, 2.6840)	<0.0001

Table 32: Median Survival Time in Days

Outcome	Benzodiazepines	No Benzodiazepines	Log-Rank Test P-Value
All-Cause Death	1091	1353	<0.0001
Suicide as Cause of Death	605	938	<0.0001
ICD-9 for Suicide Behavior	461	1023	<0.0001
ICD-9 for Suicide Thoughts	521	1105	<0.0001
ICD-9 for Suicide	421	900	<0.0001
Note Title for Suicide Behavior	287	861	<0.0001
Note Title for Suicide Thoughts	287	860	<0.0001
Note Title for Suicide	294	963	<0.0001
ICD-9 or Note Title for Suicide Behavior	434	1008	<0.0001
ICD-9 or Note Title for Suicide Thoughts	480	1065	<0.0001
ICD-9 or Note Title for Suicide	406	892	<0.0001

Table 33: Suicide Behavior Counts Using ICD-9 Codes or Note Titles

Suicide Behavior Outcome	Benzodiazepines, N (%)	No Benzodiazepines, N (%)	Total, N (%)
Suicide Behavior*	6,149 (7.51%)	8,145 (5.03%)	14,294 (5.89%)
Suicide Thoughts and Ideation	5,587 (6.82%)	7,583 (4.69%)	13,170 (5.43%)
Suicide and Self-Inflicted Injury	1,454 (1.77%)	1,632 (1.01%)	3,086 (1.27%)

Note: The kappa statistic is 0.2069 for suicide behavior, 0.1867 for suicide thoughts and ideation, and 0.0042 for suicide and self-inflicted injury. The kappa values indicate only slight agreement between the ICD-9 codes and note titles. Thus, the two methods will not be combined.
*Suicide thoughts and ideation, suicide and self-inflicted injury are not mutually exclusive to each other within benzodiazepines and no benzodiazepines groups (patients can exhibit an ICD-9 code, note title, or both)

Table 34: Hazard Rate Ratios Using ICD-9 Codes or Note Titles

Suicide Behavior Outcome	Hazard Ratio (HR)	P-Value
Suicide Behavior	1.6074 (1.5192, 1.7006)	<0.0001
Suicide Thoughts and Ideation	1.5714 (1.4783, 1.6704)	<0.0001
Suicide and Self-Inflicted Injury	1.8527 (1.6536, 2.0756)	<0.0001

CHAPTER V

DISCUSSION

Strengths/Limitations and Comparison to Prior Literature

This study was the first to describe the use of both psychotherapies and pharmacotherapies for veterans with PTSD in the national VA setting. No prior literature has looked at the total and median number of treatments/fills per class and described median treatment duration and quantity in such a large cohort. There is limited literature on the distribution of pharmacotherapies for veterans with PTSD.[142,143] Prior literature found a similar distribution as in my study for some of the pharmacotherapies; SSRIs are the most frequently prescribed followed by the SNRI venlafaxine. Benzodiazepines were found to be the next highest, around 30.5%; this is in contrast to my study, in which 7.07% of veterans receive benzodiazepines within one year after PTSD diagnosis.[142,143] Thus, the prevalence of benzodiazepines is lower in my study. There are a myriad of reasons for this difference. First, previous studies did not exclude patients who used benzodiazepines six months prior to PTSD diagnosis.[142,143] The application of this criteria resulted in excluding 121,000 patients in my study, which more than halved the total percentage of veterans who received benzodiazepines. These patients were excluded to ensure the effect of exposure on health outcomes after PTSD diagnosis and not on prior benzodiazepine use. Second, one prior study was cross-sectional and reported

benzodiazepine use for only the year 2009 while another study was longitudinal but reported annual benzodiazepine use from 1999 to 2009; this method to capture exposure differs from that employed in my study, in which benzodiazepine use was measured at one point in time - twelve months after PTSD diagnosis.[142,143] Third, my study included six different benzodiazepines, which was lower than that included in other research.[142,143] The six benzodiazepines - lorazepam, clonazepam, alprazolam, diazepam, temazepam, and chlordiazepoxide HCL - were included because they are the most commonly prescribed or longest used (chlordizaepoxide HCL) benzodiazepines to specifically treat PTSD.[1,21,38,68,144] Fourth, prior studies required no minimum days' supply; on the other hand, my study required veterans to have at least a 30 days' supply of benzodiazepines.[140,141]

Furthermore, this study was the first to evaluate the association between veterans who received benzodiazepines with health care utilization and suicide mortality. Another strength is that the study population consisted of a large number of veterans exposed to benzodiazepines, which ensured adequate power. While comparability between exposed and nonexposed is difficult to achieve in a retrospective cohort, the existence of observable systematic differences between the two treatment groups was reduced through propensity scores. In addition, this method preserved the exposed group, separated the analysis phase from the design phase, and reduced the likelihood of bias from iterative model building.

