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Characteristics of Non-Benzodiazepine Sedative Hypnotic Use Among Combat Injured U.S. Service Members with Insomnia

A dissertation submitted in partial satisfaction of the

requirements for the degree of Doctor of Philosophy

in

Public Health (Epidemiology)

by

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The dissertation of Daniel Joseph Crouch is approved, and it is acceptable in quality and form for publication on microfilm and electronically:

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Dedication

To my two children, Teresa and Madeline. Always follow your dreams

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2. Ramchandar N, Slayden T, Garcia-Rivera JA, **Crouch D**, Gallagher K, Harris D, Lane A, Ha L, Halliday M, Ruano E, Treiber D, Quast T, Feinberg J. Management of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Onboard a U.S. Navy Hospital Ship Amid a Global Omicron Surge. Mil Med. 2022 Dec 30:usac425. doi: 10.1093/milmed/usac425. Epub ahead of print. PMID: 36583720.

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Abstract of the Dissertation

Characteristics Of Non-Benzodiazepine Sedative Hypnotic Use In Combat Injured U.S. Service Members With Insomnia

by

Daniel Joseph Crouch

Doctor of Philosophy in Public Health (Epidemiology)

University of California San Diego, 2023

San Diego State University, 2023

Professor Richard A. Shaffer, Chair

Objectives: There are currently no military studies on non-benzodiazepine sedative hypnotic (n-BSH) use among combat injured active-duty service members. There were three objectives of this dissertation: (1) describe rates and patterns of n-BSH medications in this population; (2) examine how duration of n-BSH use affects perceived Health Related Quality of Life (HRQOL); and (3) examine the role of traumatic brain injury (TBI) in n-BSH prescription patterns among these injured service members.

Methods: Three population-based retrospective studies were conducted on all U.S. service members who sustained injuries during deployed operations between September 2001 and Aug 2019 and who received pharmacological treatment for insomnia. These studies utilized six data sources from the Department of Defense (DoD); the Expeditionary Medical Encounter Database (EMED), Military Health System Data Repository (MDR), Pharmacy Data Transaction System (PDTS), Defense Manpower Data Center (DMDC), Career History Archival Medical and Personnel System (CHAMPS), and the Wounded Warrior Recovery Project (WWRP). DMDC and EMED contains deployment and combat information for Operations Iraqi Freedom and Enduring Freedom. Classification of injury, TBI status, n-BSH prescription patterns, and clinical diagnoses were abstracted from the MDR and PDTS. Mental and physical wellbeing questionnaires from the WWRP were utilized to assess health related quality of life (HRQOL).

Results: n-BSHs were the most frequently prescribed medication class among service members who sustained combat injuries. Long-term prescriptions were largely driving the high prevalence rates of n-BSH, given that 42.6% of service members were prescribed n-BSHs for 6 months or longer. Additionally, they experienced high rates of post-traumatic stress disorder (50.6%), TBI (42.5%), depression (39.1%), anxiety (52.0%), and chronic pain (15.1%). After adjustment, there was no statistically significant relationship between n-BSH prescription characteristics with service members' HRQOL, or between TBI and n-BSH prescription characteristics.

Conclusions: Combat injured service members' n-BSH prescription patterns exceed Food and Drug Administration and American College of Physician guidelines. While n-BSH patterns did not differ by TBI or HRQOL, the high prevalence of long-term n-BSHs is alarming and given the high prevalence of comorbid conditions in this population, clinical management of these service members should include a multidisciplinary approach.

1. Introduction

In response to the attacks on the World Trade Centers on September 11, 2001, the United States began combat actions in Operation Enduring Freedom (OEF) and Operation Iraqi Freedom (OIF). Since the initiation of OEF and OIF, there have been more than 5 million deployments in support of these operations, with many service members experiencing multiple combat tours.[1] Among those deployed, more than 50,000 service members incurred combat injuries.[2] The increased survivability of combat casualties relative to previous conflicts emphasized the need to evaluate longer-term outcomes. Recent conflicts such as those from OEF and OIF, have shown that service members are surviving combat more frequently, but their increased survival rates following injury has brought into focus psychological morbidities sustained from war.[3]

1.1. Combat Injury and Traumatic Brain Injury in Military Service Members

Participation in wartime activities among service members of the United States military are unique stressors that may involve the perceived threat to one's life and physical disability (both acute and persistent). Additionally, physical injuries (e.g. traumatic brain injuries) have been linked to the development of psychological illness and morbidity (both acute and persistent), which can also last decades after the physical injury occurs.[4] Survivors of these injuries commonly experience post-traumatic stress syndrome (PTSD), depression, anxiety, sleep disturbances, substance abuse disorders, and others.[5] These conditions are known to interfere with functional gains and quality of life.[4] Not surprisingly, the Department of Veterans Affairs (VA) has seen a sharp rise in psychological disability compensation.[6]

Traumatic Brain Injury (TBI) is defined as a disruption in brain function due to the impact of contact forces including acceleration, deceleration, or collision, manifesting as altered

state of consciousness, neurological defect, and amnesia. The Armed Forces Health Surveillance Division includes classification for TBI severity, which is categorized as mild (with or without loss of consciousness), moderate (with or without prolonged loss of consciousness), and severe.[7,8] Mild TBI (mTBI) (i.e. concussions) have become the most commonly reported head injury of combat injuries in OEF and OIF.[9] Health issues subsequent to combat-related mTBI can often be variable and sometimes last years.[7] Commonly reported symptoms after mTBI include a variety of physical, psychological, neurological and sensory complaints.[8-12] As such, management of mTBI in a military setting typically involves integrated care.[13]

An increase in blast injuries relative to previous wars is credited for the higher prevalence of mTBI.[4] Blast injuries account for the majority of all combat injuries in Iraq and Afghanistan, and can cause mTBI by way of multiple mechanisms.[5,6] In fact, 20% of service members reporting combat exposure experienced a probable mTBI.[10,11] This high percentage of mTBI is likely due to advances in field medical care which has resulted in better injury survival rates, as well as the style of warfare fought in OIF. Additionally, improvised explosive devices are responsible for many of the attacks that were undertaken in OIF and OEF, and it's estimated that 59% of those injured by these blasts meet the criteria for TBI.[12] The primary condition of interest in sustainment of combat injury in this proposal is mTBI (both with and without loss of consciousness [LOC]) with its effect on injured service members' psychological conditions.

Objective injury measures, such as injury severity score, appear to be a poor predictor of later psychological illness,[13] so non-objective measures, such as psychological injuries, have become increasingly important measurements. Psychological consequences (e.g. PTSD) of exposure to a stressful event that someone perceives as traumatic have been associated with military combat since it was first recognized among veterans of the Vietnam war. Physical injury

has been shown to be associated with the development of PTSD and other psychological illnesses (either directly or comorbid with PTSD). Comorbid psychological diagnoses are very common in those suffering from PTSD, with depression, substance abuse, and other anxiety disorders being the most commonly reported.[5] Studies have also examined predictors of PTSD following physical injury, and some have explored common conditions such as sleep disturbances.

1.2. Insomnia In Military Service Members

Across the majority of military conflicts since the 19th century, symptoms of psychological morbidity have been documented and can include headaches, dizziness, or disturbed sleep.[14] Insomnia, a common and important sleep disorder that includes having trouble falling and/or staying asleep, is the most prevalent long-term sleep disorder in the U.S. and affects approximately 10% of its population.[15] Insomnia is a documented consequence of both combat and TBI, and can be present in as many as 46%[7] in civilians and 50%[16] of service members following TBI events. Interestingly, mTBI has been shown to be more strongly associated with insomnia than moderate to severe TBI.[17] This difference is likely due to those with moderate to severe TBI are less likely to report sleep disturbances if they are only minor complaints compared to other cognitive sequelae. Not surprisingly, insomnia is more prevalent and more severe in service members with co-occurring PTSD and TBI,[18,19] conditions shown to contribute jointly and independently to insomnia.[16]

Sleep duration and quality are linked to biological functions and psychological performance, and deficiencies in these are associated with a range of cognitive outcomes such as depression, PTSD, processing difficulties, behavioral irregularities, and anxiety.[20-26] Dificiencies are also linked to chronic health conditions such as heart disease, stroke, diabetes mellitus, and

chronic pain.[21] Due to the unique and stressfull nature of military operations, obtaining sufficent sleep can be difficult, and service members show a 2-fold increased risk of insomnia to that of the general U.S. population,[27-29] and similar rates are seen across all branches of service.[30] Veterans Affairs (VA) estimates report that while only 3.4% of veterans are diagnosed with insomnia, self reported sleep disturbances are as high as 57.2%.[20] Among active-duty members, 20% have diagnosed insomnia,[5-7] while self reported sleep disturbances are estimated as high as 54%.[31,32] Since increased diagnosis of insomnia has been linked to combat deployments,[33,34] it is not suprising that the use of pharmacological sleep aids has increased by 652% among military and veterans since 2003, spiking considerably after the invasions of Iraq and Afghanistan.[35]

While limited, military research that explored medication treatment for sleep in injured service members found that sleep restoration improved health and QOL.[36] However, studies that explore different treatment characteristics are scarce (medication classes, duration of use, or dosage). This represents an important topic since it can provide better perspective into how duration of medication use, or severity of insomnia (rather than insomnia presence) is impacted by injury and TBI.

1.3. N-BHS Use in Military Service Members

Introduced in the 1990s, n-BSHs (e.g. zolpidem, zaleplon, and eszopiclone) were marketed as safer alternatives to benzodiazepines for treatment of insomnia.[37] They have continued to be the treatment of choice for pharmacological treatment of insomnia since their introduction due to the perception of limited side effects. Recent studies, however, provide evidence that n-BSH adverse outcomes include falls,[38-41] cognitive impairment,[41-45] psychological disorders including depression[20,21] and suicidal ideation.[46,47] The high prevalence

of insomnia and inherent risk in the military profession underscores the need for a better understanding of sedative hypnotic prescribing in this population.

Findings from research in civilian populations show that long-term n-BSHs use may be associated with adverse outcomes, and these studies have prompted guidelines recommending use of these medications on a short-term basis.[48] In recently published treatment guidelines for chronic insomnia, the American College of Physicians (ACP) recommended that these medications only be used on a short-term basis and if behavioral treatments alone are ineffective.[49-51] Despite concerns for cognitive impairment, n-BSH prescriptions remains common in service members with insomnia.[27] Additionally, antipsychotics and benzodiazepines are shown to be either ineffective or are associated with significant harm in treating PTSD-related insomnia, so n-BSH have become the primary form of pharmacological treatment for service members with insomnia related to combat injury or PTSD.[52]

Long-term n-BSH Use

Alderman et al reported that approximately 70% of veterans taking n-BSHs had more than six months continuous use.[53] This is concerning because in addition to the adverse effects mentioned, studies have shown that long-term use increases risk for depression, anxiety, and mortality by as much as 75% among n-BSH users compared to non-users.[54] Although this study did not include current military members, it highlights the adverse effects that may be associated with long-term n-BSH use.[27] Military research, while limited, reports that prescribing of n-BSH has increased, and that refills rather than new prescriptions may be driving the increase.[15,27,48,55] Because sleep disorders have become more prevalent in U.S. service members, further research is needed to examine possible changes in n-BSH use.

A new VA study explored patterns of n-BSH use among a larger cohort of OIF and OEF veterans. Similar to Alderman's study above, this study found that the majority (77.3%) of veterans who received zolpidem (the most commonly prescribed n-BSH medication) were long-term users, and that long-term or high dose use was associated with conditions such as PTSD, more frequent comorbidities, and antidepressant use.[27] These VA studies were important steps in understanding n-BSH use among military service members. However, they did not discuss combinations of sleep medications, nor did they examine n-BSH use among Active-Duty Service Members. Therefore, further research on this topic is still warranted.

High Dose n-BSH Use

While research in high dose use of n-BSH is limited, a Taiwanese cohort of patients prescribed n-BSH found that high dose n-BSH use is associated with dependence, depression disorders, and depressive symptoms.[56] Another Taiwanese study in this same cohort reported higher risk for dependence compared to those consuming n-BSH at lower dosages.[57] While limited, military data also shows that higher dosages are associated with adverse psychological effects,[27] and that the largest increase was among those with PTSD and previous mental health disorders (3 fold increase ~ 7% of service members).[58] This is expected since service members with previous PTSD diagnosis also experience worse insomnia.[16] They were also shown to have relapsing insomnia, and are more likely to be chronic n-BSH users.[59] Fortunately, the frequency of high dose prescriptions is low (1%) in veteran n-BSH users, suggesting than this may be a small risk group.[27] To my knowledge, no military studies have explored high dose n-BSH use in broad Active Duty service members, let alone the higher risk group of service members who sustained combat injury.

The associations of combat injury and adverse effects with n-BSH treatment pattern is critical for improving the military's understanding of sedative hypnotics, their prescribing patterns and impact on service members to in order to improve short-term and long-term care or retention. Additionally, it illustrates the need to explore these relationships with high quality longitudinal data.

1.4. Health Related Quality of Life – Indicator for Service Member Wellbeing

Health Related Quality of life (HRQOL), a multidimensional indicator of overall well-being, is frequently degraded in combat-injured service members.[60] The US military has been interested in HRQOL research and how combat related injuries impact service members and their military retention. Due to the circumstances surrounding combat injuries, psychological trauma such as PTSD and depression are known to be associated with lower HRQOL.[20,60,61] In addition, the World Health Organization's International Classification of Functioning published a report that body system impairment resulting from combat injuries can result in activity limitations that may also have negative effects on HRQOL.[62] This can contribute to a cycle of disablement for service members, leading to impairment, activity limitation, or participation restriction, further diminishing HRQOL.[62] Due to the potential impact of persistent symptoms and disablement on low HRQOL following combat injury, it is important to understand the factors that have the greatest contribution to long-term morbidity in combat injured service members. From a clinical perspective, a greater understanding of what conditions impact HRQOL following combat injury could allow for improved treatment and long-term quality of care for injured service members, which would assist in mitigating threats to HRQOL.

Military research on insomnia suggests that service members with insomnia have reduced HRQOL, especially those with co-occurring PTSD.[16,52,63,64] However, these studies were

restricted to reporting "any treatment" for insomnia. Interestingly, they did show that HRQOL is worse among those who experience more severe injuries during combat, and suggest that long-term effects from combat injury may manifest as decreased perceived health or even experiencing more morbidities.[65] In studies among veterans, former service members with insomnia and other sleep disturbances had increased incidence of chronic conditions such as hypertension, diabetes, psychiatric disorders and reduced HRQOL.[58] They also found that the combination of insomnia co-occurring with other chronic conditions decreases HRQOL more so than each condition alone.

Few studies have examined the relationship between physical injury sustained during combat and psychological outcomes (e.g. insomnia) during military conflict, particularly the treatment patterns of psychological outcomes and how these are correlated to the need for long-term treatment. No military studies have explored medication classes for insomnia treatment among combat injured service members. Considering the increased prescription use of n-BSHs among service members in recent decades, this represents an important step to understanding how insomnia treatment (e.g. how characteristics of n-BSH use [duration and dosage]) could affect HRQOL in combat injured service members. This may have contributed to increased long-term use of n-BSH among service members and further highlights the need for additional research on these topics.

1.5. Purpose of Current Study

The purpose of this study is to describe n-BSH prescription patterns in combat injured service members, and to examine the association between characteristics of combat injury and n-BSH prescription use. This novel focus fills an important gap in current insomnia military literature. Based on the evidence in other military research, it is hypothesized that more severely

injured service members, particularly those who sustained TBI during combat operations, will have both longer duration and higher dosage of n-BSH prescriptions, and that longer duration of n-BSH prescription use is associated with poor HRQOL and other psychological outcomes. Specifically, this dissertation examines different aspects of n-BSH prescription patterns among combat injured service members by the following aims:

Aim 1: Report n-BSH prescription patterns among service members who sustained injury during combat operations from OIF and OEF. We report current n-BSH use across all DoD branches of injured service members with insomnia by demographics, injury characteristics, and diagnosed psychological comorbidities.

Aim 2: Explore the relationship between duration of n-BSH prescription patterns and HRQOL among these service members. We report duration of n-BSH prescription patterns among a subset of service members from aim 1 who are part of the WWRP, and who provided questionnaires on their mental and physical wellbeing. We will model n-BSH use with these scores to determine if longer duration of n-BSH use is associated with worse HRQOL.

Aim 3: Determine if the severity TBI sustained during combat injury is associated with longer n-BSH prescription needs among these service members. We explore TBI severity to determine if TBI impacts the duration or dosage of n-BSH prescription patterns among aim 1 service members. We will model TBI severity with adjustment on important comorbidities related to insomnia and injury severity.

Data for these three retrospective studies included for this dissertation were constructed utilizing six data sources from the department of defense (DoD). Each dataset was requested

through and is currently maintained by Naval Health Research Center (NHRC) and will be described in detail in the next section. All study procedures were approved by the Institutional Review Board at NHRC, San Diego, California.

To begin, the overall cohort of injured OIF and OEF service members with insomnia was described by their medication class, injury characteristics, and characteristics of n-BSH prescription patterns (Aim 1). Service members' n-BSH prescription patterns were then examined as predictors for HRQOL following both combat injury and insomnia diagnosis (Aim 2). Finally, an analysis was conducted to examine TBI characteristics of combat injury with n-BSH prescription patterns (Aim 3). All statistical analyses were conducted using SAS (version 9.4; SAS Institute Inc., Cary, North Carolina).

2. Building The Military Insomnia Clinical Encounter Repository (MICER)

Data for this dissertation was a compilation of six military and Veteran Affair (VA) data sources. Construction of this database was challenging and consisted of six formal data requests, data merges, and data cleaning in order to create a usable data base for combat injured service members with insomnia. The MICER's six data sources were merged in numerical order (starting with the first data source listed below) using SAS Enterprise (version 7.1; SAS Institute Inc., Cary, North Carolina). Data Cleaning, variable creation, etc. was all completed using SAS (version 9.4; SAS Institute Inc., Cary, North Carolina) as described elsewhere in this document. Data sources consist of the Expeditionary Medical Encounter Database (EMED), Defense Manpower Data Center (DMDC), Pharmacy Data Transaction System (PDTS), Career History Archival Medical and Personnel System (CHAMPS), the Military Health System Data Repository (MDR), and the Wounded Warrior Recovery Project (WWRP), all of which are described below and referenced in each of the methods sections of their respective manuscript. I consulted with Mr. James Zouris, a statistician from the Department of Medical Modeling and Simulation at NHRC, who supervised these data merges to ensure the MICER was constructed correctly. Details of the MICER construction are included in the Appendix.

(1) The EMED includes all service members with history of combat exposure and combat injury who deployed to Iraq, Afghanistan, or Kuwait between January 2001 and August 2021. It includes service member identification numbers and injury characteristics and is an important data source for combat injury research at NHRC. This was the first data source used and all other data sources were merged into this for the MICER development. Since this was the first dataset used, I created a subset of the EMED to start the MICER, which included a wound date between September 2001 and August 2019 (conclusion of OIF and OEF theatre involvement) and a

documented injury with severity score. The most severe injury recorded where a TBI occurred was the injury recorded for the MICER. If no TBI was ever documented, the most severe injury was recorded. All service members who died directly from combat injury removed from the MICER (designated as "killed in action" in EMED). The manuscripts themselves excluded death within 2 years, while the MICER did not (to allow future research opportunity).

(2) DMDC is an electronic deployment database from the DoD. It also contains service member deployment data that includes start and end dates for each deployment and location. It currently consists of over 2.7 million records of service members who have deployed at any time since 2001. Deployment dates and locations were then merged into the EMED by NHRC subject identification numbers. This dataset was used to ascertain previous deployment history.

(3) The PDTS was used to obtain pharmacy records for n-BSH use. The PDTS provides detailed listings of outpatient medications prescribed to all military service members. It includes medication names, dispensing dates, etc. It lists medication names and classes by their therapeutic codes (281604, 282400, 282404, 282408, 282492, and 562208) for each service member for every dispensed prescription. I requested all medications for EMED service members and merged the insomnia medications into the MICER file.

(4) CHAMPS includes demographic data for all service members associated with the EMED. CHAMPS contains administrative information for service members that include demographic data such as race/ethnicity, age, rank, etc. However, due to user agreements with the CHAMPS data sources, I was limited in what information was available with CHAMPS, so I also used the EMED and MDR (below) to supplement demographic data for MICER service members.

(5) The MDR is a comprehensive database that collects and validates DoD medical treatment facilities and from TRICARE Purchased Care program for service members. The MDR contains several integrated datasets, such as the Standard Inpatient Data Record, Comprehensive Ambulatory Provider Encounter Record, Military Health System GENESIS, TRICARE Encounter Data Institutional/Non-Institutional, and the Pharmacy Data Transaction Services (PDTS described above). Ultimately, the MDR is a comprehensive data source for all military health visits and diagnosed conditions. It includes patients identified for disease and injury management programs and provides complete records of inpatient and outpatient health encounters. It was used to obtain disease/condition diagnoses and comorbidities related to insomnia. I merged all ICD-9 codes to each MICER service member subject ID, and defined conditions related to insomnia or combat injury in the MICER dataset (e.g. PTSD, depression, anxiety, chronic pain, insomnia). At this step, there was no restriction to the frequency of medical conditions each subject included. Specific medical conditions are mentioned in each manuscript in subsequent sections and were coded as "present vs absent" for the diagnosed condition of interest for each manuscript. TBI was originally categorized according to the Barrel Matrix as per the proposal defense. However, TBI categorizations was then updated in December 2022 to match the Armed Forces Health Surveillance Branch (AFHSB) case definitions, which includes updated guidance on categorizing TBI severity. I ultimately used the Barrel Matrix to categorize injury bodily location but not for TBI categorization.

(6) The WWRP was originally initiated by NHRC to examine long-term patient-reported physical and mental outcomes of injured service members and represents the only prospective study that collects long-term quality of life data from enrolled active-duty service members and veterans that were wounded in combat. It includes patient-reported physical and mental

outcomes for enrolled service members since 2001. In 2017, the WWRP Introduced the Short Form – 36 (SF-36). These self-reported HRQOL scores are for both current service members and veterans after discharge that are enrolled into the WWRP. Quality of life scores were then imported to the MICER by subject identification number. Many participants in the WWRP study have taken surveys multiple times. I included the first quality of life survey score for each service members that was at least 730 days (2 years) after the recorded date of injury.

DoD data sources for this study are managed by two DoD agencies: 1) Defense Health Agency (DHA), which oversees the MDR and PDTS, and WWPR, and 2) Defense Manpower Data Center (deployment and personnel data), which oversees the DMDC and CHAMPS. I submitted three IRB requests via the NHRC IRB request procedures and was approved under the IRB protocol for the EMED (NHRC.2003.0025). Requested data sets included subject identification numbers with no personal identifiable characteristics. NHRC uses internal servers for data storage and management. Each server has a hard drive with system backups running biweekly. All data received from DoD or other sources are housed on site at NHRC. It is NHRC policy that that no data is stored, saved, or transferred outside these servers. As the principal investigator, I have overall responsibility for data management of the MICER over the course of this project and beyond.

This compiled MICER includes all U.S. service members who have deployed during OIF or OEF and were injured in combat operations, survived their injuries, were diagnosed with insomnia after injury, and received at least one prescription for insomnia treatment. This repository includes the injured service members' demographics, deployment data, and any clinically diagnosed condition following their injury. Ultimately, the MICER provides a complex

data source for combat injured service members that will be used for many future projects at NHRC and other military research commands.

3. N-BSH Use Among U.S. Combat Injured Service Members: A Descriptive Review

3.1. Abstract

Introduction: Non-benzodiazepine sedative hypnotics (n-BSH) have become the most prescribed treatment option for insomnia in military service members, but no military studies have explored n-BSH among those injured during combat operations. **Methods**: In this descriptive study, we identified all service members deployed to Operations Iraqi Freedom (OIF) or Enduring Freedom (OEF) between 2001 and 2019 that (1) were injured during combat, (2) were diagnosed with insomnia, and (3) received pharmacological treatment for insomnia within 2 years following injury. Injury severity and body location were classified according to the Injury Severity Score and Barell Matrix respectively. We used chi squared frequency statistics to compare n-BSH prescriptions with other pharmacological treatment classes with the Defense Pharmacy Data Transaction System. We compared injury severity with both duration of n-BSH use and dosage type, as well as explored the annual proportions of n-BSH following injury. **Results**: N-BHSs were prescribed in 61.6% of service members, with Zolpidem being the most frequent medication (54.2%) prescribed overall. Diagnosed comorbidities were more common in n-BSH users. Those with mild to moderate injuries were more likely to report shorter duration of prescriptions, while service members with serious to severe injuries were more likely to be prescribed n-BSH for at least 6 months. **Conclusion**: N-BSH medications were the most frequently prescribed medication class among service members with insomnia who sustained combat injuries 2 years following injury. Long-term prescriptions are largely driving the high prevalence rates of n-BSH, which is correlated with the severity of injury sustained during combat.

3.2. Introduction

In response to the attacks on the World Trade Centers on September 11, 2001, the United States began combat actions in Operation Enduring Freedom (OEF) and Operation Iraqi Freedom (OIF). Since the initiation of OEF and OIF, there have been more than 5 million deployments in support of these operations, with many service members experiencing multiple combat tours.[1] Among those deployed, more than 50,000 service members incurred combat injuries.[2] The increased survivability of combat casualties relative to previous conflicts emphasizes the need to evaluate longer-term outcomes. These outcomes include sleep disturbances such as insomnia, which are particularly common among injured service members.[34]

Insomnia is associated with a range of cognitive outcomes such as depression, post-traumatic stress disorder (PTSD), processing difficulties, behavioral irregularities, and anxiety.[20-26] Due to the unique and stressful nature of military operations, obtaining sufficient sleep can be difficult, and service members show a 2-fold increased risk of insomnia relative to that of the general U.S. population.[27-29] Similar rates are seen across all branches of military service.[30] Veterans Affairs (VA) estimates show that 3.4% of veterans are diagnosed with insomnia,[20] but active duty estimates show insomnia diagnosis as high as 20%.[5-7] Since combat deployments are associated with increased diagnosis of insomnia,[33,34] it is not surprising that the use of pharmacological sleep aids has increased by 652% among military and veterans since 2003, spiking considerably after initiation of the conflicts in Iraq and Afghanistan.[35] Pharmacological treatment for insomnia in service members is reported as high as 42% of those with diagnosed sleeping disorders, increasing considerably since 2009.[35]

Introduced in the 1990s, non- benzodiazepine sedative hypnotics (n-BSH) (e.g. zolpidem, zaleplon, and eszopiclone) were marketed as safer alternatives to benzodiazepines for treatment of insomnia.[37] They have continued to be the treatment of choice in military populations for pharmacological treatment of insomnia since their introduction due to the perception of limited side effects. Recent studies, however, provide evidence that n-BSH have adverse outcomes, which include falls,[38-41] cognitive impairment,[41-45] psychological disorders including depression[20,21] addiction, and suicidal ideation.[46,47] Additionally, long-term n-BSH use increases risk for depression, anxiety, and mortality by as much as 75% among n-BSH users compared to non-users.[54] Research in civilian populations shows that long-term use of n-BSH may be associated with adverse outcomes, and these studies have prompted guidelines recommending use of these medications on a short-term basis.[48] In recently published treatment guidelines for chronic insomnia, the American College of Physicians recommended that n-BSH be used only on a short-term basis and only if behavioral treatments alone are ineffective.[66]

Despite concerns for cognitive impairment, n-BSH remain commonly prescribed in military service members with insomnia.[27] An Australian military study reported that approximately 70% of those taking n-BSH had more than six months of continuous use.[53] While US military research is limited, reports show that prescribing of n-BSH has increased and that refills may be driving the increase.[15,27,48,55] Unfortunately, no military research has explored n-BSH use among combat injured service members. Considering successful treatment of service members with combat injuries is necessary for retention, understanding n-BSH use in this unique population is critical. The current study's aim is to describe pharmacological prescribing patterns of n-BSH in combat injured service members.

3.3. Methods

Study Participants

We identified all U.S. service members who were injured in combat during operations Iraqi Freedom (OIF) and Enduring Freedom (OEF) from the Expeditionary Medical Encounter Database (EMED).[67] This study included all U.S. service members who were injured in combat who received a clinical diagnosis for insomnia (*International Classification of Diseases, 9th Revision* [ICD-9] 307.42; 327.00; 327.01; 327.02; 327.09; 780.51; 780.52 codes and their corresponding *10th Revision* [ICD-10] F51.01; F51.03; F51.04; F51.05; F51.09; G47.00; G47.01; G47.09)[59,67] and who received pharmacological treatment for insomnia within 2 years of sustaining combat injury from deployment in operations OIF or OEF between January 2001 and August 2019.[65,67] We excluded those who died due to injury or during the follow-up period (n=519).

Measures

Injury severity was classified via the injury severity score (ISS), an anatomical scoring system that values the combined effects of multiple injuries, calculated by certified nurse coders following review of the EMED clinical records.[68] ISS ranges from 1 to 75, and in the current study, was categorized as 1–8 (mild-to-moderate injuries) or 9 or greater (serious-to-severe injuries) similar to others.[65,68,69] Only one injury event was recorded per service member, which was the most severe injury event according to their ISS. Injury bodily location was categorized according to the Barrell injury diagnosis matrix, a CDC endorsed matrix for the classification of traumatic injuries by anatomical location.[70] We coded injury location according to injury severity

and included the most severe injury for each member,[3] and categorized them as head and neck, spine and back, torso, extremities, and other.

Pharmaceutical medications for insomnia were obtained from the Pharmacy Data Transaction System (PDTS), which provides detailed listings of outpatient medication names and dispensing dates of all prescribed medications for military service members. Medication use is provided by the PDTS under the MDR medication therapeutic codes (i.e., 281604, 282400, 282404, 282408, 282492, and 562208). We explored n-BSH prescription patterns in service members as they compare to other pharmacological treatment classes. Service members with a prescription lasting equal to or greater than 30 consecutive days were categorized as a prescribed user of that medication class.[35,48] We categorized medication classes as n-BSH (Eszopiclone, Zaleplon, Zolpidem), benzodiazepines (Estazolam, Flurazepam, Temazepam, Triazolam), melatonin receptor agonists, or MRA (ramelteon), Antihistamines (Diphenhydramine, Doxylamine, Hydroxyzine), and antidepressants (Trazodone, Doxepin, Mirtazapine).[71] Antidepressant medications were only recorded if dosing was within guidelines for insomnia treatment (as opposed to higher doses needed for depression treatment), which include Trazodone (<=100mg),[72] Doxepin (<=6mg),[71] and Mirtazapine (<=30mg).[73] We calculated prevalence rates of n-BSH use (proportion of n-BSH use / number of participants with insomnia) and annual prevalence rates (proportion of n-BSH use for that given year / number of participants with insomnia). We then summed the total number of days service members received n-BSH prescriptions from the PDTS database.

Duration of n-BSH use was categorized in the following ways: (1) prescription for n-BSH less than 90 days after diagnosis of insomnia,[35] (2) greater than 90 days and less than 180 days,[48,74] and (3) greater than 180 days and less than two years.[47,48] Participants who used more

than one n-BSH were categorized according to duration of use (short-, mid-, and long-term use as described above) for each n-BSH. We then coded these participants according to the n-BSH they used the longest.[48,75] Participants with n-BSH refills more than 60 days apart indicated breaks in medication use and were separately coded as intermittent n-BSH users. We also explored duration of use and dosage type (e.g. normal vs high dose) of n-BSH for two years following combat injury.[67] Dosage was defined dichotomously in the following ways: (1) normal dose (eszopiclone ≤3mg, zaleplon ≤10 mg, zolpidem immediate release: ≤10mg for males and ≤5 for females, zolpidem tartrate extended release: ≤12.5mg for males and ≤6.25mg for females), and (2) high dose (eszopiclone >3mg, zaleplon, >10mg, zolpidem immediate release: >10mg for males and >5mg for females, zolpidem tartrate extended release >12.5mg for males and >6.25mg for females).[22,36]

Demographic characteristics were included to describe participants by n-BSH use. Age was calculated from participants' date of birth at the time of injury and was categorized as 10 year increments (<24, 25-34, 35-44, 45-64, 65+).[35] Sex was dichotomized as male and female. Race and ethnicity were categorized as Non-Hispanic white, Non-Hispanic black, Hispanic, other as consistent with other military research on depression.[76] Branch of service was extracted from the DMDC records and categorized as Air Force, Army, Navy, and Marine Corps.[35] Number of previous deployments was also recorded from DMDC records based on the beginning and ending dates for all deployments to Iraq (OIF) or Afghanistan (OEF). Deployment is defined as greater than 30 days but less than 18 months for each deployment.[77] We recorded the number of deployments prior to the deployment causing injury and then reported deployment history dichotomously (yes/no).[77]

We extracted clinically diagnosed conditions to characterize psychiatric and medical comorbidities for each service member similarly to other military research.[27] We used ICD-9 and corresponding ICD-10 codes from the MDR as dichotomous variables (yes/no). These include obstructive sleep apnea (ICD-9 327.20, 327.21, 327.23, 327.29, 786.03, 780.53 and ICD-10 G47.30, G47.33, G47.39), anxiety (ICD-9 300.0, 300.2, 300.3, 309.8 and ICD-10 F41.9), chronic pain (ICD-9 338.2, 338.4 and ICD-10 G89.2, G89.21, G89.4), history of traumatic brain injury, or TBI (ICD-9 850, 851, 852, 853. 854.0 and ICD-10 S02.0, S02,1, S02.8, S02.91, S04.02, S04.03, S04.04, S06.9, S09.8 S09.90), depression (ICD-9 296.20; 296.22; 296.21; 296.23; 296.24; 296.30; 296.31; 296.32; 296.33; 296.34; 296.82; 298.0; 300.4; 309.0, 309.1; 311 and ICD-10 F43.21; F32.89; F32.0; F32.2; F32.3; F32.9; F34.1; F43.21; F32.3; F33.3; F33.2; F33.0; F33.1; F33.9) and PTSD (ICD-9: 309.81 and ICD-10: F43.12).[78] We reported comorbid conditions individually and as the total number co-morbidities for each participant, which were then categorized as none, one, or 2+.[3,36,77,79]

Statistical Analysis

All descriptive statistical analyses were conducted using SAS (version 9.4; SAS Institute Inc., Cary, North Carolina). The overall sample of combat injured service members with insomnia were reported according to their demographic characteristics and injury severity and type at baseline.

3.4. Results

Table 1 describes insomnia prescription classes by demographic and comorbidity characteristics. Of the 8071 participants in this database, 90.2% were less than 34 years old, males (96.3%) and non-Hispanic Whites (75.1%). The most frequently prescribed insomnia

medication was n-BSH (61.6%), followed by low dose antidepressants (39.3%), antihistamines (15.9%), benzodiazepines (7.8%), and lastly melatonin receptor agonists (2.1%). Prescriptions did not vary significantly across age groups or the number of previous deployments. The number of diagnosed comorbidities also related to medication prescriptions. Those with more comorbid conditions (PTSD, depression, anxiety, and chronic pain) were more likely to receive any of the prescription medication classes than those with fewer comorbidities. Specifically, n-BSH and antidepressant prescriptions represented the largest proportion of prescriptions in service members with PTSD, depression, anxiety, and chronic pain. ISS also varied by medication use, and those with more severe injuries sustained during combat represented a larger proportion of all classes of prescriptions except BZDs.

Table 2 describes prescription use patterns by medication class as well as medication names in non-mutually exclusive groups. N-BSH use was the most common medication group (61.6%), followed by any antidepressant use (39.3%), antihistamines (15.9%), benzodiazepines (7.8%) and lastly melatonin receptor agonists (2.1%). Additionally, chronic medication users were more likely to be prescribed n-BSH and antidepressants, but Service members receiving antidepressants were less likely to be intermittent users. Most antihistamine prescriptions (59.3%) were prescribed for less than 30 days. As expected, the benzodiazepine use group were less likely to be intermittent or chronic prescriptions. The most frequently prescribed medications were Zolpidem (54.2%), Trazodone (35.4%), and Eszopiclone (22.1%). Of the n-BSH medications (Zolpidem, Eszopiclone, Zaleplon), zolpidem was prescribed more frequently for 30 days or less (40.2%), eszopiclone was prescribed more frequently for 90 or more days of continuous use (36.8%), while zaleplon only represented 1.2% of n-BSH prescriptions but was also prescribed more frequently for 30 days or less (56.7%). Of the low dose antidepressants

medications prescribed for insomnia (Trazodone, Doxepin, Mirtazapine), all three were prescribed more frequently for less than thirty days (43.0%, 67%, 48.8% respectfully). Among prescribed benzodiazepines (Temazepam, Triazolam, Flurazepam, Estazolam), Temazepam was more frequently prescribed for 90 days or more (22.9%) while Triazolam was more frequently prescribed 30 days or less (77.9%).

Table 3 describes duration of use and dosage for n-BSH prescriptions according to the severity of injury sustained in combat operations. Of the 4,968 Service members who were prescribed n-BSH at any time within two years following insomnia diagnosis, 32.6% received prescriptions for less than three months, 24.8% between three and six months, and 42.6% for at least six months following insomnia diagnosis. Those with mild to moderate injuries were more likely to receive shorter duration of prescriptions, while serious to severe injuries were more likely to receive n-BSH for at least six months. Service members prescribed high dose n-BSH only represented 0.5% of our population. Of these 40 high dose participants, 10 (25.0%) received serious to severe injuries but these results were not significant.

Figure 1 shows the annual breakdown of the proportion of service members being prescribed n-BSHs compared to all insomnia treatment classes according to the year of their combat injuries. Although most service members in this study were injured between 2006 and 2013, n-BSH prescription rates remained consistently between 50% and 70% of all insomnia prescriptions until approximately 2013, where they decreased through the remaining years of OIF and OEF for newly injured service members. Initially, those with prescriptions under 3 months was the largest n-BSH group, but by 2005, prescriptions longer than 6 months contributed to the largest proportion of users until the end of OIF and OEF. Additionally, in 2016, n-BSH prescriptions decreased to the lowest level of n-BSH use during this time period,

but prescriptions for 3 months or more continued to represent the largest proportion of n-BSH use.

3.5. Discussion

To our knowledge, this is the first U.S. military study on insomnia treatment that includes all service members injured in combat during OIF and OEF. In addition, we report all prescription treatment classes for insomnia, including low dose antidepressants documented by the PDTS. Overall, 61% of prescriptions for combat injured service members were n-BSH, which was consistent in all military branches, illustrating that n-BSHs are the most commonly prescribed pharmacological treatment class for insomnia in combat injured service members. Additionally, 67.4% of n-BSH prescriptions are at least 3 months, which exceeds the Food and Drug Administration (FDA) warning labels for these treatment classes.[80] This is concerning since research shows that n-BSH use is associated with increased mortality rates,[54] cognitive impairment,[41-45] psychological disorders including depression[20,21] and suicidal ideation.[46,47] It is also concerning since the American College of Physicians (ACP) guidelines limit prescriptions to short-term periods after a trial of behavioral therapy such as cognitive behavioral therapy for insomnia treatment (CBT-I).[49-51] Given the military's interest in treatment and rehabilitation of injured service members, these results are important since they show the current status of n-BSH prescription patterns in active duty service members who sustained combat injury during OIF or OEF.

Our results align with a recent military study about n-BSH use, which showed that many n-BSH users receive prescriptions longer than 6 months (42.6%) and that long-term use is driving increased prescription trends.[53] Only 32.6% of service members in our cohort were prescribed n-BSH medications for short-term periods, which is lower than the 80% reported

among service members in Thelus Jean et al's study.[35] However, our study population includes combat injured Service members with insomnia, suggesting these injuries and subsequent insomnia treatment may lead to a larger proportion of longer-term medication users. Considering 26.2% of those who experienced serious to severe injury were prescribed n-BSH for at least 6 months while only 19.5% were prescribed n-BSH for less than 3 months, it is plausible that more severe injuries lead to worse conditions (including worse insomnia) that led to longer n-BSH prescription patterns for treatment. While 42% of our population reported n-BSH use for at least 6 months, a VA study from Australia reports n-BSH use for at least 6 months is as high as 70% in Australian veterans.[53] This could indicate that after service members leave active duty, the likelihood of continuing n-BSH use is high. Although we explored whether service members with more severe injuries were prescribed higher n-BSH doses, our results were inconclusive due to the small number with high dose prescriptions.