This study had some limitations. The major limitation of propensity score matching is that it only accounts for measured confounders and only to the extent that they are accurately measured. For example, there is no structured data available in the

VHA on education and employment. There was no attempt made to adjust for these two risk factors along with any other unobserved confounders and thus, some unmeasured confounding may be present in this study. However, more proximal risk factors were used and an exhaustive search of the literature ensured all potential confounders and risk factors were included in the propensity score model.

A second limitation of this study is information bias that stems from potential mismeasurement of study variables. ICD-9 codes were used to classify veterans by mental health status. However, the overall positive predictive value is 75% for at least one PTSD diagnosis in VA databases; this means that 75% of the individuals with at least one PTSD diagnosis in the VA databases truly have PTSD.[112] There could also be misclassification of the outcome, particularly suicide behavior. Nondifferential misclassification would bias results towards the null (HR=1). The strongest outcome for suicide behavior is death by suicide as determined by the SDR. On the other hand, there is unreliability in coding and documentation for ICD-9 codes and suicide behavior note titles. ICD-9 codes only include patients who presented to a VA for medical treatment following a suicide attempt or crisis; similarly, the presence of a suicide behavior note title depends on a veteran's decision to present and disclose self-injury at a VA visit and also a clinician's reliability in entering a note title. Nonetheless, similar patterns in the hazard ratios across note titles, ICD-9 codes, and the SDR suggest that the results present in the first two are not largely attributable to errors or limitations in those methods.

There are two more limitations in this study. First, the population limits external validity to a specific cohort of veterans; male veterans who were diagnosed with/sought care for PTSD outside the VHA were not included in this study. Thus, the study results

are not generalizable to all veterans with PTSD. However, veterans who did seek some care outside (and inside) the VA were included if they did meet the cohort eligibility criteria. Second, patients were considered exposed for the entire study period if they were new users of benzodiazepines in the initial one-year period after diagnosis. While exposure status can vary over time, the initiation period was limited to one year; the ITT analysis adjusted for variables at the time of drug initiation through propensity scores that included risk factors and confounders in the year prior to PTSD diagnosis. Furthermore, an ITT analysis reflects the real-world setting and minimizes type I error.

There are three final limitations of this study. The first is misclassification of non-VA medication use. Patients who use benzodiazepines may have received this medication outside of the VA but not within the VA. However, there is an incentive for veterans to seek care at the VA because co-pays for the majority of medications, including benzodiazepines, are much lower in the VA than outside. Second, PTSD symptom severity was not adjusted for in the propensity score model. There were two reasons for this. First, there is no structured data field in the VHA that captures symptom severity; scales such as the Posttraumatic Diagnostic Scale (PDS) that measure symptom severity are not consistently implemented. Second, severity was indirectly adjusted for through the inclusion of comorbidities such as bipolar disorder, anxiety disorder, and depression. Finally, baseline suicide behavior was not adjusted for in the propensity score model. However, the standardized differences of 0.012 for suicide thoughts/ideation and 0.008 for suicide attempts/self-inflicted injury in the matched cohort indicate that these variables were well balanced between the benzodiazepine and nonbenzodiazepine users.

Conclusion

The overall distribution of therapies in the cohort is similar to that outlined in the 2010 VA PTSD Clinical Practice Guidelines.[38,143] However, after the first-line psychotherapies and SSRIs, the not recommended benzodiazepines (7.07%) and atypical antipsychotics (7.53%) have the highest prevalence. The median number of benzodiazepine fills is nine (IQR of 21) and the median duration is three months. The distribution of first or second therapies is similar to that seen in the overall distribution, with the not recommended benzodiazepines (4.01%) and atypical antipsychotics (4.14%) having the highest prevalence after the first-line psychotherapies and SSRIs. The third-most frequent overlapping therapy (0.49%) includes benzodiazepines in conjunction with SSRIs.