Almost half (42.6%) of n-BSH users received medications for least 6 months. Most users of 3 other classes (BZD, MRA, and Antihistamines) only received medications for less than 3 months, suggesting that Service members prescribed BZD, MRA, and Antihistamines had milder forms of insomnia or transitioned to other classes if treatment was unsuccessful. Zolpidem was the most frequently prescribed medication (54.2% of all prescriptions), implying that either Zolpidem is the n-BSH medication of choice for treatment of insomnia post injury or that Service members transitioned to Zolpidem after other classes were unsuccessful. Low-dose Trazadone, an antidepressant, was the second most frequently prescribed medication. An approved and common treatment for insomnia after head injuries is either Trazadone or n-BSH, so it is expected that these two would be frequently prescribed among combat injured Service

members given the relative high rate of concurrent TBI diagnosis (42.5%) and previous military studies show that combat injuries have a high rate of TBI.[3,67]

Figure 1 shows that the proportion of n-BSH prescriptions decreased slightly over time compared to other treatment classes. However, the most prominent subgroup for n-BSH prescriptions was long-term (6 months or more) prescriptions, as this group remained the highest prescribed subgroup of n-BSH users despite the decrease in overall n-BSH prescriptions in 2016 and 2017. The FDA introduced several recommendations and warnings on n-BSH medications between 2013 and 2019; including recommending lower doses (2014), warned against driving after daily use (2013) or when combed with opioid medications (2016), and warned of risks of serious injuries caused by sleepwalking (2019).[80] These warnings may account for the some of the reduction in new n-BSH prescriptions in these service members, but given that most n-BSH prescriptions still exceeded 3 months even by the end of 2017, these service members still exceeded these revisions throughout these conflicts. It is important to note that this figure only reports the annual proportion of pharmacological prescription treatments among combat injured service members and does not illustrate the total number of pharmacological treatments in combat injured service members. However, it may suggest that other non-pharmacological treatment options are likely underutilized in the DoD given the high proportion of use and high rate of longer treatments of n-BSH. Therefore, While this figure shows a decrease in n-BSH, it is possible that the total burden of pharmacological insomnia treatment is still increasing as shown in VA studies.[58]

The high prevalence of service members who exceed the FDA's guidelines of n-BSH medications provides evidence that other treatment options for insomnia (e.g. Cognitive Behavioral Therapy, or CBT-I) need additional recourses within military treatment systems in

order to be utilized more frequently. CBT-I is shown more effective than pharmacological treatment alone for long-term insomnia.[81] CBT-I has traditionally been limited in military health new technology, but integration of remote CBT-I courses may increase this availability to broader military service members.[82,83]

This descriptive paper has a number of strengths. First, participants include all eligible service members from OIF and OEF who sustained a combat injury and who are prescribed pharmacological treatment for insomnia, meaning this study represents the largest and most comprehensive data source of combat injured service members with insomnia to-date. Additionally, this cohort can be used for future insomnia research, given its linkage to important pharmacological and clinical sources. Second, participants were followed for 2 years following injury, regardless of frequent military reassignments or changes to clinical treatment locations. Third, we used prescription records for insomnia treatment characteristics, rather than self-report data, which increases the accuracy of data concerning dosing and duration of any treatment plan prescribed over the 2 years of follow up. Finally, we included a variety of longitudinal variables on clinical characteristics of services members (e.g., PTSD or insomnia diagnosis) and their health behaviors.

While this study has many strengths, there are noteworthy limitations to consider. First, this study is restricted to service members treated pharmacologically for insomnia and does not capture the use of behavioral therapies and strategies. Since n-BSH is indicated only for insomnia treatment, we can conclude that our population represents the most complete cohort of injured service members with insomnia that is severe enough for prescription treatment, therefore we felt that comparing n-BSH to other medication classes is more appropriate than comparing n-BSH to non-treatment. Second, measuring n-BSH use using pharmacy records

cannot account for individual adherence to their prescriptions. Service members who were prescribed multiple medications for insomnia treatment could be an indication for non-adherence and not just severity of insomnia or injury. However, the accuracy of the PDTS is still superior to self-reported medication use given that the two-year follow up and the importance of accurate measurements for duration of use. Third, defining n-BSH use from prescription patterns brings inherent limitations of not knowing how long service members were diagnosed with insomnia prior to beginning treatment. This cohort only includes those diagnosed with insomnia after injury, so we can at least ensure that any treatment occurred as a result (either directly or indirectly) from combat injury. Lastly, we restricted follow up to 2 years following combat injury since we were primarily concerned with insomnia treatment as a result of combat injury. While this 2-year restriction limits our availability to explore longer term use (>2years), it prevents complications caused by diagnosed conditions several years afterwards that may be difficult to attribute to the injury.

In conclusion, this study is an important step in the military's understanding of n-BSH prescription patterns since it includes all U.S. military Service members who sustained combat injuries and were prescribed pharmacological treatments for insomnia. These results confirm that n-BSH use is common among Service members who were injured in combat, and that long-term (6 or more months of continuous use) prescriptions are the most common proportion of n-BSH use. Importantly, the majority of n-BSH prescriptions among combat injured service members exceed the FDA's recommendations. Considering long-term n-BSH use is shown to have a variety of deleterious cognitive and physical effects, our results are alarming and merit better clinical alternatives to insomnia treatment for injured service members. A large body of research demonstrates the efficacy of behavioral interventions to effectively treat insomnia, especially

cognitive behavioral therapy for insomnia, and has now become the first line of treatment for insomnia.[84] Training of military health care providers in such techniques could be a worthwhile investment.

Table 1. Demographic characteristics of combat injured service members with pharmacological treatment for insomnia within 2 years of combat injury (n=8071)

		Medication Class, n (%)				
Characteristics	Total (%)	n-BSH	BZD	MRA	Antihist	AntiDep
Total	8071	4968 (61.6)	633 (7.8)	173 (2.1)	1281 (15.9)	3173 (39.3)
Age						
<24	4282 (53.1)	2637 (32.7)	327 (51.7)	95 (54.9)	**723 (56.4)**	1709 (53.9)
25 - 34	2990 (37.1)	1841 (22.8)	254 (40.1)	65 (27.6)	**465 (36.3)**	1158 (36.5)
35 - 44	700 (8.7)	430 (5.3)	47 (7.4)	11 (6.4)	**83 (6.5)**	271 (8.5)
45 - 64	99 (1.2)	60 (0.7)	5 (0.8)	2 (1.2)	**10 (0.8)**	35 (1.1)
Sex						
Female	297 (3.7)	**163 (2.0)**	**21 (3.3)**	**5 (2.9)**	60 (4.7)	**107 (3.4)**
Male	7773 (96.3)	**4805 (96.7)**	**612 (96.7)**	**168 (97.1)**	1221 (95.3)	**3065 (96.6)**
Race/Ethnicity						
Non-Hisp White	6063 (75.1)	**3789 (46.6)**	**478 (75.5)**	133 (76.9)	980 (76.5)	2415 (76.1)
Non-Hisp Black	692 (8.6)	**404 (5.0)**	**49 (7.7)**	7 (4.0)	91 (7.1)	256 (8.1)
Hispanic	887 (11.0)	**531 (6.6)**	**75 (11.9)**	21 (12.1)	144 (11.2)	337 (10.6)
API	225 (2.8)	**130 (2.6)**	**12 (1.9)**	5 (2.9)	41 (3.2)	225 (2.6)
Other	204 (2.5)	**114 (39.2)**	**19 (3.0)**	7 (5.8)	25 (2.0)	83 (2.6)
Branch of Service						
Army	6340 (78.6)	**3852 (77.54)**	**529 (83.6)**	**110 (63.6)**	976 (76.2)	**2447 (77.1)**
Air Force/Other	59 (0.7)	**44 (0.9)**	**4 (0.6)**	**0 (0.0)**	7 (0.6)	**15 (0.5)**
Marine Corps	1539 (19.1)	**984 (19.8)**	**90 (14.2)**	**58 (33.5)**	275 (21.5)	**657 (20.7)**
Navy	133 (1.7)	**88 (1.8)**	**10 (1.6)**	**5 (2.9)**	23 (1.8)	**54 (1.7)**
No. Prev Deployments						
No	4529 (56.1)	2775 (55.9)	358 (56.6)	99 (57.2)	**740 (57.8)**	1827 (57.6)
Yes	3542 (43.9)	2193 (44.1)	275 (43.4)	74 (42.8)	**541 (42.2)**	1346 (42.4)
No. of Comorbs						
None	2027 (25.1)	**926 (18.6)**	**64 (10.1)**	**13 (7.5)**	**156 (7.7)**	**382 (12.0)**
1	3718 (46.1)	**2320 (46.7)**	**271 (42.8)**	**70 (40.5)**	**535 (14.4)**	**1439 (45.4)**
2+	2326 (28.8)	**1722 (34.7)**	**298 (47.1)**	**90 (52.0)**	**590 (25.4)**	**1352 (42.6)**
PTSD Diagnosis						
No	3988 (49.4)	**2138 (43.0)**	**193 (30.5)**	**36 (20.8)**	**422 (32.9)**	**1052 (33.2)**
Yes	4083 (50.6)	**2830 (57.0)**	**440 (69.5)**	**137 (79.2)**	**859 (67.1)**	**2121 (66.9)**
TBI Diagnosis						
No	4645 (57.5)	**2758 (55.5)**	**391 (61.8)**	109 (63.0)	**767 (59.9)**	**1890 (68.5)**
Yes	3426 (42.5)	**2210 (44.5)**	**242 (38.2)**	64 (37.0)	**514 (40.1)**	**1283 (40.4)**
Depression Diagnosis						
No	4917 (60.9)	**2746 (55.3)**	**280 (44.2)**	**78 (45.1)**	**611 (47.7)**	**1526 (48.1)**
Yes	3154 (39.1)	**2222 (44.7)**	**353 (55.8)**	**95 (54.9)**	**670 (52.3)**	**1647 (51.9)**
Anxiety Diagnosis						
No	3877 (48.0)	**2109 (42.5)**	**194 (30.7)**	**41 (23.7)**	**392 (30.6)**	**1111 (35.0)**
Yes	4194 (52.0)	**2859 (57.5)**	**439 (69.3)**	**132 (76.3)**	**889 (69.4)**	**2062 (65.0)**
Chronic Pain						
No	6848 (84.9)	**4015 (80.8)**	**513 (81.0)**	**131 (75.7)**	**1022 (79.8)**	**2534 (79.9)**
Yes	1223 (15.1)	**953 (19.2)**	**120 (19.0)**	**42 (24.3)**	**259 (20.2)**	**639 (20.1)**
Injury Severity						
Mild to moderate	5794 (71.8)	**3284 (66.1)**	473 (74.7)	**105 (60.7)**	**867 (67.7)**	**2143 (67.5)**
Serious to severe	2277 (28.2)	**1684 (33.9)**	160 (25.3)	**68 (39.3)**	**414 (32.3)**	**1030 (32.5)**

* medication classes are notmutually exclusive, so percentages do not total 100%

bolded numbers indicate p values below 0.05

Abbreviations of Terms: PTSD = Post Traumatic Stress Disorder, TBI = Traumatic Brain Injury, n-BSH = non-benzodiazepine sedative hypnotic, BZD = benzodiazepine, MRA = Melatonin Receptor Agonist

Table 2. Medication classes and names reported by duration of use category

		Type of Use* (row %)		
Characteristic	Total (col %)	Acute	Intermittent	Continuous
Medication Class				
n-BSH	4968 (61.6)	1622 (32.7)	1232 (24.8)	2114 (42.6)
BZD	633 (7.8)	333 (52.6)	161 (25.4)	139 (22.0)
MRA	173 (2.1)	90 (52.0)	36 (20.8)	47 (27.2)
Antihistamine	1281 (15.9)	759 (59.3)	306 (23.9)	216 (16.9)
Antidepressant	3173 (39.3)	1229 (38.7)	742 (23.4)	1202 (37.9)
Individual Breakdown (not mututally exclusive)				
Zolpidem	4377 (54.2)	1758 (40.2)	1148 (26.2)	1471 (33.6)
Trazodone	2855 (35.4)	1229 (43.0)	670 (23.5)	956 (33.5)
Eszopiclone	1784 (22.1)	717 (40.2)	411 (23.0)	656 (36.8)
Hydroxyzine	1281 (15.9)	759 (59.3)	306 (23.9)	216 (16.9)
Mirtazapine	699 (8.7)	341 (48.8)	166 (23.7)	192 (27.5)
Ramelteon	173 (2.1)	90 (52.0)	36 (20.8)	47 (27.2)
Zaleplon	97 (1.2)	55 (56.7)	19 (19.6)	23 (23.7)
Triazolam	86 (1.1)	67 (77.9)	13 (15.1)	6 (7.0)
Temazepam	560 (0.70)	282 (3.5)	150 (1.9)	128 (22.9)
Doxepin	52 (0.6)	35 (67.3)	11 (21.2)	6 (11.5)
Flurazepam	4 (0.1)	2 (50.0)	2 (50.0)	0 (0.0)
Estazolam	1 (0.0)	1 (100.0)	0 (0.0)	0 (0.0)

* Acute users are defined as therapy lasting less than 30 days, intermittent users 31-89 days or breaks in refills of at least 31 days, and Continuous users are those with 90+ days of continuous use

Table 3. The severity of combat injury sustained during combat by n-BSH characteristics

		Injury Severity		
N-BSH use	Total (%)	Mild to Moderate	Serious to Severe	p -value
Duration of use				0.001
non n-BSH user	3103 (38.5)	2510 (43.3)	593 (26.0)	
<3 months	1622 (20.1)	1178 (20.3)	444 (19.5)	
3 - 6 months	1232 (15.3)	802 (13.8)	430 (18.9)	
6 - 24 months	2114 (26.2)	1304 (22.5)	810 (26.2)	
Dosage Type				0.65
normal	8031 (99.5)	5764 (99.5)	2267 (99.6)	
high	40 (0.5)	30 (0.5)	10 (0.4)	

* Duration of n-BSH use is the cumulative number of days receiving prescriptions for n-BSH

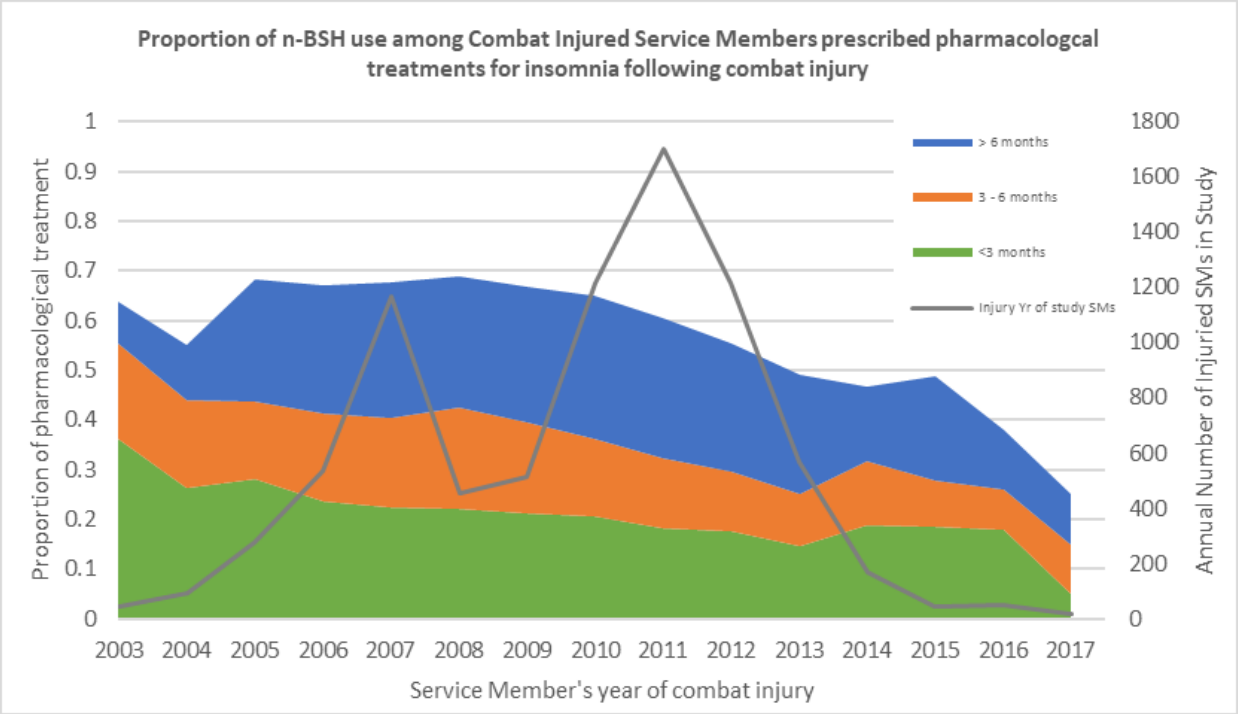

Figure 1: Proportion of n-BSH use among Combat Injured Service Members prescribed pharmacological treatments for insomnia following combat injury

Chapter 3 in part, us currently being prepared for submission for publication of the material. Crouch DJ, Macgregor AJ, Galarneau MR, Zouris JM, Kaufmann K, Malhotra A, Brodine SK, Gallo LC, Martin NH, Jain S, Shaffer RA. The dissertation author was the primary researcher and author of this paper.

4. N-BSH And Health Related Quality Of Life Among Injured Service Members

4.1. Abstract

Introduction: In this study, we examined how duration of n-BSH use affects the quality of life among service members after sustaining injury during combat operations in Operations Iraqi Freedom (OIF) or Enduring Freedom (OEF). **Methods:** This retrospective cohort follows 521 service members from the Expeditionary Medical Encounter Database (EMED) who sustained combat injuries during deployment operations between 2001 and 2019 and were prescribed n-BSH for insomnia. Duration of n-BSH use was assessed via the military Pharmacy Data Transaction System (PDTS). Health Related Quality of Life (HRQOL) was measured using physical and mental health composite scores from a Wounded Warrior Recovery Project questionnaire provided to injured service members. Multivariable linear regressions were used to calculate adjusted odds ratios and 95% confidence intervals for n-BSH use and each composite score. **Results:** Long-term prescriptions are largely driving the high prevalence rates of n-BSH, given that almost half (42.6%) of injured service members were prescribed this class for at least 6 months of continued use. There was no statistically significant relationship between duration or dosage (e.g. high vs low) of n-BSH with physical composite scores measuring service members' quality of life. **Conclusion:** While n-BHS use did not directly impact HRQOL after adjustment, combat injured service members with n-BSH treatment experienced lower average HRQOL mental and physical scores than those without insomnia prescriptions and of the general population.

4.2. Introduction

Insomnia is the most prevalent long-term sleep disorder in the U.S. and affects approximately 10% of the population.[15] Sleep duration and quality are linked to biological functions and psychological wellbeing, and sleep deficiencies or poor sleep are associated with a range of psychological outcomes such as depression, post-traumatic stress disorder (PTSD), processing difficulties, behavioral irregularities, and anxiety.[20-26] Short and long-term effects of insomnia are associated with a variety of physical and psychological health conditions, including stroke, coronary heart disease, type 2 diabetes mellitus, depression, and anxiety.[21] As such, effective treatment for insomnia has become an important research topic to promote health and quality of life.

Introduced in the 1990s, non-benzodiazepine sedative hypnotics (n-BSHs), e.g. zolpidem, zaleplon, and eszopiclone, were marketed as safer alternatives to benzodiazepines for treatment of insomnia.[37] They have continued to be the treatment of choice in military populations for pharmacological treatment of insomnia since their introduction due to the perception of limited side effects. Recent studies, however, provide evidence that n-BSH adverse outcomes include falls,[38-41] cognitive impairment,[41-45] psychological disorders including depression[20,21] and suicidal ideation.[46,47] Long-term n-BSH use increases risk for depression, anxiety, and mortality by as much as 75% among n-BSH users compared to non-users.[54] In recently published treatment guidelines for chronic insomnia, the American College of Physicians recommended that these medications be used only on a short-term basis and if behavioral treatments alone are ineffective.[66] Despite these concerns, n-BSH use remains commonly prescribed in service members with insomnia.[27] Alderman et al. reported that approximately 70% of veterans taking n-BSHs had more than six months continuous use.[53] Military research, while limited, reports that

n-BSH prescriptions have increased, and that refills rather than new prescriptions are driving the increase.[15,27,48,55] Insomnia and its associated pharmacological treatment have been documented consequences of combat and sustaining injury during combat operations.[16,17]Conditions often linked with combat injury (e.g. post-traumatic stress disorder [PTSD], traumatic brain injury [TBI]) have also been associated with insomnia and it's treatment.[18,19] Because insomnia have become more prevalent in U.S. service members, including those who were injured during combat operations, further research is needed to examine possible changes in n-BSH use in this population.

Health Related Quality of life (HRQOL) is a multidimensional indicator of overall well-being and is often used in military research to estimate a service member's perception of health. HRQOL is frequently degraded in combat-injured service members, so military research has interest in how injuries impact service members and their retention.[60] In addition, the World Health Organization's International Classification of Functioning published a report that body system impairment resulting from combat injuries can result in activity limitation that may have negative effects on HRQOL.[62] Due to the circumstances surrounding combat, psychological trauma is a prevailing consequence of combat injuries, and outcomes such as PTSD and depression are known to be associated with lower HRQOL in service members.[20,60,61] In studies among veterans, former service members with insomnia also had increased incidence of chronic conditions such as hypertension, diabetes, psychiatric disorders and reduced HRQOL.[58] Due to the potential impact of persistent symptoms and disablement on low HRQOL following combat injury, it is important to understand the factors that have the greatest contribution to long-term morbidity in this population.

Military research on HRQOL suggests that combat injured service members report lower HRQOL relative to those who did not sustain injury, and HRQOL is even lower in those with PTSD.[16,52,63,64] Psychotics and benzodiazepines are shown to be either ineffective or associated with significant harm in treating PTSD-related insomnia, and therefore n-BSH have become the primary form of pharmacological treatment for service members with insomnia related to combat injury or PTSD.[52] To our knowledge, no military studies have explored n-BSH use specifically, nor have any explored how its use affects reported HRQOL. Considering this is the most common class of pharmacological treatment for insomnia among injured service members, there is an important gap in our understanding of n-BSH use in military research. Therefore, this study explores how n-BSH use (both overall use and duration of use) affect HRQOL in service members following combat injury. This retrospective study aims to determine the association between n-BSH use and self-reported quality of life among combat injured service members.

4.3. Methods

Study Participants

This retrospective study includes military service members who met the following criteria: (1) had a clinical record for combat injury sustained in operations Iraqi Freedom (OIF) or Enduring Freedom (OEF) in the Expeditionary Medical Encounter Database (EMED) between January 2001 and August 2019;[65,67] (2) completed a HRQOL survey at least 2 years or more following combat injury; (3) received a clinical diagnosis of insomnia (*International Classification of Diseases, 9th Revision* 307.42; 327.00; 327.01; 327.02; 327.09; 780.51; 780.52 codes and their corresponding *10th Revision;* F51.01; F51.03; F51.04; F51.05; F51.09; G47.00; G47.01; G47.09) within 2 years following the date of combat injury, [59,67] which we obtained from the Military Health System Data Repository (MDR);[67] and (4) prescription data for n-BSH

for at least 30 days (or at least 2 pharmacy fills) for insomnia treatment within 2 years of combat injury. The EMED is a deployment health database that contains patient information from military treatment facilities near the point of injury in theater through rehabilitative outcome.[3] The Pharmacy Data Transaction System (PDTS) provides detailed listings of all outpatient medication names and dispensing dates of prescribed medications for all military service members.

Measures

Prescription n-BSH use was defined as any use greater than 30 consecutive days or at least two prescription fill[35,48] for eszopiclone (1 mg, 2 mg, 3 mg), zaleplon (5 mg, 10 mg), zolpidem (5 mg, 6.25 mg, 10 mg, 12.5 mg), or zolpidem tartrate (1.75 mg, 5 mg [spray and tablet], 6.25 mg, 10 mg, 12.5 mg).[48,66,85,86] We totaled the number of days service members received each medication and categorized prescription use as follows: (1) prescription for n-BSH less than 90 days,[35] (2) greater than 90 days and less than 180 days,[48,74] and (3) greater than 180 days and less than two years.[47,48]

HRQOL was assessed using a 36-Item Short Form Survey (SF-36) form the WWRP that was provided to injured EMED service members. The WWRP is a 15-year longitudinal study of patient-reported outcomes among service members and veterans who were injured on oversees contingency operations in OEF/OIF.[60,87] Individuals who sustained a documented injury of any severity after December 2001 were identified in the EMED and invited via email and/or postal mail to participate in the WWRP. Recruitment began in November 2012 and continues on a rolling basis. In 2017, the WWRP updated the SF-36 and introduced questions assessing physical and mental health domain to the WWRP survey in 2017.[88-91] These include questions about diagnosed medical conditions, functioning state, emotional and physical state, alcohol and

tobacco use, occupation, etc., and summarized into two categories.[65,92] Responses from these categories include the physical component summary (PCS) score and mental component summary (MCS) score based on a standardized norm-based scoring algorithm that scores functional limitations due to (1) physical health, and (2) emotional problems, energy and fatigue, emotional wellbeing, social functioning, pain, and general health. Both PCS and MCS range from 1 to 100, with lower scores indicating greater limitation in function and lower HRQOL and health status.[93-95] We used these scores directly as an indicator for service member HRQOL. We included the first survey completed at least 2 years following injury for each service member. Only one participant had previously completed the SF-36 questionnaire during follow-up so this service member was removed from our analysis.

Covariates included in each linear regression model were chosen as the minimally sufficient number of variables to reduce confounding bias between n-BSH use and HRQOL, and include demographic and military service characteristics, as well as pertinent health conditions designated from our literature review and constructed directed acyclic graph (DAG). **Age** was calculated using date of birth and date of injury, and categorized into 10 year increments (<20, 20-29, 30-39, 40+) consistent with other military research.[76] **Sex** was dichotomized as male and female.[76,79] **Race and ethnicity** was categorized as Non-Hispanic white, Non-Hispanic black, Hispanic, other (including Asian and Pacific Islander).[76] We extracted **branch of service** data from Defense Manpower Data Center (DMDC) records, and categorized service members as Air Force, Army, Navy, and Marine Corps.[76] The DMDC also includes all deployment beginning and ending dates for Iraq (OIF) or Afghanistan (OEF). We calculated the total **number of previous deployments** prior to the most recent deployment where injury occurred and dichotomized them as yes/no for presence of previous deployments.[67] We obtained **severity of**

the injury sustained in combat using the Injury Severity Score (ISS), an anatomical scoring system that values the combined effects of multiple injuries, which was calculated by certified nurse coders following review of the EMED clinical records.[ref] ISS ranges from 1 to 75, and we categorized ISS as 1–8 (mild-to-moderate injuries) and 9 or greater (serious-to-severe injuries).[65,96] We extracted conditions to characterize psychiatric and medical comorbidities.[27] We used ICD-9 and corresponding ICD-10 codes from the MDR. These include anxiety (ICD-9 300.0, 300.2, 300.3, 309.8 and ICD-10 F41.9), chronic pain (ICD-9 338.2, 338.4 and ICD-10 G89.2, G89.21, G89.4), traumatic brain injury (TBI; ICD-9 850, 851, 852, 853. 854.0 and ICD-10 S02.0, S02,1, S02.8, S02.91, S04.02, S04.03, S04.04, S06.9, S09.8 S09.90), depression (ICD-9 296.20; 296.22; 296.21; 296.23; 296.24; 296.30; 296.31; 296.32; 296.33; 296.34; 296.82; 298.0; 300.4; 309.0, 309.1; 311 and ICD-10 F43.21; F32.89; F32.0; F32.2; F32.3; F32.9; F34.1; F43.21; F32.3; F33.3; F33.2; F33.0; F33.1; F33.9) and PTSD (ICD-9: 309.81 and ICD-10: F43.12).[78] We reported each condition dichotomously (yes/no) for each service member. Next, we totaled the **number of co-morbidities** for each participant, and then categorized them as none, one co-morbidity, and 2 or more co-morbidities similar to others in order to describe service members' quantity of co-occurring insomnia related conditions.[3,36,67,79] Finally, we defined service members' **presence of mental health conditions**, coded dichotomously as yes/no for all service members' with diagnoses of any of the following conditions: (1) PTSD,[76,97] (2) anxiety, or (3) depression.[98,99]

Statistical Analysis

This study was designed to have sufficient statistical power (>0.80 for all analyses) with a sample size of 202 an odds ratio of 1.30. We used chi squared and fisher's exact tests for descriptive statistics. For the analysis of n-BSH use and quality of life, we used two

multivariable generalized linear models, the first for the physical component scores and the second for the mental component scores. We did not include race/ethnicity, military service characteristics, or the number of comorbidities in our model since they did not vary by exposure and did not impact our model results. Our models were adjusted on age, sex, injury severity, and presence of mental health conditions (PTSD, anxiety, or depression). P-values less than 0.05 were considered statistically significant. All statistical analyses were conducted using SAS (version 9.4; SAS Institute Inc., Cary, North Carolina).

4.4. Results

Overall, this study had 521 service members who were prescribed n-BSH for insomnia treatment following injuries sustained during combat operations. Table 1 describes service member demographic and comorbid conditions by the duration of n-BSH prescriptions. The majority of service members in this study were less than 34 years old (86.0%), were male (95.6%), white (75.1%) and in the Army (82.3%). Of the 521 service members in this study, 251 (44%) were prescribed n-BSHs less than 90 days, 129 (25%) were prescribed n-BSHs between three and six months, and 142 (27%) were prescribed n-BSHs at least six months during the study follow up. The number of comorbidities that service members had also varied by duration of use in a dose response pattern. Specifically, 19.1% of service members who reported no comorbidities were prescribed n-BSHs less than 90 days while 6% were prescribed n-BSH at least 6 months. In contrast, 31.9% of service members who had 2 or more comorbidities were prescribed n-BSHs less than 90 days while 42.6% of those were prescribed n-BSH at least 6 months. 84.6% of service members had at least one diagnosed comorbidity with their insomnia. Specifically, these comorbidities show that PTSD, TBI, and anxiety was present in at least half of these service members. The least frequently reported condition was chronic pain (19%).

HRQOL was moderately low for both PCS and MCS scores with reported means of 39 and 37 respectively. The overall MCS mean, as well as each n-BSH category was lower in MCS than in PCS. However, neither MCS nor PCS scores varied by duration of n-BSH use in statistical significance. The number of years since service members completed the survey after injury was approximately eight in all n-BSH categories.

Table 2 details the results of the adjusted association between the duration of n-BSH use and reported HRQOL in our participants. Overall, there was no evidence to suggest that either PCS or MCS varied by the duration of n-BSH prescription patterns in combat injured service members with insomnia. The PCS model shows both negative effects in service members receiving longer prescriptions of n-BSH across both 90-179 days of use (β = -2.00, SE=1.17) and 180+ days of use (β = 0.24, SE=1.13). However, the PCS model was not statistically significant (and had a poor overall model fit (R^2 = 0.065). The MCS model showed negative effects for both prescription duration groups for n-BSH for both 90-179 days of use (β = -0.53, SE=1.46) and 180+ days of use (β = -0.86, SE=1.52), but was also not statistically significant (p=0.63, 0.57 respectively) and was a poor model fit (R^2 = 0.040).

4.5. Discussion

This is the first study to describe duration of n-BSH prescription patterns with self-reported HRQOL in service members following combat injury. We used a novel comprehensive database that includes all documented service members who were prescribed n-BSH treatment within 2 years of combat injury related to OIF or OEF. Additionally, we identified the prevalence of important physical and psychological comorbidities that may affect treatment. We found that more than half (52%) of these service members receive prescriptions longer than 30 days, indicating that most prescriptions exceeded clinical guidelines of n-BSH

recommendations.[100] After adjustment, our results did not show evidence for a relationship between the duration of n-BSH use and reported physical HRQOL. There was a negative effect for n-BSH and MCS score, which strengthened in longer duration of n-BSH prescriptions. (-0.53 to -0.86), but this association was not statistically significant. Additional research using a larger sample may be helpful to examine further the association between duration of n-BSH use and mental HRQOL.

Among our population of injured service members with insomnia who received n-BSH treatment, mean PCS and MCS scores (38.95 and 37.20 respectively) were lower than those of Rusch et als study (43.8 and 41.6 respectively) who did not restrict service members to those injured in combat or to n-BSH users.[90] Further, our results were also lower than MacGregor et als study (45.0 and 41.1 respectively) who included combat injured service members but did not restrict inclusion to insomnia or n-BSH treatment.[65] For reference, mean PCS and MCS scores for the general population are normalized at 50 points with a standard deviation of 10, which is 12 points higher than scores reported from service members in our study.[101] This illustrates the burden that combat injury and subsequent n-BSH treatment may have on these service members given their low HRQOL scores. Considering the higher prevalence of diagnosed comorbidities among our participants, this may also suggest that those with n-BSH prescriptions have lower HRQOL either directly related to their insomnia or due to their comorbidities. Additionally, severe injuries were more prevalent in those with longer n-BSH, suggesting that injury severity may also be related to insomnia and n-BSH treatment duration. Specifically, the prevalence of severely injured participants in our study was more than three times (32.3% vs 7.0%) that of HRQOL research in MacGregor et al's research, which supports this possibility.[65] More research on insomnia's influence on HRQOL with injury severity and comorbidities is needed.

Considering MacGreggor et al's previous research on HRQOL report that sleep problems were present in a variety of symptom profiles following combat injury, it's not surprising that our results show high prevalence of many comorbid conditions.[3] Shayegani et al also reported similar rates of comorbid conditions in n-BSH veterans, suggesting that both active duty and veteran members affected by combat injury have high prevalence of these diagnosed psychiatric conditions that persist for many years.[27] This is particularly alarming given the interest in treatment and retention of service members with insomnia. Additional military research is needed to address how psychiatric conditions can be improved in active-duty service members with n-BSH insomnia treatment plans. While PTSD was lower in our participants than in veterans from Shayegani's report, we still note a high prevalence of PTSD in our participants, which has previously been shown to associated with poor sleep and insomnia.[53] Therefore, we recommend psychological assessment in combat injured service members who receive n-BSH prescriptions.

This paper has three important and unique strengths vs. other military articles assessing insomnia and HRQOL. First, we have accurate measurements of n-BSH use from by the PDTS database, which is unaffected by recall biases common in other insomnia research from early OIF and OEF. Second, all HRQOL surveys occurred after the 2-year follow up (mean of 10 years in all exposure groups), ensuring that the timeline of injury rehabilitation would not confound our results. Third, due to the methodology of WWRP, surveys could be completed while on active-duty or following separation, ensuring that we minimized attrition-related bias.

Four important limitations are also noted. First, these health component scores were introduced in 2017, we were limited on when HRQOL could be assessed in relation to injury and n-BSH treatment. Future studies will have access to repeated SF-36 PCS and MCS data, which

will allow assessment of HRQOL changes over time. Second, we recognize that multiple factors could potentially impact long-term health throughout service members' follow up period. Degradation of HRQOL could be explained by many factors (e.g. survivor bias) that cannot be controlled in regression models. Third, in conjunction with the previous limitation, the sample size of this study was not large in relation to the total number of combat injured service members with n-BSH treatment plans for insomnia due to limited WWRP data. While this study is sufficiently powered, we noted the small sample size and then compared this sample to that of the entire combat injured database. Fortunately, characteristics of our study population were similar to those with all injured service members who completed the WWRP.[60] Fourth, we are limited in that our assessment of n-BSH is through prescription fills, rather than actual medication use. We cannot determine treatment effectiveness or adherence to each service member and must rely on the assumption that the prescription treatment plan was followed as indicated. Additionally, the high proportion of service members with multiple comorbid psychiatric conditions could suggest the presence of competing conditions that do not impact n-BSH treatment plans but may be important factors to a service member's HRQOL. While these limitations are important, we feel the strengths provided by our methods are needed to increase our understanding of n-BSH prescription patterns in this unique population.

In conclusion, there was no evidence that HRQOL varied by duration of n-BSH prescription use, suggesting that long-term n-BSH treatment alone was not a salient predictor of long-term HRQOL in injured service members. However, HRQOL scores among these service members were overall lower than other miliary studies excluding insomnia treatment. More research is needed to understand insomnia and HRQOL in service members in order to help

revise insomnia treatment plans that reduce the need for long-term n-BSH prescriptions to improve HRQOL and retention.

Table 1. Demographic characteristics of n-BSH use by duration of use among combat injured service members (n=521)

		n-BSH Duration of Use			
Characteristics	total (%)	< 90 days	90 - 179 days	180 days to 2 yrs	p - value
n (%)	521 (100.0)	251 (48.2)	129 (24.8)	141 (27.1)	
Age [f]					0.24
<24	218 (41.8)	111 (44.2)	59 (45.7)	48 (34.0)	
25 - 34	230 (44.2)	110 (43.8)	55 (42.6)	65 (46.1)	
35 - 44	64 (12.3)	26 (10.4)	13 (10.1)	25 (17.7)	
45 - 64	9 (1.7)	4 (1.6)	2 (1.6)	3 (2.1)	
Sex (Female) [f]	23 (4.4)	7 (2.8)	5 (3.9)	11 (7.8)	0.07
Race/Ethnicity					0.14
Non-Hisp White	391 (75.1)	190 (75.7)	103 (79.8)	98 (69.5)	
Non-Hisp Black	35 (6.7)	14 (5.6)	9 (7.0)	12 (8.5)	
Hispanic	67 (12.9)	35 (13.9)	11 (8.5)	21 (14.9)	
Other	29 (5.6)	12 (4.8)	6 (4.7)	10 (7.1)	
Branch of Service [f]					0.68
Army	429 (82.3)	209 (83.3)	105 (81.4)	115 (81.6)	
Air Force/Other	7 (1.3)	2 (0.8)	1 (0.8)	4 (2.8)	
Marine Corps	76 (14.6)	37 (14.7)	20 (15.5)	19 (13.5)	
Navy	9 (1.7)	3 (1.2)	3 (2.3)	3 (2.1)	
Prev Deployment History	228 (43.8)	106 (42.2)	58 (45.0)	64 (45.4)	0.79
Number of Comorbs					0.01
none	80 (15.4)	48 (19.1)	23 (17.8)	9 (6.4)	
one	256 (49.5)	123 (49.0)	63 (48.8)	72 (51.1)	
2+	183 (35.1)	80 (31.9)	43 (33.3)	60 (42.6)	
Comorbid Conditions					
TBI Diagnosis	294 (56.4)	138 (55.0)	73 (56.6)	83 (58.9)	0.76
PTSD	310 (59.5)	141 (56.2)	71 (55.0)	98 (69.5)	0.02
Depression Diagnosis	236 (45.3)	98 (39.0)	66 (51.2)	72 (51.1)	0.02
Anxiety Diagnosis	310 (59.5)	143 (57.0)	72 (55.8)	95 (67.4)	0.08
Chronic Pain	94 (18.0)	35 (13.9)	22 (17.1)	37 (26.2)	0.01
Injury Severity Score					0.003
Mild to Moderate (1-8)	351 (67.4)	182 (72.5)	90 (69.8)	79 (56.0)	
Serioius to Severe (9+)	170 (32.3)	69 (27.5)	39 (30.2)	62 (44.0)	
Quality of Life Score					
PCS (Mean, SD)	38.95 (10.21)	39.74 (10.43)	38.16 (9.82)	38.25 (10.14)	0.22
MCS (Mean, SD)	37.20 (13.00)	37.47 (13.25)	37.00 (11.89)	36.91 (13.58)	0.90
Time between Injury and WWRP Survey					
Mean (SD)	8.38 (2.77)	8.58 (2.77)	8.52 (2.66)	7.39 (2.60)	0.01

Abbreviations of Terms: PTSD = Post Traumatic Stress Disorder, TBI = Traumatic Brain Injury, n-BSH = non-benzodiazepine sedative hypnotic

f= used fisher's exact test for p-value rather than chi square.

Table 2. Standardized regression coefficients from adjusted linear regression analyses for effects between duration of n-BSH use and HRQOL in combat injured service members

			Adjusted Quality of Life Scores			
	PCS	MSC	PCS		MCS	
Characteristic	mean, SD	mean, SD	β (SE)	p-value	β (SE)	p-value
Intercept			37.41 (4.68)	<0.001	40.97 (6.05)	<0.001
n-BSH Use						
<90 days	39.74 (10.43)	37.47 (13.26)	ref		ref	
90 - 179 days	38.16 (9.81)	37.00 (11.89)	-2.00 (1.17)	0.97	-0.53 (1.46)	0.63
180 days - 2 yrs	38.49 (10.15)	37.05 (13.61)	0.24 (1.13)	0.09	-0.86 (1.52)	0.57
Model Fit (R^2)			0.065		0.040	

* models adjusted on age, sex, diagnosed mental health condition (depression, anxiety, or PTSD) and ISS score

statistically significant at $^{a}p < 0.05$

Chapter 4 in part, is currently being prepared for submission for publication of the material. Crouch DJ, Macgregor AJ, Galarneau MR, Zouris JM, McCabe CT, Kaufmann K, Malhotra A, Brodine SK, Gallo LC, Martin NH, Jain S, Shaffer RA. The dissertation author was the primary researcher and author of this paper.

5. N-BSH Use Among Service Members Who Sustained Traumatic Brain Injuries During Combat

5.1. Abstract

Introduction: We examined the association of traumatic brain injury (TBI) sustained in combat operations with patterns of non-benzodiazepine sedative hypnotic (n-BSH) prescriptions for two years following injury. **Methods:** This retrospective cohort consists of 4,116 service members from the Expeditionary Medical Encounter Database (EMED) who sustained combat injuries during deployment operations between 2001 and 2019 and who were prescribed n-BSH medications for insomnia treatment within two years following injury. Diagnosed TBI was defined as mild (with and without loss of consciousness) and moderate to severe in accordance with the Armed Forces Health Surveillance Branch definitions. Dosage and duration of n-BSH prescribing patterns were assessed via the Pharmacy Data Transaction System. Multivariable multinomial regressions were used to calculate adjusted odds ratios and 95% confidence intervals for TBI sustainment during combat injury with dose and duration of n-BSH use, respectively. **Results:** 60.2% of participants were diagnosed with TBI (mostly mild) due to their combat injuries. There was no evidence to suggest that dose or duration of n-BSH prescriptions varied by TBI. However, injury severity and psychological comorbidities (post-traumatic stress disorder, depression, anxiety, and chronic pain) were all highly prevalent among these participants. **Conclusion:** While TBI was not associated with n-BSH prescriptions among combat injured service members, the high prevalence of diagnosed comorbid conditions are likely important factors in n-BSH prescription patterns and should be considered for future research.