Veterans with PTSD who received benzodiazepines have significantly higher incidence rate ratios for almost all types of health care visits. This includes hospitalizations (1.27), ED (1.16), general outpatient (1.18), total mental outpatient (1.37), and mental outpatient visits (1.48). The suicide mortality hazard rate between benzodiazepine users and nonusers is 2.73; regardless of whether suicide behavior was defined through ICD-9 codes or Note Titles, all hazard ratios indicated that benzodiazepines are associated with a greater risk for suicide behavior, suicide thoughts, and attempted suicide.

The evidence from this study reveals that benzodiazepines, at approximately 7%, are one of the pharmacotherapies prescribed for patients with PTSD and that they are associated with greater health care utilization and suicide outcomes. Most importantly, this study strengthens the empirical evidence against the use of benzodiazepines in

veterans with PTSD and that ultimately, prescribers should weight the benefits and risks – especially the almost three-fold increase in suicide death – when deciding to prescribe benzodiazepines to a veteran with PTSD.

APPENDIX

Table 35: PTSD Diagnoses Definitions from DSM III to DSM-5 (1980-2013)

DSM-III (1980)	DSM-III-R (1987)	DSM-IV-R (1994 and 2000)	DSM-5 (2013)
One Recognizable Stressor -Evoke distress in everyone	**Stressor** -Events that are outside the range of human experience -Usually experienced with intense fear, terror, and helplessness	**Exposure to a traumatic event** -Person experienced, witnessed, or was confronted with an event that involved actual or threatened death, serious injury, or threat to the physical integrity of oneself or others -Response had to involve fear, helplessness, or horror	**Exposure to a traumatic event** -Exposure to actual or threatened death, serious injury, or sexual violence in one or more of the following ways: 1. Directly experiencing the traumatic events 2. Witnessing, in person, the event(s) as it occurred to others 3. Learning that the traumatic event(s) occurred to a close family member or friend. In cases of actual or threatened death of a family member or friend, the event(s) must have been violent or accidental. 4. Experiencing repeated or extreme exposure to aversive details of the traumatic event(s)
One Re-Experiencing Symptom -Recurrent Recollections -Recurrent Dreams -Acting as if traumatic event were recurring	**One Re-Experiencing Symptom** -Recurrent Recollections -Recurrent Dreams -Acting as if traumatic event were recurring	**One Re-Experiencing Symptom** -Recurrent Recollections -Recurrent Dreams -Acting as if traumatic event were recurring-Physiological reactivity upon stimulus exposure	**One Intrusion Symptom** -Recurrent, involuntary, and intrusive recollections -Traumatic nightmares -Dissociative Reactions -Intense or prolonged distress after exposure to traumatic reminders -Marked physiological reactivity after exposure to trauma-related stimuli

Table 35: Continued

One Indicator of Reduced Involvement -Diminished interest in activities -Feelings of detachment and disinterest -Constricted affect	**Three Avoidance Symptoms** -Efforts to avoid thoughts of the traumatic event -Efforts to avoid reminders of the traumatic event -Numbing -Foreshortened future -Amnesia	**Three Avoidance Symptoms** -Efforts to avoid thoughts of the traumatic event -Efforts to avoid reminders of the traumatic event -Numbing -Foreshortened future -Amnesia	**One Avoidance Symptom** -Trauma-related thoughts or feelings -Trauma related external reminders (people, places, conversations, activities, objects, or situations)
Two Other Symptoms -Hyperarousal or startle -Sleep disturbance -Survivor guilt -Memory impairment -Trouble concentrating -Avoidance of activities reminiscent of trauma -Intensification of Symptoms when exposed to reminiscent events	**Two Arousal Symptoms** -Startle -Hypervigilance -Physiological reactivity upon stimulus exposure -Irritability/anger -Sleep problems -Difficulty concentrating	**Two Arousal Symptoms** -Startle -Hypervigilance -Irritability/anger -Sleep problems -Difficulty concentrating	**Two Negative Alterations in Cognition and Mood Symptoms** -Dissociative Amnesia -Persistent negative beliefs -Persistent distorted blame of self or others -Negative trauma-related emotions -Markedly diminished interest in (pre-traumatic) significant activities -Feeling alienated from others -Constricted affect
	Duration -At Least One Month	**Duration** -At Least One Month	**Two Arousal Symptoms** -Irritable or aggressive -Self-destructive or reckless -Hypervigilance -Startle -Difficulty concentrating -Sleep problems
	Significant Distress or Functional Impairment	**Significant Distress or Impairment in Some Realm of Functioning**	**Duration** -At Least One Month
			Significant Distress or Impairment in Some Realm of Functioning
			Not Due to Medication, Substance, or Illness

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