5.2. Introduction

Traumatic brain injury (TBI) is defined as a disruption in brain function due to the impact of contact forces including acceleration, deceleration, or collision, manifesting as altered state of consciousness, neurological changes, and amnesia.[17] TBI is often classified as mild, moderate, and severe, depending on the presence and duration of symptoms.[8,17] TBI has become the notable injury of warfare following military operations in Iraq (Operation Iraqi Freedom, or OIF) and Afghanistan (Operation Enduring Freedom, or OEF), with mild TBI (i.e. concussions) considered the most important injury of both theatres.[17] In fact, 20% of service members with combat exposure experienced a probable TBI (i.e. blow to the head with alteration in/loss of consciousness).[10] Health consequences of combat related TBI are varied and can last for years. These include a variety of physical, psychological, and neurological effects, such as insomnia, post-traumatic stress disorder (PTSD), and reduced quality of life (QOL), among others.[36,102-104] As such, clinical management of TBI and its health consequences involves integrated medical and behavioral healthcare.[105]

Insomnia is the most commonly reported symptom among patients suffering from TBI following injury.[7] While the proportion of those sustaining TBI that report insomnia varies, reports show insomnia may be as high as 50%[16] in military veterans and as high as 29%[7] in active-duty service members. Importantly, all estimates of military members are higher than their civilian counterparts, indicating them as uniquely higher risk for either insomnia or TBI. Untreated insomnia following TBI has been shown to have a serious impact on service members' cognitive function.[7] Additionally, insomnia and other sleep disturbances are reported more frequently in service members with co-occurring PTSD who sustained combat injury.[18,19] In fact,

PTSD has been shown to be associated with insomnia at all levels of TBI severity; the association is especially strong among those with mild TBI.[7,17] Regardless of injury severity, insomnia research is of particular interest in military populations due to the relatively high prevalence of TBI among service members.[28]

Introduced in the 1990s, non-benzodiazepine sedative hypnotics (n-BSH) (e.g. zolpidem, zaleplon, and eszopiclone) have been the pharmacological treatment of choice for insomnia due to the misperception of limited side effects.[37] Military research, while limited, reports that prescribing of n-BSH has increased, and that refills rather than new prescriptions may be driving the increase.[15,27,48,55] In fact, one study found that as much as 20% of veterans reported more than 6 months of n-BSH use.[74] This is concerning as newer clinical guidelines limit n-BSH use.[50] This is in view of studies showing that n-BSH results in adverse outcomes, including falls,[38-41] cognitive impairment,[41-45] psychological disorders including depression[20,21] and suicidal ideation.[46,47] As TBI itself can result in cognitive impairment, current recommendations are to avoid n-BSH in these patients; first line therapy for insomnia, particularly for these patients is to use behavioral strategies such as cognitive behavioral therapy for insomnia (CBT-I-I).[106] Unfortunately, no military studies have explored how TBI impacts insomnia medication use in general, or among current service members in particular. Considering the prevalence of n-BSH use in the military, understanding its correlates represents an important topic and will provide better perspective into how patterns of medication use are impacted by TBI sustained in combat. We propose a study that explores TBI and both duration and dosage of n-BSH and hypothesize that sustaining TBI in combat will increase the risk of longer use and higher dosing of n-BSH medications to treat insomnia.

5.3. Methods

Study Participants

We identified all U.S. service members who were injured in combat during operations Iraqi Freedom (OIF) and Enduring Freedom (OEF) between January 2001 and August 2019 by utilizing the Expeditionary Medical Encounter Database (EMED).[65,67] The EMED is a deployment health database that contains patient information from military treatment facilities near the point of injury in theater through rehabilitative outcome.[98] For service members with multiple injuries recorded during OIF/OEF, we recorded the most severe injury with a recorded TBI. For service members with no recorded TBI, we included the most severe injury that was recorded in the EMED. Each injured service member was followed for 2 years after combat injury. Of those eligible, we included only those who received a clinical diagnosis for insomnia (*International Classification of Diseases, 9th Revision* 307.42; 327.00; 327.01; 327.02; 327.09; 780.51; 780.52 codes and their corresponding *10th Revision;* F51.01; F51.03; F51.04; F51.05; F51.09; G47.00; G47.01; G47.09) between 1 and 730 days (2 years) after injury, [59,67] which we obtained from the Military Health System Data Repository (MDR).[67] Additionally, we only included participants who were prescribed n-BSH medications for at least 30 days (an initial prescription and at least 1 refill) for n-BSH treatment. We excluded those who died due to injury or during the 730 day follow up period (n=519), leaving 4,116 service members available for this study.

Measures

Service members who sustained a TBI during combat were provided by the EMED under diagnostic codes from *International Classification of Diseases, 9th Revision* (ICD-9: 800, 801, 803, 804, 850, 851, 852, 853, 854) and the corresponding *International Classification of Diseases, 10th Revision* (ICD-10: S02.0, S02,1, S02.8, S02.91, S04.02, S04.03, S04.04, S06.9,

S09.8 S09.90).[79] TBI was categorized according to severity: no TBI, mild TBI with no LOC, mild TBI with LOC, moderate to severe TBI, consistent with other liturature[3,79] and as defined by the DoD Standard Surveillance Case Definition for TBI from the Armed Forces Health Surveillance Branch.[8] We also created a dichotomous category representing service members who sustained any type of TBI (presence vs absence).

We used the PDTS to obtain n-BSH prescription history for injured service members. The PDTS provides a detailed listing of all outpatient medication names, dispensing dates, and duration totals for prescribed medications for all military service members. We included those with at least 30 consecutive days of eszopiclone (1 mg, 2 mg, 3 mg), zaleplon (5 mg, 10 mg), zolpidem (5 mg, 6.25 mg, 10 mg, 12.5 mg), or zolpidem tartrate (1.75 mg, 5 mg [spray and tablet], 6.25 mg, 10 mg, 12.5 mg).[48,66,85,86] We totaled the number of days service members received any of the above n-BSH medication and categorized their use as follows: (1) prescription for n-BSH between 30 days and 90 days,[35] (2) between 90 days and 180 days,[48,74] and (3) greater than 180 days.[47,48] N-BSH dosage was defined dichotomously in the following ways: (1) normal (eszopiclone $\leq$3mg, zaleplon $\leq$10 mg, zolpidem immediate release: $\leq$10mg for males and $\leq$5 for females, zolpidem tartrate extended release: $\leq$12.5mg for males and $\leq$6.25mg for females), and (2) high (eszopiclone >3mg, zaleplon, >10mg, zolpidem immediate release: >10mg for males and >5mg for females, zolpidem tartrate extended release >12.5mg for males and >6.25mg for females).[22,27,36]

Covariates included in each linear regression model were chosen as the minimally sufficient number of variables to reduce confounding bias between n-BSH use and HRQOL, including demographics, military service characteristics, and pertinent health conditions designated from our literature review. **Age** was calculated using date of birth at the time of

injury, and categorized into 10 year increments (<20, 20-29, 30-39, 40+) consistent with other military research.[76] **Sex** was dichotomized as male and female.[76,79] **Race and ethnicity** were categorized as Non-Hispanic white, Non-Hispanic black, Hispanic, other.[76] We extracted **branch of service** data from Defense Manpower Data Center (DMDC) records, and categorized service members as Air Force, Army, Navy, and Marine Corps.[76] The DMDC also includes all deployment beginning and ending dates for Iraq (OIF) or Afghanistan (OEF). We calculated the **presence of previous deployments** prior to the most recent deployment in which the service member's combat injury occurred, and dichotomized this as yes/no.[67] We obtained **severity of the injury** sustained in combat using the Injury Severity Score (ISS), an anatomical scoring system that values the combined effects of multiple injuries, which was calculated by certified nurse coders following review of the EMED clinical records.[ref] ISS ranges from 1 to 75, and we categorized ISS as 1–8 (mild-to-moderate injuries) and 9 or greater (serious-to-severe injuries).[65,96] We extracted conditions to characterize psychiatric and **medical comorbidities**.[27] First, we used ICD-9 and corresponding ICD-10 codes from the MDR. These included anxiety (ICD-9 300.0, 300.2, 300.3, 309.8 and ICD-10 F41.9), chronic pain (ICD-9 338.2, 338.4 and ICD-10 G89.2, G89.21, G89.4), depression (ICD-9 296.20; 296.22; 296.21; 296.23; 296.24; 296.30; 296.31; 296.32; 296.33; 296.34; 296.82; 298.0; 300.4; 309.0, 309.1; 311 and ICD-10 F43.21; F32.89; F32.0; F32.2; F32.3; F32.9; F34.1; F43.21; F32.3; F33.3; F33.2; F33.0; F33.1; F33.9) and PTSD (ICD-9: 309.81 and ICD-10: F43.12).[78] We reported each condition dichotomously (yes/no) for each service member. Next, we summed the total **number of co-morbidities** for each participant, and categorized them as none, one co-morbidity, and 2 or more co-morbidities.[3,36,67,79] Finally, we defined service members' **presence of mental health**

conditions, which was coded dichotomously as yes/no for all service members' with diagnoses of any of the following conditions: (1) PTSD,[76,97] (2) anxiety, or (3) depression.[98,99]

Statistical Analysis

We used chi squared tests for descriptive statistics. For the analysis of TBI and n-BSH use, we used two multivariate logistic regressions. The first was a multinomial logistic regression examining the association of TBI categories (mild with no LOC, mild with LOC, and moderate to severe) with duration of n-BSH and the second was a simple logistic regression examining TBI (presence vs absence) with dosage type (normal vs high dose). Covariates included in each regression were chosen as the minimally sufficient needed to reduce confounding bias from our literature review,[27,35,36,74] and included age, sex, injury severity, diagnosed mental health condition (PTSD, anxiety, or depression), and history of other insomnia medication use. Statistical significance was set to alpha 0.05, two-tailed, with 0.80 power for all analyses. Results are reported in adjusted odds ratios with 95% confidence intervals. Further, in a sensitivity analysis, we repeated our analysis while removing the adjustments of comorbidities, chronic pain, and presence of other medication use.

All statistical analyses were conducted using SAS (version 9.4; SAS Institute Inc., Cary, North Carolina).

5.4. Results

Table 1 describes demographic and comorbid conditions of our study's participants. Of the 4,116 eligible service members for our study, most were less than 34 years old (89.8%), male (96.6%), non-Hispanic White (76.3%), and were in the Army (77.4%). 60.2% of participants were diagnosed with a TBI with their combat injury and 83.1% of participants had at least one

diagnosed comorbidity. More severe injuries were more prevalent in those with more severe TBI. PTSD and anxiety conditions were prevalent in more than half (59.9% and 59.8% respectively) of participants, depression was prevalent in nearly half (46.8%), and chronic pain only prevalent in 20.4% of participants. Each condition was more common in participants with a more severe TBI. Half (51.1%) of participants were prescribed n-BSH for at least 3 months, and half of these (25.5% total) were prescribed n-BSH medications for 6 months or longer. However, the duration or dose of n-BSH use did not vary by TBI category.

Table 2 shows the adjusted associations between TBI with both duration and dose type of n-BSH use. While none of the adjusted odds ratios for TBI severity and n-BSH use were statistically significant, the risk of long-term n-BSH prescriptions use was higher among service members who sustained mild TBI with no LOC (OR: 1.40, 95% CI: [0.96, 2.03]) and among service members who sustained moderate to severe TBIs (OR: 1.78, 95% CI: [0.73, 4.38]), but not meaningful in those who sustained mild TBI with LOC (OR: 1.08, 95% CI: [0.68, 1.86]) compared to those who did not sustain a TBI during combat operations. There was no evidence to suggest mid-term n-BSH use (prescriptions between 9 days and 6 months) differed by TBI severity. There was also no evidence to suggest that the n-BSH dose differed by presence of TBI during combat injury (OR: 0.70, 95% CI: [0.22, 2.08]).

5.5. Discussion

To our knowledge, this is the first study to explore TBI and characteristics of n-BSH prescription patterns in U.S. service members following combat injury. Additionally, this is a novel cohort that includes a large sample of service members across DoD services who sustained combat injury since 2001 and who were prescribed n-BSH pharmacological treatment for insomnia following injury. The primary finding of this study shows that there was no statistically

significant association between TBI sustained at injury and n-BSH use after adjustment on age, sex, severity of injury, diagnosed psychiatric conditions (PTSD, anxiety, or depression), chronic pain, and history of other insomnia medication use. These results were consistent while exploring both duration and dosage of n-BSH by TBI severity.

Given the null results, the high rate of n-BSH prescriptions among these injured service members may be driven primarily by other factors such as the severity of combat injury or the subsequent comorbid conditions as supported in prior military research.[36,74] A recent VA study examining long-term n-BSH use (specifically zolpidem use) found that those with comorbidities such as PTSD and depression were at higher odds for long-term n-BSH use than veterans without these comorbidities.[27] In our study, we adjusted for the presence of these conditions to assess the direct effects of TBI severity and n-BSH prescriptions and found no association. It is possible that these conditions are strong mediators between TBI and n-BSH treatment and contribute to the high prevalence of long-term users. In a sensitivity analysis (shown in Table 3), we repeated our n-BSH analysis while adjusting on age only (removed adjustments for comorbidities, chronic pain, and presence of other insomnia medications) and found that service members who sustained TBIs with LOC were more likely to have longer n-BSH prescriptions than those who did not sustain a TBI during combat (mid vs short-term OR: 1.26, 95% CI: [1.03, 1.54], long vs short-term OR: 1.25, 95% CI: [1.02, 1.53]). A full account of comorbid conditions following TBI and their relationship with insomnia is warranted to better understand these intermediate pathways. Regardless, these results further support research suggesting that comorbidities related to combat injury (e.g. PTSD, depression, chronic pain) are largely the driving force for both morbidity and longer medication prescriptions for insomnia treatment.

Considering military research in TBI patients with insomnia shows a decrease in adverse PTSD symptoms after restorative sleep, the proper management of insomnia is crucial for improvements in health and wellbeing among injured service members.[36]

This study shows that approximately half (51.2%) of these service members are prescribed n-BSH longer than 90 days and one fourth (25.5%) longer than 180 days, both of which are higher than their veterans and non-injured active-duty colleagues.[35,74] This is alarming given the warning labels for n-BSH use from the Food and Drug Administration (FDA). Additionally, guidelines from the American College of Physicians (ACP) state n-BSH should only be used for short-term, and in conjunction with non-pharmacological options.[49-51] The continued n-BSH prescription use may suggest a lack of alternate treatment options within the DoD health care systems that provide non-pharmacological treatment to those with chronic insomnia. Given that this population experienced higher rates of diagnosed comorbidities than their non injured service members,[74] it also illustrates the challenges with treating these individuals effectively. We recognize these challenges and the complexity of clinical management of insomnia, and feel these findings provide additional advocacy to improved access to non-pharmacological, evidence based treatment options such as cognitive behavioral therapy for insomnia (CBT-I-I).[27,74] Even internet based healthcare delivery (e.g. e-health or telehealth) has been shown to be effective and could be a means to extend treatment access in military or veteran populations and may be an effective option for clinicians.[107] Given the shortage of access to these approaches, it is not surprising that long-term n-BSH use is so common among these service members.[74]

This study selected combat injured service members with insomnia and a n-BSH prescription history, which is a subset of the EMED injury database. This subset had higher rates

of PTSD, depression, anxiety, chronic pain, TBI prevalence, and worse injury scores compared to the EMED, suggesting these comorbidities and insomnia are correlated. Service members' psychological comorbidities were even more prevalent in those with the most severe TBIs sustained during combat. While we expected n-BSH medications to be higher given that zolpidem is often recommended for treatment of sleep disturbances in patients with co-existing PTSD,[27] it illustrates the relative burden of these conditions among injured service members and further supports research stating that these psychological conditions are the largest driving force of insomnia treatment patterns. Given the long-term effects of combat injury, proper treatment of insomnia and other sleep disturbances following combat is imperative to address service members' treatment needs and insomnia burden following military service, and merits further research.

This study has two important strengths. First, we have accurate assessments of n-BSH use measured by the PDTS database that is unaffected by recall biases common in some insomnia research from early OIF and OEF. Second, we used clinically confirmed ICD-9 coded definitions for TBI categories, which is also important given the variability in TBI research. Several limitations of this study are also noted. First, we are limited in that our assessment of n-BSH is through prescription fills, rather than actual use. We cannot determine treatment effectiveness or actual consumption of treatment for each service member. Therefore, the true effect on n-BSH use with TBI may be attenuated. Second, the high prevalence of service members with multiple comorbid psychiatric conditions could suggest the presence of competing conditions that don not impact n-BSH treatment plans but are critically important in other aspects of the service member's injury and recovery. Third, we restricted our analysis to service members diagnosed with insomnia after injury. While this was an effective way to ensure

insomnia was related to injury, we recognize there may have been service members with undiagnosed insomnia unrelated to combat injury included in this study, or undiagnosed insomnia related to combat injury that didn't merit their inclusion into this study.

In conclusion, the prevalence of TBI diagnosis was high among service members with insomnia who sustained injury during combat operations in OIF/OEF. There was no statistical relationship between TBI severity and the dose or duration of n-BSH use within two years following injury. Other important factors such as comorbid psychological conditions or insomnia severity may be driving n-BSH prescription patterns. Given that this cohort is a comprehensive representation of injured service members with insomnia across the DoD, these results are important for TBI research in the military and provide evidence these service members would benefit from expanded non-pharmacological treatment options in the DoD, such as Cognitive Behavioral Therapy.

Table 1. Demographic characteristics by TBI group among combat injured service members (n=4,116)

		TBI Category				
Characteristics	Total (%)	no TBI	mild TBI no LOC	mild TBI w LOC	mod - sev TBI	p-value
n (%)	4116 (100)	1638 (39.8)	1453 (35.3)	859 (20.9)	166 (4.0)	
Age						0.34
<24	2153 (52.3)	867 (52.9)	737 (50.7)	457 (53.2)	92 (55.4)	
25 - 34	1546 (37.5)	598 (36.5)	568 (39.1)	319 (37.4)	61 (36.8)	
35 - 44	369 (9.0)	153 (9.3)	125 (8.6)	78 (9.1)	13 (7.8)	
45+	48 (1.2)	20 (1.2)	23 (1.6)	5 (0.6)	0 (0.0)	
Age, continuous (Mean, SD)	25.93 (5.9)	25.96 (6.0)	26.18 (6.1)	25.67 (5.7)	25.32 (5.2)	0.12
Sex (Female)	139 (3.4)	39 (2.4)	80 (5.5)	14 (1.6)	6 (3.6)	0.001
Race/Ethnicity						0.84
Non-Hisp White	3139 (76.3)	1250 (76.3)	1117 (76.9)	650 (75.7)	122 (73.5)	
Non-Hisp Black	348 (8.5)	131 (8.0)	124 (8.5)	77 (9.0)	16 (9.6)	
Hispanic	443 (10.8)	186 (11.4)	149 (10.3)	91 (10.6)	17 (10.2)	
Other	186 (4.5)	71 (4.3)	63 (4.3)	41 (4.8)	11 (6.6)	
Branch of Service						0.32
Army	3184 (77.4)	1293 (78.9)	1125 (77.4)	645 (75.1)	121 (72.9)	
Air Force	37 (0.9)	16 (1.0)	12 (0.8)	6 (0.7)	3 (1.8)	
Marine Corps	823 (20.0)	301 (18.4)	289 (19.9)	195 (22.7)	38 (22.9)	
Navy	72 (1.8)	28 (1.7)	27 (1.9)	13 (1.5)	4 (2.4)	
History of Prev Deployments	1839 (44.7)	683 (41.7)	692 (47.3)	395 (46.0)	69 (41.6)	0.007
Injury Severity Score						<0.0001
Mild to Moderate (1-8)	2695 (65.5)	850 (51.9)	1176 (80.9)	627 (73.0)	42 (25.3)	
Serioius to Severe (9+)	1421 (34.5)	788 (48.1)	277 (19.1)	232 (27.0)	124 (74.7)	
Comorbid Conditions						
PTDS	2467 (59.9)	956 (58.4)	854 (58.8)	548 (63.8)	109 (65.7)	0.02
Depression Diagnosis	1927 (46.8)	748 (45.7)	668 (46.0)	417 (48.5)	94 (56.6)	0.03
Anxiety Diagnosis	2462 (59.8)	916 (55.9)	879 (60.5)	551 (64.1)	116 (69.9)	<0.0001
Chronic Pain	839 (20.4)	414 (25.3)	261 (18.0)	136 (15.8)	28 (16.9)	<0.0001
Number of Comorbs						0.03
none	676 (16.4)	271 (16.5)	250 (17.2)	140 (16.3)	15 (9.0)	
1	1912 (46.5)	782 (47.7)	678 (46.7)	374 (43.5)	78 (47.0)	
2+	1528 (37.1)	585 (35.7)	525 (36.1)	345 (40.2)	73 (44.0)	
N-BSH Duration of Use						0.31
30 - 90 days	2002 (48.9)	826 (50.4)	706 (48.6)	391 (45.5)	79 (47.6)	
90 - 179 days	1051 (25.7)	406 (24.8)	369 (25.4)	237 (27.6)	39 (23.5)	
180 days - 2 yrs	1042 (25.5)	396 (24.2)	373 (25.7)	226 (26.3)	47 (28.3)	
N-BSH Dose Type						0.54
Normal	4076 (99.0)	1626 (99.3)	1436 (98.8)	849 (98.8)	165 (99.4)	
High	40 (1.0)	12 (0.7)	17 (1.2)	10 (1.2)	1 (0.6)	

Abbreviations of Terms: PTSD = Post Traumatic Stress Disorder, TBI = Traumatic Brain Injury, n-BSH = non-benzodiazepine sedative hypnotic, LOC = Loss of conciousness

Table 2. Multivariable regression analysis for duration of n-BSH use and TBI among combat injured service members

	n-BSH Duration of Use				n-BSH Dosage	
	mid vs short-term		long vs short-term		n-BSH high vs normal	
Category	aOR	(95% CI)	aOR	(95% CI)	aOR	95% CI
TBI*						
none	ref	ref	ref	ref		
mild no LOC	1.09	(0.74, 1.66)	1.40	(0.96, 2.03)	-	-
mild with LOC	1.13	(0.68, 1.86)	1.08	(0.68, 1.86)	-	-
moderate - severe	0.73	(0.21, 2.52)	1.78	(0.73, 4.38)	-	-
TBI (presence vs absense)+	-	-	-	-	0.70	(0.22, 2.08)
Age (continuous)	1.01	(0.97, 1.04)	1.05	(1.02, 1.08)	0.91	(0.80, 1.04)
Sex (female)	0.57	(0.17, 1.84)	0.94	(0.39, 2.26)	2.23	(0.27, 18.52)
ISS Score (serious to severe)	0.97	(0.67, 1.42)	0.80	(0.57, 1.13)	1.78	(0.60, 5.26)
Mental Health Diagnosis	0.65	(0.35, 1.22)	0.71	(0.41, 1.23)	N/A	N/A
Other Insomnia Medication Used	0.84	(0.57, 1.23)	0.73	(0.51, 1.03)	0.38	(0.08, 1.73)

models adjusted on age, sex, injury severity, diagnosed mental condition (PTSD, anxiety, or depression), chronic pain, and history of other insomnia medication

* TBI categories for duration of use model

+ TBI variable collapsed in n-BSH dosage model due to limited data for high dose users

Definitions: Short-term n-BSH use: daily n-BSH prescriptions for 30-90 days. Mid-term b-BSH use: daily n-BSH prescriptions for 90-180 days.

Long-term use: daily n-BSH prescriptions for 180 days to end of 2 year follow up.

Table 3. Sensitivity analysis for duration of n-BSH use and TBI status among combat injured service members

	n-BSH Duration of Use			
	mid vs short-term		long vs short-term	
Category	aOR	(95% CI)	aOR	(95% CI)
TBI*				
none	ref	ref	ref	ref
mild no LOC	1.08	(0.91, 1.29)	1.10	(0.93, 1.31)
mild with LOC	1.26	(1.03, 1.54)	1.25	(1.02, 1.53)
moderate - severe	1.03	(0.69, 1.54)	1.30	(0.89, 1.91)
Age (continuous)	1.00	(0.99, 1.02)	1.04	(1.03, 1.06)

model for sensitivity analysis adjusted on age and sex.

Chapter 5 in part, is currently being prepared for submission for publication of the material. Crouch DJ, Macgregor AJ, Galarneau MR, Zouris JM, Kaufmann K, Malhotra A, Brodine SK, Gallo LC, Martin NH, Jain S, Shaffer RA. The dissertation author was the primary researcher and author of this paper.

6. Discussion of the Dissertation

N-BSH use is highly prevalent among military personnel following injury related to combat operations, and understanding this relationship is important. Combat injures have been linked to the development of PTSD and other psychological outcomes among military populations.[98,99,108,109] With the advances in survivability from combat injuries over the years, individuals who would have previously died in combat related operations are now surviving and are at risk for physical and mental sequelae of their injuries.[109] This research, conducted among a population of injured combatants during OIF and OEF (a), describes the characteristics of n-BSH prescriptions in combat injured service members, and proposed that (b), longer use of n-BSH is associated with worse HRQOL compared to shorter n-BSH prescription use, and (c), service members who sustained TBIs during combat injury are associated with longer n-BSH prescription compared to those who did not sustain TBIs during injury. These studies focus primarily on 8071 battle-injured personnel with pharmacological treatment for insomnia. The second aim incorporated a subset of MICER personnel who are also part of the WWRP (521 personnel) to assess HRQOL, and third aim incorporated only those in the MICER who were prescribed n-BSH medications (4116 personnel).

6.1. N-BSH Prescription Trends

The proportion of n-BSH prescriptions in this cohort represented between 50 and 70% of all prescriptions for insomnia treatment. While the EMED included 2001 and 2002 service members, the first service members to meet the inclusion criteria of this study were injured in 2003 and continued through 2017. The proportion of n-BSH users were initially very high in early phases of OIF and OEF, and then decreased by 2016 and 2017 (see Figure 1). However, this figure only illustrated the proportion of n-BSH compared to other treatment classes, and not

the total number of prescriptions. I overlayed this data with service members' injury dates, which allows improved visualization on how the proportion of n-BSH prescriptions compares to the total number of new prescriptions based on the date the service member enters the study for their first prescription for insomnia treatment. Interestingly, While the proportion of n-BSH prescriptions remained mostly constant (except for the slight downward trend) before 2016, the annual rate of new n-BSH prescriptions among newly injuries service members varied throughout OIF and OEF. Importantly, largest subgroup of n-BSH was long-term use, and these results support previous research that shows that total insomnia prescriptions may be are on the rise,[27,55,58] Further, During this time, the Food and Drug Administration (FDA) introduced several recommendations and warnings on n-BSH medications between 2013 and 2019; including recommended lower doses (2014) and warned against driving after daily use (2013), when combined with opioid medications, and risks of serious injuries caused by sleepwalking (2019).[80] Despite the FDA safety warning about dosing recommendations for n-BSH, this study shows that 25.5% of combat injured service members who are prescribed n-BSHs receive prescriptions longer than 180 days, 5% higher rates than other studies in veterans[74] and active duty service members.[35]

The most commonly prescribed medication class among this cohort of service members was n-BSH (61%), which was consistent with other military and VA research.[54] Interestingly, among service members who were prescribed other pharmaceutical treatment classes (benzodiazepines, melatonin receptor agonists, or antihistamines), most were only prescribed for less than 3 months. However, of those who were prescribed n-BSH, almost half (43%) received n-BSH prescriptions longer than 6 months, a larger proportion than other military studies exploring long-term use.[35] While 25.5% of our population reported n-BSH use for at least 6

months, a VA study from Australia reports n-BSH use for at least 6 months is as high as 70% in Australian veterans.[53] This could indicate that after service members leave active duty, the likelihood of continuing n-BSH use is high. The same was true for those with antidepressant prescriptions, suggesting injuries and subsequent insomnia diagnoses may lead to a larger proportion of longer-term medication users among those who were injured in combat and were subsequently diagnosed with insomnia.

6.2. N-BSH Prescriptions and Comorbidities

Three out of four service members in this dissertation study (74.9%) were diagnosed with at least one comorbid condition. Among n-BSH users, the proportion diagnosed with 2 or more comorbidities was higher (34.5%) than that of the entire cohort (28.8%), suggesting a possible association between n-BSH and the number of comorbidities. The most commonly diagnosed comorbidity was PTSD (50.6%), followed by depression (39.1%) which is higher in this cohort than other military research with combat injured service members, further illustrating the high rate of morbidity among those with insomnia following their combat injuries.[3,61,77,79] While PTSD was lower among participants than in veterans from Shayegani's report, we still note a high prevalence of PTSD in our participants, which has been shown to associated with poor sleep and insomnia.[53] This also highlights the possibility that these conditions may be diagnosed after follow up considering the higher prevalence among veteran populations. Future research is needed to explore these relationships over time. Service members' recorded psychological comorbidities (PTSD, depression, and anxiety) showed a dose-response pattern across severity groups of TBI (noted in paper 3). Given that n-BSH medications are the recommended pharmacological treatment for sleep disturbances in patients with co-existing PTSD, it is important to understanding how injuries sustained in combat may affect insomnia, insomnia

treatment the best treatment options of these service members. Specifically, exploration of how these comorbidities correlate to long-term care among CBT-I users and how that relates to pharmacological treatments seen in this dissertation.

6.3. N-BSH Prescriptions and Injury Severity

This dissertation study shows that service members with moderate to severe injuries were prescribed n-BSH for longer than those with mild injuries, which may suggest that those with more severe injuries needed longer treatment plans or had higher rates of chronic insomnia. Specifically, 26.2% of service members who experienced serious to severe injuries were prescribed n-BSH for at least 6 months, while only 19.5% of service members who experienced serious to severe injuries were prescribed n-BSH for less than 3 months. While these data were descriptive and do not adjust on potential confounders, they show the relative burden of injury and its severity within n-BSH treatment plans. Demographic data frequently used in military research (age, sex, race, ethnicity, deployment history, branch of service) were not significantly different across n-BSH prescriptions levels, suggesting that the injury sustained during combat and subsequent diagnosed comorbidities among these service members play a much larger role in insomnia treatment needs. Considering injured service members had higher rates of long-term n-BSH prescriptions than non-injured service members,[74] it may suggest that injury severity is directly associated with worse or chronic insomnia, which led to longer n-BSH prescriptions.

Injury severity was also an important factor in the WWRP subset of this study population. The prevalence of severely injured participants among our cohort of n-BSH users that completed the WWRP surveys were more than three times (32.3% vs 7.0%) that of combat injured service members in MacGregor et al's research.[65] Shayegani et al also reported similar rates of comorbid conditions in n-BSH veterans, suggesting that both active duty and veteran

members affected by combat injury have high prevalence of these diagnosed psychiatric conditions that persist for many years.[27] Additional research on how injury severity affects insomnia treatment patterns over time (both pharmacological and non-pharmacological) is needed using this cohort.

6.4. N-BSH Prescriptions and Health Related Quality of Life

There was no significant evidence to suggest that duration of n-BSH use impacted HRQOL in combat injured service members with insomnia. While statistically insignificant, there was a negative effect for n-BSH and MCS score, which strengthened in longer duration of n-BSH prescriptions. (-0.53 [SE= 1.46] to -0.86[SE=1.52]). This may suggest that the association between duration of n-BSH use and mental HRQOL may worsen with longer n-BSH use even after adjusting on diagnosed psychological conditions (e.g. PTSD, anxiety, and depression). However, this relationship was not seen in physical HRQOL. This could indicate that treatment plans for insomnia, especially long-term plans, may not be affected by the duration of n-BSH treatment plans. However, this has not been explored in military research, and presents an excellent opportunity for future studies.

One important finding from this study shows that the mean PCS and MCS scores among these WWRP participants (38.95 and 37.20 respectively) were lower than mean scores of OIF and OEF combat injured service members (45.0 and 41.1 respectively).[65] While there wasn't a direct relationship between n-BSH use and HRQOL, injured service members with n-BSH treatment experienced lower physical and mental HRQOL compared to those who were not prescribed n-BSH treatment plans (shown in other studies), regardless of comorbidity or injury characteristics. Interestingly, the average time between injury and completing the WWRP questionnaire was 8 years (due to HRQOL questions being including in surveys as of 2017),

indicating that this reduction in average HRQOL was present even years after the date of injury. Although n-BSH prescription characteristics did not directly impact HRQOL, these service members experience lower HRQOL nonetheless. Understanding why these service members are experiencing lower HRQOL needs further study.

6.5. Traumatic Brain Injuries and n-BSH Prescriptions

Forty-two percent of service members in this cohort were diagnosed with a TBI from their combat related injury. Among those prescribed n-BSH medications, there was no evidence to suggest that characteristics (duration or dose) of n-BSH prescriptions varied by TBI categorization (mild TBI no LOC OR=0.76 [0.56, 1.02], mild TBI with LOC OR=0.99 [0.68, 1.43], moderate to severe TBI OR=0.55 [0.26, 1.16]) after adjustment on age, sex, history of psychological diagnoses (PTSD, anxiety, or depression), injury severity, and insomnia severity. These results could also indicate that insomnia treatment patterns among those with TBI may vary by other factors associated with these service members. We see evidence that factors that impact n-BSH prescription characteristics include comorbidities, the severity of the injury, or even other characteristics of the injury (e.g. extremity injuries vs head injuries, number of bodily injuries sustained) may all contribute to insomnia severity and n-BSH treatment plans. Additionally, it could indicate that service members who sustained a TBI during combat received the clinically indicated treatment for their insomnia, and that the n-BSH was more effective in those who sustained severe TBIs than those with less severe or no TBI during injury.

6.6. Limitations of this Dissertation

Two important limitations should be considered when interpreting the results of this dissertation study. The MICER cohort utilizes pharmacy dispensing data to quantify the duration

and dosage of pharmacological treatment for insomnia. The PDTS or MDR does not include information on adherence to treatment plans of service members. A limitation of using PDTS databases is that it is impossible to assess how well an individual follows medication directions without utilizing other data sources (e.g. service member interviews). Side effects of non-adherence include withdrawal, which could also increase poor health outcomes or cause a lower reported HRQOL, which could adversely affect the modeled relationships for n-BSH use and HRQOL. Additionally, those taking multiple medications for insomnia treatment could indicate non-adherence to their medication treatment plan and not just the severity of insomnia. This limitation may have attenuated the effects of associations examined in studies 2 and 3 if service members frequently miss doses or take medication inconsistently (e.g. 2 days per week rather than daily). To address this limitation, n-BSH use is described as prescription patterns rather than actual use or consumption in these manuscripts.

Confounding by indication is also a threat to the validity of the analyses for aims 2 and 3. Confounding by indication is a bias where individuals receiving the treatment are more likely to have the outcome of interest due to their underlying health profile for which the medication is used to treat.[110] For example, individuals being prescribed n-BSH may be more likely to experience poor health outcomes simply because of competing health factors related to their insomnia diagnosis that needs longer treatment. They may also be more likely to report worse HRQOL on the WWRP survey. However, this limitation was addressed in two ways: 1) all service members included in this dissertation have been diagnosed with insomnia after injury (there are no comparisons of those without insomnia); and 2) the studies adjusted for important co-morbidities shown to correlate with poor outcomes and health. Since MDR data includes all clinical diagnoses for each participant, it allowed for accurate comparisons of injured service

members with a variety of comorbidities. However, the extent the MDR adequately controlled for this confounding influence is dependent on these service members seeking care for their conditions/health concerns. It cannot capture those who did not seek care (i.e., stigma of seeking treatment in military, minor complaints that do not "justify" care, etc.). Future studies are needed to explore these possibilities.

6.7. Future Studies and Direction

The data sources utilized in this study had limitations which may have influenced the results. Several future study opportunities exist using the MICER database in its current state. Service members with psychological comorbidities often have complex biological processes involved. Future studies on the relationship between TBI and n-BSH prescription use will consider these complexities such as direct and indirect causal pathways of n-BSH use using mediation analyses between characteristics of the severity of injury and n-BSH prescription patterns or comorbid conditions. Specifically, injury severity characteristics might include examining the role of injuries to other body regions that may affect the severity of TBI and/or n-BSH prescription use, while comorbid conditions characteristics might include exploration of conditions like PTSD or depression as potential mediators to insomnia treatment and HRQOL rather than confounders. We can also further explore relationships between comorbid conditions and insomnia treatment among all injured service members in this cohort, rather than focusing only on n-BSH prescription users.

Several future opportunities exist that require expanding on the MICER database. First, given the limitation of the PDTS on assessing n-BSH use, we are unable to determine the actual frequency of use for each service members. Frequency of consumption (e.g. daily use vs 2-3 times per week) may also be important considerations within insomnia research and these data

are not currently available. I will be working with NHRC in incorporating additional questions into the WWRP and other surveys for EMED service members that inquire about frequency of prescription use for insomnia treatment. This data could then be included into the MICER for research projects that add frequency of use characteristics.

Second, with the exception of HRQOL data provided by WWRP, the data sources used to construct the MICER only follow service members while on active duty. Department of Veterans Administration (VA) databases should be linked to these service members following discharge in order to provide post-service follow-up clinical data. This will ensure we can compare the same service members as they transition to VA and civilian health care services, something not previously done in military insomnia studies. We could also visualize multiple surveys per service member and compare HRQOL trends over time. Additionally, linking this data source to VA sources will allow assessment of clinical outcomes that are yet to be clinically diagnosed or manifested.

Third, projects might include exploration of n-BSH and opioids and alcohol use, as well as inclusion of psychotherapy (CBT-I, Cognitive Processing Therapy, or CPT, relaxation techniques, breathing exercises, stress reduction, etc) treatment comparisons in this population given that CBT-I is shown more effective than pharmacological treatment alone for long-term insomnia.[81] CBT-I was not explored within this population yet. CBT-I has traditionally been limited in military health new technology and integration of remote CBT-I courses may increase this availability to broader military service members.[82,83] This will increase the available data that can be included into the MICER service, and increase research opportunities in this unique group.

6.8. Conclusion

The present research examined the relationship between combat injured military service members and their subsequent n-BSH prescription use to treat insomnia. This is the first military cohort that explores n-BSH among combat injured service members in the DoD. This research compared n-BSH prescription patterns to other pharmacological treatment classes and to the severity of the injury sustained during combat operations. This research assessed duration of n-BSH prescription use with HRQOL among a subset of injured service members who were also part of the WWRP cohort, and finally evaluated how TBI status at the time of injury impacted n-BSH prescription patterns. This study found that n-BSH is the most commonly reported insomnia pharmaceutical treatment class prescribed among injured service members with insomnia, and that these service members are exceeding FDA and clinical guidelines for duration of use. Additionally, these service members had a higher prevalence of psychiatric comorbidities (e.g. PTSD, depression, anxiety, and chronic pain) than injured service members without insomnia as reported in other research. This study also showed that more severe injuries and diagnosed comorbid conditions were more common in service members with longer n-BSH prescriptions, but were not associated by TBI status or higher dosage of n-BSH prescriptions. While longer n-BSH prescriptions were not directly associated with lower HRQOL, this study shows that these service members experienced lower average HRQOL than their injured counterparts without insomnia shown in other military studies. These results suggest that clinical management of insomnia for combat injured service members needs re-evaluated to include alternate treatment plans that include non-pharmacological options (e.g. CBT-I) and support in order to reduce long-term pharmacological care for these service members. Given that CBT-I is shown to be more effective than pharmacological methods for insomnia treatment, these service

members would greatly benefit from inclusion in these therapies. It's possible that improving treatment plans for injures service members with chronic insomnia will improve their HRQOL, and in turn their military performance and retention. Service members are surviving their combat related injuries at a greater rate during OIF and OEF compared to previous conflicts, so management of the long-term effects associated with their combat injuries and related psychological morbidities are essential, as problems and HRQOL may persist long after combat operations have ceased.

The views expressed in this dissertation reflect the results of research conducted by the author and do not necessarily reflect the official policy or position of the Department of the Navy, Department of Defense, nor the United States Government.

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Appendix

Manuscript 1 SAS CODE (the MICER Data base)

Step 1: Merging the datafiles via SAS Enterprise

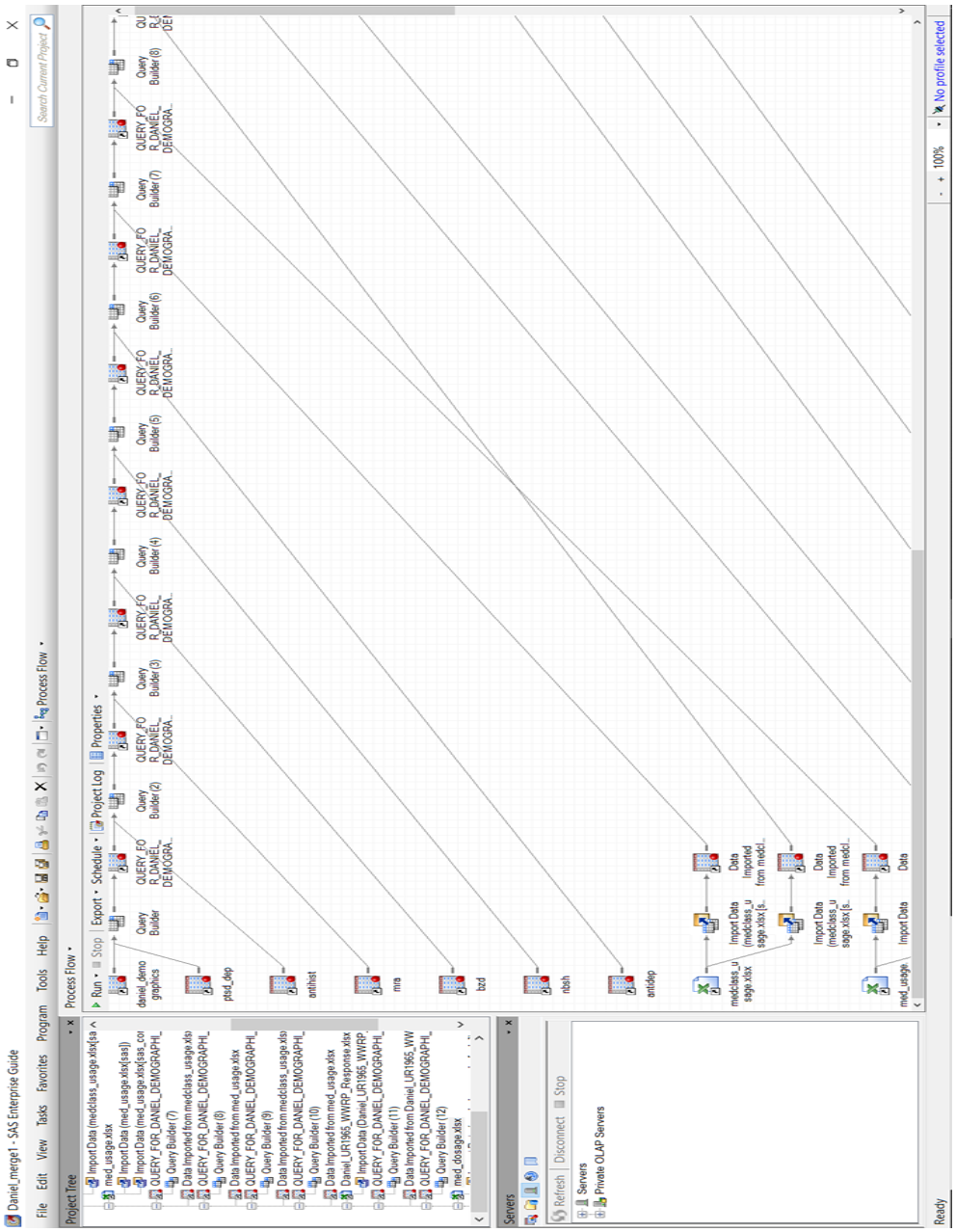

Figure 2. Merging PDTS into EMED

Figure 3. Merging MDR and DMDC into EMED

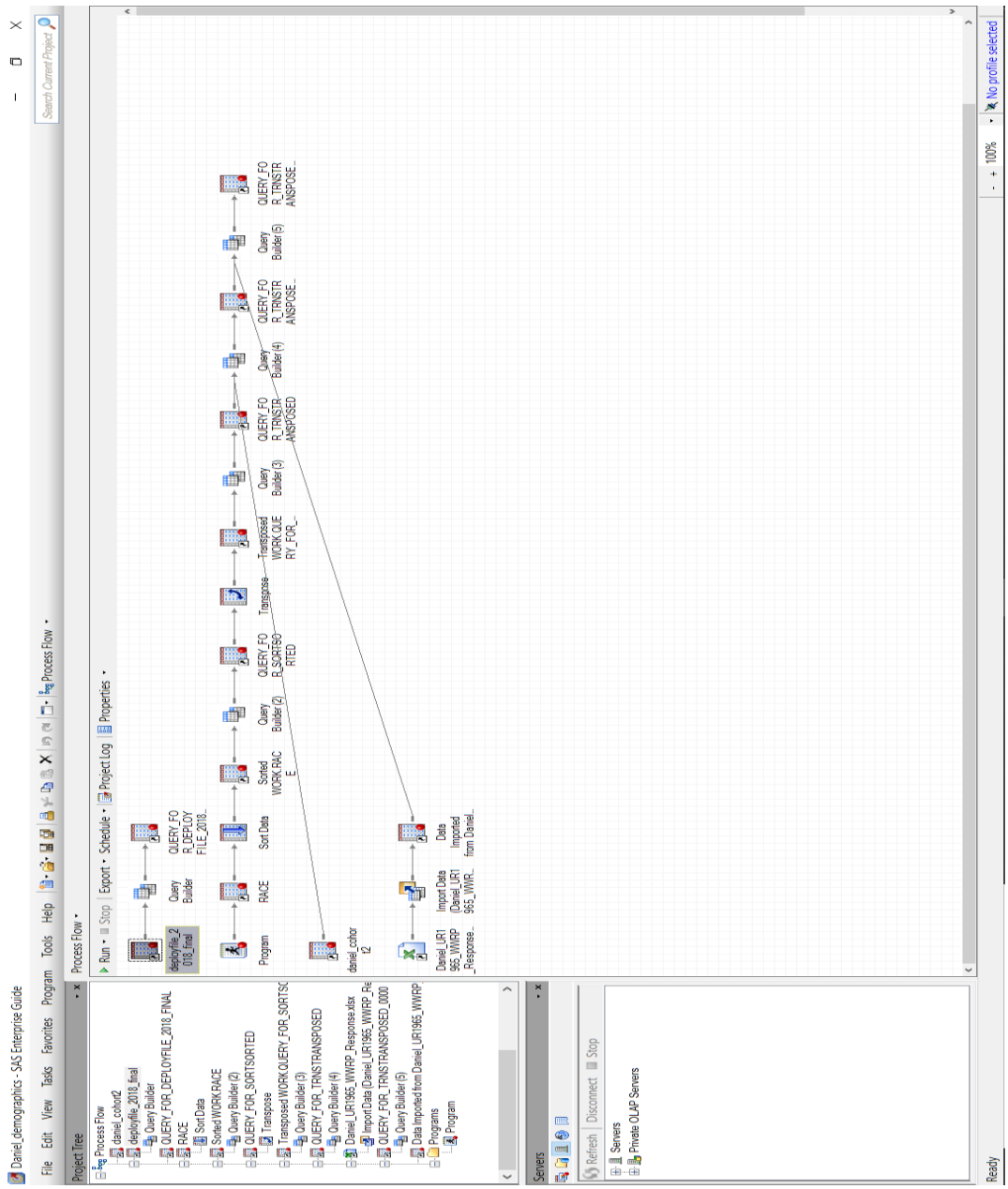

Figure 4. Merging WWRP into EMED

Step 2: Building the MICER - defining inclusion criteria

```
PROC IMPORT DATAFILE="P:\_CTR(FOUO-PrivacySensitive)\Daniel
      Crouch\Dissertation\EMED_NHRCID_djc.xlsx"
      DBMS=XLSX OUT=EMED1 REPLACE;
      GETNAMES=YES;
      RUN;

*PROC FREQ DATA=EMED1;
*     TABLE GENDER RANK BOS DEATH ISS;
*     RUN;
      *NOTE: VARIABLES IN RAW DATASET NEEDED RENAMED TO SINGLE NAMES SUCH AS
      "PAY GRADE" SINCE IT HAS A LOT MORE COMPLETE INFO THAN "RANK";
      * variables of interest:
      caseid
      nhrc_id
      calculatedAge
      gender
      Pay Grade/Rank
      BOS
      MOI_X
      episodeid
      Trauma Code
      WoundedDate
      disposition Date
      Disposition
      TreatmentType
      death
      Death Date
      ISS
      AIS_1
      ICD9_1
      ICD10_1;

*ITEMS TO CONSIDER:
* 1) EVERY EPISODE NEEDS TO BE ON IT'S OWN LINE (TO MATCH DATASETS);
* 2) HOW MANY WILL HAVE DIFFERENCE CASEIDS FROM EACH EPISODE. (FLAG EPISODES
      THAT ARE THE SAME CASE_id);
* 3) CLEAN EMED
* 4) CHECK DATA WITH ANDY
* 5) INCLUDE BURRELL MATRIX SO WE CAN SEE WHAT THE INJURIES ARE FOR EACH
      EPISODE;
* 6) DESCRIBE DATA FOR PAPER
      ;

*** BUILDING THE EMED POPULATION FOR OUR DATASET *** ;
DATA EMED_A;
      * 154598 RECORDS TO START;
      SET EMED1;
      * REMOVE THOSE WITHOUT BATTLE INJURIES;
      WHERE CLASS_1 = "BI";
      * 69931 RECORDS TO THIS POINT;
      * REMOVE THOSE WITHOUT ISS SCORES;
      IF ISS = " " THEN DELETE;
      IF ISS = 0 THEN DELETE;
      Inj_date=Input(substr(wounded_date,6,2) || "/" ||
```

```
      substr(wounded_date,9,2) || "/" || wounded_date,1,4),mmddyy10.);
      RUN;
      * 55993 RECORDS TO THIS POINT;

* REMOVING DUPLICATE EPISODES;
PROC SORT DATA=EMED_A OUT=EMED_A_NODUP NODUPKEY;
      BY CASEID EPISODEID;
      RUN;
      * 24161 RECORDS REMOVED.
      * 31832 RECORDS TO THIS POINT;

* REMOVING DUPLICATES WITH MULTIPLE / DUPLICATE INJURIES. PER WWRP PROCESS,
      WE ARE KEEPING THE ENTRY WITH THE HIGHEST ISS SCORE;
PROC

PROC SORT DATA=EMED_A_NODUP OUT=EMED_B;
      BY CASEID NHRC_ID DESCENDING ISS;
      RUN;

PROC SORT DATA=EMED_B OUT=EMED_B_NODUP NODUPKEY;
      BY CASEID NHRC_ID;
      RUN;
      * 1446 OBSERVATIONS REMOVED;
      * 30386 RECORDS AT THIS POINT;

* REMOVING THOSE WHO DIED;
DATA EMED_C;
      SET EMED_B_NODUP;
      IF FINALDISPOSITION = "DIED" THEN DELETE;
      IF (DISPOSITION = "KIA" | DISPOSITION="CRO-DIED OUT OF FAC/DOA") THEN
      DELETE;
      IF (EMED_KIA_DOW = "KIA" | EMED_KIA_DOW = "DOW") THEN DELETE;
      RUN;
      * 519 OBSERVATIONS REMOVED;
      * 29867 RECORDS TO THIS POINT;

* DELETE THOSE MISSING ICD CODES AND AIS CODES;
DATA EMED_D;
      SET EMED_C;
      IF AIS_1 = " " THEN DELETE;
      IF ICD9_1=" " AND ICD10_1=" " THEN DELETE;
      *IF MISSING(ICD9_1) AND MISSING (ICD10_1) THEN DELETE; *THIS ALSO
      WORKS;
      RUN;
      * 45 OBSERVATIONS REMOVED;
      * 29822 RECORDS AT THIS POINT;

* REMOVING ANYONE OUTSIDE MARCH 2001 TO APRIL 2019;
DATA EMED_FINAL;
      SET EMED_D;
      WHERE WOUNDED_DATE BETWEEN "2001-03-01" AND "2019-04-01";
      * filling in missing rate data from ranks;
                  IF (RANK = "2NDLT" | RANK = "2LT" | RANK = "ENS" ) AND
      PAY_GRADE = " " THEN PAY_GRADE = "O1";
                  IF (RANK = "1STLT" | RANK = "LTJG" | RANK = "1LT" ) AND
      PAY_GRADE = " " THEN PAY_GRADE = "O2";
                  IF (RANK = "CPT" | RANK = "LT" ) AND PAY_GRADE = " " THEN
```

```
      PAY_GRADE = "O3";
                  IF (RANK = "MAJ" | RANK = "LCDR" ) AND PAY_GRADE = " " THEN
      PAY_GRADE = "O4";
                  IF (RANK = "LCOL" | RANK = "LTC" | RANK = "LTCOL" | RANK =
      "CDR") AND PAY_GRADE = " " THEN PAY_GRADE = "O5";
                  IF (RANK = "COL" | RANK = "CAPT" ) AND PAY_GRADE = " " THEN
      PAY_GRADE = "O6";
                  IF (RANK = "PVT" | RANK = "PV1" | RANK = "SR" ) AND
      PAY_GRADE = " " THEN PAY_GRADE = "E1";
                  IF (RANK = "PV2" | RANK = " AMN" | RANK = "SA" ) AND
      PAY_GRADE = " " THEN PAY_GRADE = "E2";
                  IF (RANK = "PFC" | RANK = "LCPL" | RANK = "SN" ) AND
      PAY_GRADE = " " THEN PAY_GRADE = "E3";
                  IF (RANK = "CPL" | RANK = "SPC" | RANK = "PO3" | RANK =
      "SRA" ) AND PAY_GRADE = " " THEN PAY_GRADE = "E4";
                  IF (RANK = "SGT" | RANK = "PO2" ) AND PAY_GRADE = " " THEN
      PAY_GRADE = "E5";
                  IF (RANK = "SSG" | RANK = "SSGT" | RANK = "PO1" | RANK =
      "TSGT" ) AND PAY_GRADE = " " THEN PAY_GRADE = "E6";
                  IF (RANK = "GYSGT" | RANK = "SFC" | RANK = "CPO" ) AND
      PAY_GRADE = " " THEN PAY_GRADE = "E7";
                  IF (RANK = "1SG" | RANK = "1STSGT" | RANK = "SCPO" ) AND
      PAY_GRADE = " " THEN PAY_GRADE = "E8";
                  IF (RANK = "MSG" | RANK = "MSGT" | RANK = "SMSGT" ) AND
      PAY_GRADE = " " THEN PAY_GRADE = "E8";
                  IF (RANK = "CSM" | RANK = "SGM" | RANK = "SGTMAJ" | RANK =
      "MCPO" | RANK = "MCPON" ) AND PAY_GRADE = " " THEN PAY_GRADE = "E9";
                  IF (RANK = "WO1" | RANK = "WO-1" ) AND PAY_GRADE = " " THEN
      PAY_GRADE = "W1";
                  IF (RANK = "CW2" | RANK = "CWO2" | RANK = "CWO-2" ) AND
      PAY_GRADE = " " THEN PAY_GRADE = "W2";
                  IF (RANK = "CW3" | RANK = "CWO-3" | RANK = "CWO3" ) AND
      PAY_GRADE = " " THEN PAY_GRADE = "W3";
                  IF (RANK = "CW4" | RANK = "CW04" ) AND PAY_GRADE = " " THEN
      PAY_GRADE = "W4";
                  * I used US mil site to verify all ranks in data and merge
      them to the included paygrades;
      IF ISS LT 9 THEN ISS_CAT=0;
      IF ISS GE 9 THEN ISS_CAT=1;
      RUN;
      * 279 OBSERVATIONS REMOVED;
      * 29544 RECORDS AT THIS POINT FOR FINAL EMED DATASET;

PROC FREQ DATA=EMED_FINAL;
      TABLE Rank;
      Where Pay_Grade= " ";
      run;
      * ONLY 51 MEMBERS WITHOUT RANK/RATE; * 49 missing, and two ranks that
      are unknown (SP4 and WO);

PROC FREQ DATA=EMED_FINAL;
      TABLE ISS_CAT ISS GENDER BOS;
      RUN;

PROC UNIVARIATE DATA=EMED_FINAL;
      VAR ISS CALCULATEDAGE ;
      HISTOGRAM;
```

```
      RUN;

PROC PRINT DATA=EMED_FINAL;
      WHERE ICD9_45 NE " ";
      RUN;

PROC SORT DATA=EMED_FINAL;
      BY NHRC_ID;
      RUN;

LIBNAME JZ "P:\_CTR(FOUO-PrivacySensitive)\Transfer\From_Daniel\To_James";

DATA JZ.HDS99;
      SET HDS99;
      RUN;

*** NOW TO ADD THE BARELL MATRIX TO MY DATA *** ;

PROC FREQ DATA=EMED_FINAL;
      TABLE  ICD9_3 - ICD9_54;
               *ONLY TWO PEOPLE HAVE ICD9 CODES PAST 40, AND ONLY ONE PERSON
      HAS ICD9 CODES PAST 41;
      RUN;

proc transpose data=EMED_FINAL out = ICD9_long (rename=(col1=dx1)
      drop = _NAME_
      where = (dx1 is not null));
      by nhrc_id;
      var ICD9_3 - ICD9_54;
      run;

PROC PRINT DATA=ICD9_LONG; RUN;

Data do_over;
      array x ICD9_1-ICD9_100;
      do over x;
            if not missing(X) then do;
                  /* commands for each ICD-9 columns */
            end;
      end;
      run;

data ICDCodes;
      set ICD9_LONG;
      dx15=compress(dx1, ".");
      dx13=substr(dx15,1,3);
      dx14=substr(dx15,1,4);
      d5=substr(dx15,5,1);
      if not missing(dx1);
      /*PUT(t1.ISRCODE, 2.) || "_" || PUT(t1.ISRSITE2, 1.) */
      run;

DATA work.HDS99;
      set work.ICDCodes;
      IF ('800' <=DX13<= '829') THEN ISRCODE=1;
      IF DX13 GE '830' AND DX13 LE '839' THEN ISRCODE=2;
      IF DX13 GE '840' AND DX13 LE '848' THEN ISRCODE=3;
```

```
IF ('860'<=DX13<='869') OR ('850'<=DX13<='854') OR DX13='952' OR
DX15='99555' THEN ISRCODE=4;
IF ('870' <=DX13<= '884') OR ('890' <=DX13<= '894') THEN ISRCODE=5;
IF ('885' <=DX13<= '887') OR ('895' <=DX13<= '897') THEN ISRCODE=6;
IF DX13 GE '900' AND DX13 LE '904' THEN ISRCODE=7;
IF DX13 GE '910' AND DX13 LE '924' THEN ISRCODE=8;
IF DX13 GE '925' AND DX13 LE '929' THEN ISRCODE=9;
IF DX13 GE '940' AND DX13 LE '949' THEN ISRCODE=10;
IF (DX13 GE '950' AND DX13 LE '951') OR ('953'<=DX13<='957') THEN
ISRCODE=11;
IF DX13= '959' THEN ISRCODE=12;
IF ('930'<=DX13<='939') OR ('960'<=DX13<='994') OR ('905'<=DX13
<='908') OR ('9090'<=DX14<='9092') OR DX13='958' OR
('99550'<=DX15<='99554') OR DX15='99559'
OR DX14='9094' OR DX14='9099'
OR ('99580'<=DX15<='99585') THEN ISRCODE=13;

IF ('8001'<=DX14<='8004') OR ('8006'<=DX14<='8009') OR
('80003'<=DX15<='80005') OR ('80053'<=DX15<='80055') OR
('8011'<=DX14<='8014') OR ('8016'<=DX14<='8019') OR
('80103'<=DX15<='80105') OR ('80153'<=DX15<='80155') OR
('8031'<=DX14<='8034') OR ('8036'<=DX14<='8039') OR
('80303'<=DX15<='80305') OR ('80353'<=DX15<='80355') OR
('8041'<=DX14<='8044') OR ('8046'<=DX14<='8049') OR
('80403'<=DX15<='80405') OR ('80453'<=DX15<='80455') OR
('8502'<=DX14<='8504') OR ('851'<=DX13<='854') OR
('9501'<=DX14<='9503') OR DX15='99555' THEN ISRSITE=1;

IF DX15='80000' OR DX15='80002' OR DX15='80006' OR DX15='80009' OR
DX15='80100' OR DX15='80102' OR DX15='80106' OR DX15='80109' OR
DX15='80300' OR DX15='80302' OR DX15='80306' OR DX15='80309' OR
DX15='80400' OR DX15='80402' OR DX15='80406' OR DX15='80409' OR
DX15='80050' OR DX15='80052' OR DX15='80056' OR DX15='80059' OR
DX15='80150' OR DX15='80152' OR DX15='80156' OR DX15='80159' OR
DX15='80350' OR DX15='80352' OR DX15='80356' OR DX15='80359' OR
DX15='80450' OR DX15='80452' OR DX15='80456' OR DX15='80459' OR
DX14='8500' OR DX14='8501' OR DX14='8505' OR DX14='8509' THEN
ISRSITE=2;

IF DX15='80001' OR DX15='80051' OR
DX15='80101' OR DX15='80151' OR
DX15='80301' OR DX15='80351' OR
DX15='80401' OR DX15='80451' THEN ISRSITE=3;

IF (DX13='951') OR (DX14='8730' OR DX14='8731' OR DX14='8738'
OR DX14='8739') OR (DX13='941' AND D5='6')
OR DX15='95901' THEN ISRSITE=4;

IF DX13='802' OR DX13='830' OR DX14='8480' OR DX14='8481' OR
DX13='872' OR ('8732'<=DX14<='8737') OR
(DX13='941' AND D5='1') OR (DX13='941' AND '3'<=D5<='5') OR
(DX13='941' AND D5='7') THEN ISRSITE=5;

IF DX14='9500' OR DX14='9509' OR ('870'<=DX13<='871') OR
DX13='921' OR DX13='918' OR DX13='940' OR (DX13='941'
AND D5='2') THEN ISRSITE=6;
```

```
IF ('8075'<=DX14<='8076') OR DX14='8482' OR DX14='9252'
OR DX14='9530' OR DX14='9540' OR DX13='874' OR
(DX13='941' AND D5='8') THEN ISRSITE=7;

IF DX14='9251' OR DX13='900' OR DX14='9570' OR DX13='910'
OR DX13='920' OR DX14='9470' OR DX15='95909' OR
(DX13='941' AND (D5='0' OR D5='9')) THEN ISRSITE=8;
IF ('8060'<=DX14<='8061') OR (DX14='9520') THEN ISRSITE=9;
IF ('8062'<=DX14<='8063') OR (DX14='9521') THEN ISRSITE=10;
IF ('8064'<=DX14<='8065') OR (DX14='9522') THEN ISRSITE=11;
IF ('8066'<=DX14<='8067') OR ('9523'<=DX14<='9524') THEN ISRSITE=12;
IF ('8068'<=DX14<='8069') OR ('9528'<=DX14<='9529') THEN ISRSITE=13;
IF ('8050'<=DX14<='8051') OR ('8390'<=DX14<='8391') OR DX14='8470'
THEN ISRSITE=14;
IF ('8052'<=DX14<='8053') OR ('83921'=DX15 OR '83931'=DX15) OR
DX14='8471' THEN ISRSITE=15;
IF ('8054'<=DX14<='8055') OR ('83920'=DX15 OR '83930'=DX15) OR
DX14='8472' THEN ISRSITE=16;
IF ('8056'<=DX14<='8057') OR ('83941'=DX15 OR '83942'=DX15)OR
('83951'<=DX15<='83952') OR ('8473'<=DX14<='8474') THEN ISRSITE=17;
IF ('8058'<=DX14<='8059') OR ('83940'=DX15 OR '83949'=DX15)
OR ('83950'=DX15 OR DX15='83959') THEN ISRSITE=18;
IF ('8070'<=DX14<='8074') OR DX15='83961' OR DX15='83971' OR
('8483'<=DX14<='8484') OR DX15='92619' OR ('860'<=DX13<='862')
OR DX13='901' OR DX14='9531' OR DX13='875' OR DX14='8790' OR
DX14='8791' OR DX14='9220' OR DX14='9221' OR DX15='92233'
OR (DX13='942' AND (D5='1' OR D5='2')) THEN ISRSITE=19;

IF ('863'<=DX13<='866') OR DX13='868' OR ('9020'<=DX14<='9024')
OR DX14='9532' OR DX14='9535' OR ('8792'<=DX14<='8795') OR
DX14='9222' OR (DX13='942' AND D5='3') OR DX14='9473'
THEN ISRSITE=20;

IF DX13='808' OR DX15='83969' OR DX15='83979' OR DX13='846' OR
DX14='8485' OR DX14='9260' OR DX15='92612' OR DX13='867' OR
DX14='9025' OR ('90281'<=DX15<='90282') OR DX14='9533' OR ('877'
<=DX13<='878') OR DX14='9224' OR (DX13='942' AND D5='5') OR
DX14='9474' THEN ISRSITE=21;

IF DX13='809' OR ('9268'<=DX14<='9269') OR DX14='9541' OR
('9548'<=DX14<='9549') OR ('8796'<=DX14<='8797') OR
('9228'<=DX14<='9229') OR DX13='911' OR (DX13='942' AND D5='0')
OR (DX13='942' AND D5='9') OR DX14='9591' THEN ISRSITE=22;
IF DX14='8479' OR DX15='92611' OR DX13='876' OR DX15='92232'
OR DX15='92231' OR (DX13='942' AND D5='4') THEN ISRSITE=23;

IF ('810'<=DX13<='812') OR DX13='831' OR DX13='840' OR DX13='880' OR
'8872'<=DX14<='8873' OR (DX13='943' AND '3'<=D5<='6') OR DX13='912' OR
DX14='9230' OR DX14='9270' OR DX14='9592' THEN ISRSITE=24;
IF DX13='813' OR DX13='832' OR DX13='841' OR (DX13='881' AND
'0'<=D5<='1') OR ('8870'<=DX14<='8871') OR DX14='9231' OR DX14='9271'
OR (DX13='943' AND '1'<=D5<='2') THEN ISRSITE=25;
IF ('814'<=DX13<='817') OR ('833'<=DX13<='834') OR DX13='842' OR
(DX13='881' AND D5='2') OR '882'<=DX13<='883' OR '885'<=DX13<='886' OR
'914'<=DX13<='915' OR '9232'<=DX14<='9233' OR '9272'<=DX14<='9273' OR
DX13='944' OR '9594'<=DX14<='9595' THEN ISRSITE=26;
IF DX13='818' OR DX13='884' OR '8874'<=DX14<='8877' OR DX13='903' OR
```

```
        DX13='913' OR DX14='9593' OR '9238'<=DX14<='9239' OR
        '9278'<=DX14<='9279' OR DX14='9534' OR DX13='955' OR (DX13='943' AND
        (D5='0' OR D5='9')) THEN ISRSITE=27;
        IF DX13='820' OR DX13='835' OR DX13='843' OR DX15='92401' OR
        DX15='92801' THEN ISRSITE=28;
        IF DX13='821' OR '8972'<=DX14<='8973' OR DX15='92400' OR DX15='92800'
        OR (DX13='945' AND D5='6') THEN ISRSITE=29;
        IF DX13='822' OR DX13='836' OR '8440'<=DX14<='8443' OR DX15='92411' OR
        DX15='92811' OR (DX13='945' AND D5='5') THEN ISRSITE=30;
        IF '823'<=DX13<='824' OR '8970'<=DX14<='8971' OR DX13='837' OR
        DX14='8450' OR DX15='92410' OR DX15='92421' OR DX15='92810' OR
        DX15='92821' OR (DX13='945' AND '3'<=D5<='4') THEN ISRSITE=31;
        IF '825'<=DX13<='826' OR DX13='838' OR DX14='8451' OR '892'<=DX13<=
        '893' OR '895'<=DX13<='896' OR DX13='917' OR DX15='92420' OR DX14=
        '9243' OR DX15='92820' OR DX14='9283' OR (DX13='945' AND '1'<=D5<='2')
        THEN ISRSITE=32;
        IF DX13='827' OR '8448'<=DX14<='8449' OR '890'<=DX13<='891' OR
        DX13='894' OR '8974'<=DX14<='8977' OR '9040'<=DX14<='9048' OR
        DX13='916' OR '9244'<=DX14<='9245' OR DX14='9288' OR DX14='9289' OR
        '9596'<=DX14<='9597' OR (DX13='945' AND (D5='0' OR D5='9')) THEN
        ISRSITE=33;
        IF DX13='828' OR DX13='819' OR DX15='90287' OR DX15='90289' OR
        DX14='9538' OR '9471'<=DX14<='9472' OR DX13='956' THEN ISRSITE=34;
        IF DX13='829' OR '8398'<=DX14<='8399' OR '8488'<=DX14<='8489' OR
        DX13='869' OR ('8798'<=DX14<='8799') OR DX14='9029' OR DX14='9049' OR
        DX13='919' OR '9248'<=DX14<='9249' OR DX13='929' OR DX13='946' OR
        '9478'<=DX14<='9479' OR '948'<=DX13<='949' OR DX14='9539' OR
        DX14='9571' OR '9578'<=DX14<='9579' OR '9598'<=DX14<='9599' THEN
        ISRSITE=35;
        IF ('930'<=DX13<='939') OR ('960'<=DX13<='994') OR ('905'<=DX13
        <='908') OR ('9090'<=DX14<='9092') OR DX13='958' OR ('99550'<=DX15
        <='99554') OR DX15='99559' OR DX14='9094' OR DX14='9099' OR
        ('99580'<=DX15<='99585') THEN ISRSITE=36;

        IF ISRSITE >=1 AND ISRSITE <=3 THEN ISRSITE2=1;
        IF ISRSITE >=4 AND ISRSITE <=8 THEN ISRSITE2=2;
        IF ISRSITE >=9 AND ISRSITE <=13 THEN ISRSITE2=3;
        IF ISRSITE >=14 AND ISRSITE <=18 THEN ISRSITE2=4;
        IF ISRSITE >=19 AND ISRSITE <=23 THEN ISRSITE2=5;
        IF ISRSITE >=24 AND ISRSITE <=27 THEN ISRSITE2=6;
        IF ISRSITE >=28 AND ISRSITE <=33 THEN ISRSITE2=7;
        IF ISRSITE >=34 AND ISRSITE <=35 THEN ISRSITE2=8;
        IF ISRSITE  = 36 THEN ISRSITE2 = 9;

        IF ISRSITE >=1 AND ISRSITE <=8 THEN ISRSITE3=1;
        IF ISRSITE >=9 AND ISRSITE <=18 THEN ISRSITE3=2;
        IF ISRSITE >=19 AND ISRSITE <=23 THEN ISRSITE3=3;
        IF ISRSITE >=24 AND ISRSITE <=33 THEN ISRSITE3=4;
        IF ISRSITE >=34 AND ISRSITE <=36 THEN ISRSITE3 = 5;
        run;

PROC FORMAT;
        VALUE ISM
        1='TYPE 1 TBI'
        2='TYPE 2 TBI'
        3='TYPE 3 TBI'
        4='OTHER HEAD'
```

```
5='FACE'
6='EYE'
7='NECK'
8='HEAD,FACE,NECK UNSPEC'
9='CERVICAL SCI'
10='THORACIC/DORSAL SCI'
11='LUMBAR SCI'
12='SACRUM COCCYX SCI'
13='SPINE+BACK UNSPEC SCI'
14='CERVICAL VCI'
15='THORACIC/DORSAL VCI'
16='LUMBAR VCI'
17='SACRUM COCCYX VCI'
18='SPINE,BACK UNSPEC VCI'
19='CHEST'
20='ABDOMEN'
21='PELVIS+UROGENITAL'
22='TRUNK'
23='BACK+BUTTOCK'
24='SHOULDER&UPPER ARM'
25='FOREARM&ELBOW'
26='HAND&WRIST&FINGERS'
27='OTHER&UNSPEC UPPER EXTREM'
28='HIP'
29='UPPER LEG&THIGH'
30='KNEE'
31='LOWER LEG&ANKLE'
32='FOOT&TOES'
33='OTHER&UNSPEC LOWER EXTREM'
34='OTHER,MULTIPLE,NEC'
35='UNSPECIFIED'
36='SYSTEM WIDE & LATE EFFECTS';

VALUE I2M
1='TBI'
2='OTH HEAD,FACE,NECK'
3='SCI'
4='VCI '
5='TORSO'
6='UPPER EXTREMITY'
7='LOWER EXTREMITY'
8='OTHER & UNSPECIFIED'
9='SYSTEM WIDE & LATE EFFECTS';

VALUE I3M
1='HEAD&NECK'
2='SPINE&BACK'
3='TORSO'
4='EXTREMITIES'
5='UNCLASSIFIABLE BY SITE';

VALUE INM
1='FRACTURES '
2='DISLOCATION'
3='SPRAINS&STRAINS'
4='INTERNAL ORGAN '
5='OPEN WOUNDS'
```

```
       6='AMPUTATIONS'
       7='BLOOD VESSELS'
       8='SUPERFIC/CONT'
       9='CRUSHING'
       10='BURNS'
       11='NERVES'
       12='UNSPECIFIED'
       13='SYSTEM WIDE & LATE EFFECTS';
       run;

PROC FREQ ;
       FORMAT ISRCODE INM. ISRSITE2 I2M. ISRSITE ISM. ;
       TABLES (ISRSITE ISRSITE2)*ISRCODE/LIST ;
       *TABLES ISRSITE2*ISRCODE/LIST ;
       *TABLES opfinal*(ISRSITE ISRSITE2)*ISRCODE/LIST ;
       RUN;
```

Step 3: Code for Paper 1

```
libname djc 'P:\AESOP\Daniels_data';

* defining data for paper one.
inclusion criteria:
insomnia diagnosis
combat injury with no death;

DATA PAPER1;
       SET djc.daniels_finaldata;
       IF NOT (death_dt - inj_date GE 0 and death_dt - inj_date LE 730);
       WHERE INSOMNIA=1;
       IF TBI_CLASS=TBI_1 THEN TBI_CAT=1;
       ELSE IF TBI_CLASS=TBI_2 THEN TBI_CAT=1;
       ELSE IF TBI_CLASS=TBI_3 THEN TBI_CAT=1;
       ELSE TBI_CAT=0;
       IF (ZALEPLON_DOSE=ZALEPLON_LOW |  ESZOPICLONE_DOSE=ESZOPICLONE_LOW |
       ZOLPIDEM_DOSE=ZOLPIDEM_LOW) THEN NBSH_DOSE=1;
       ELSE NBSH_DOSE=0;
       IF NBSH_USE2="acute" THEN NBSH_ACUTE=1;
       ELSE NBSH_ACUTE=0;
       IF NBSH_USE2="intermittent" THEN NBSH_INT=1;
       ELSE NBSH_INT=0;
       IF NBSH_USE2="chronic" THEN NBSH_CHRON=1;
       ELSE NBSH_CHRON=0;
       IF (MRA_TOT GE 1 | ANTIDEP_TOT GE 1 | BZD_TOT GE 1 | ANTIHIST_TOT GE 1)
       & Missing(NBSH_TOT) THEN NBSH_USER_TYPE=0; * non n-BSH user;
       IF (MRA_TOT GE 1 | ANTIDEP_TOT GE 1 | BZD_TOT GE 1 | ANTIHIST_TOT GE 1)
       & NBSH_TOT >= 1 THEN NBSH_USER_TYPE=1; * combo user;
       IF (MRA_TOT=" " & ANTIDEP_TOT=" " & BZD_TOT=" " & ANTIHIST_TOT=" ") &
       NBSH_TOT >= 1 THEN NBSH_USER_TYPE=2; * n-BSH only user;
       *COMPARING CODE TO CHECK MY CODE;
       kcomp= kcompress(nbsh || bzd || mra || antihist || antidep);
```

```
If kcomp in
( 'AntiDep'
'antihist'
'antihistAntiDep'
'BZD'
'BZDAntiDep'
'BZDantihist'
'BZDantihistAntiDep'
'MRA'
'MRAAntiDep'
'MRAantihist'
'MRAantihistAntiDep')
   THEN  combo = "Non_users";

if kcomp in
( 'NBSHAntiDep'
'NBSHantihist'
'NBSHantihistAntiDep'
'NBSHBZD'
'NBSHBZDAntiDep'
'NBSHBZDantihist'
'NBSHBZDantihistAntiDep'
'NBSHBZDMRA'
'NBSHBZDMRAAntiDep'
'NBSHBZDMRAantihist'
'NBSHBZDMRAantihistAntiDep'
'NBSHMRA'
'NBSHMRAAntiDep'
'NBSHMRAantihist'
'NBSHMRAantihistAntiDep')

THEN combo="combo";

if kcomp =
"NBSH"

THEN combo="users";
      RUN;
      *8071 observations;

PROC CONTENTS DATA=PAPER1;
      RUN;

PROC FREQ DATA=PAPER1;
      TABLE NBSH_USER_TYPE*COMBO;
      RUN;

PROC FREQ DATA=PAPER1;
      TABLE COMBO;
      RUN;

*EXPLORING DATA FURTHER;
proc MEANS MEAN MEDIAN MIN MAX data=paper1;
      VAR calculatedage;
      run;
      * AGE DISTRIBUTION IS RIGHT SKEWED. AGE MIN=18, AGE MAX=56, AGE
      MEAN=26, AGE MEDIAN=24;
```

```
PROC UNIVARIATE DATA=PAPER1;
      VAR ISS;
      HISTOGRAM;
      RUN;
      * ISS DISTRIBUTION IS RIGHT SKEWED. ISS MIN=1, ISS MAX=75, ISS
      MEAN=7.2, ISS MEDIAN=5, STD=8.5;

PROC FREQ DATA=PAPER1;
      TABLE TBI_TOT NO_COMORBID;
      RUN;
      * TBI MIN=0, TBI MAX=5 (ONLY 1 PERSON). 96% HAVE EITHER 0 OR 1.
      * COMORBS MIN=0 COMORBS MAX=5 (61 PEOPLE). 1,2,3 COMORBS ALL EVENLY
      SPLIT WITH 30% EACH.;

* DESCRIPTIVE STATISTICS FOR TABLE 1 IN PAPER 1;
PROC FREQ DATA=PAPER1;
      TABLE (AGE_GRP GENDER RACE_GRP BOS PAY_GRADE NO_DEP COMORBID_GRP PTSD
      TBI_TOT DEPRESSION CHRONIC_PAIN ANXIETY ISS_CAT)*NBSH / missing chisq;
      RUN;
PROC FREQ DATA=PAPER1;
      TABLE (AGE_GRP GENDER RACE_GRP BOS PAY_GRADE NO_DEP COMORBID_GRP PTSD
      TBI_TOT DEPRESSION CHRONIC_PAIN ANXIETY ISS_CAT)*BZD / missing chisq;
      RUN;
PROC FREQ DATA=PAPER1;
      TABLE (AGE_GRP GENDER RACE_GRP BOS PAY_GRADE NO_DEP COMORBID_GRP PTSD
      TBI_TOT DEPRESSION CHRONIC_PAIN ANXIETY ISS_CAT)*MRA / missing chisq;
      RUN;
PROC FREQ DATA=PAPER1;
      TABLE (AGE_GRP GENDER RACE_GRP BOS PAY_GRADE NO_DEP COMORBID_GRP PTSD
      TBI_TOT DEPRESSION CHRONIC_PAIN ANXIETY ISS_CAT)*ANTIHIST / missing
      chisq;
      RUN;
PROC FREQ DATA=PAPER1;
      TABLE (AGE_GRP GENDER RACE_GRP BOS PAY_GRADE NO_DEP COMORBID_GRP PTSD
      TBI_TOT DEPRESSION CHRONIC_PAIN ANXIETY ISS_CAT)*ANTIDEP / missing
      chisq;
      RUN;

* TABLE 2 FOR PAPER 1 DESCRIPTIVES;
PROC FREQ DATA=PAPER1;
      TABLE NBSH_USE2*NBSH / missing chisq;
      RUN;
PROC FREQ DATA=PAPER1;
      TABLE BZD_USE2*BZD / missing chisq;
      RUN;
PROC FREQ DATA=PAPER1;
      TABLE MRA_USE2*MRA / missing chisq;
      RUN;
PROC FREQ DATA=PAPER1;
      TABLE (ANTIHIST_USE2)*ANTIHIST / missing chisq;
      RUN;
PROC FREQ DATA=PAPER1;
      TABLE (ANTIDEP_USE2)*ANTIDEP / missing chisq;
      RUN;
PROC FREQ DATA=PAPER1;
      TABLE (ZOLPIDEM_USE TRAZADONE_USE ESZOPICLONE_USE TEMAZEPAM_USE
```

```
      TRIAZOLAM_USE DOXEPIN_USE ZALEPLON_USE RAMELTEON_USE FLURAZEPAM_USE
      ESTAZOLAM_USE ANTIHIST_USE2 HYDROXYZINE_USE MIRTAZAPINE_USE) / missing
      chisq;
      RUN;

* NEW TABLE 2 DESCRIPTIVE STATISTICS (NBSH, COMBO, AND NON NBSH USERS);
PROC FREQ DATA=PAPER1;
      TABLE (AGE_GRP GENDER RACE_GRP BOS NO_DEP COMORBID_GRP PTSD TBI_CAT
      DEPRESSION CHRONIC_PAIN ANXIETY ISS_CAT)*NBSH_USER_TYPE / MISSING
      CHISQ;
      RUN;

* TABLE 3 FOR PAPER 1 (LOOKING AT INJURY SEVERITY);
PROC FREQ DATA=PAPER1;
      TABLE (NBSH_USE2 NBSH_DOSE)*ISS_CAT / missing chisq;;
      RUN;

*GRAPH FOR YEARLY PREVALECE RATES;
*OVERALL PREV RATES FOR NBSH USE;
PROC MEANS DATA=PAPER1 MEAN STD MIN MAX N ;
      *VAR NBSH_COUNT;
      VAR NBSH_COUNT;
      CLASS YR;
      OUTPUT OUT=DJC.GRAPH_STATS
      MEAN()= / AUTONAME AUTOLABEL WAYS INHERIT;
      RUN;
* PREV RATES BY USE TYPE (ACUTE, INT, AND CHRONIC);
PROC MEANS DATA=PAPER1 MEAN STD MIN MAX N ;
      VAR NBSH_ACUTE;
      *VAR NBSH_CHRON;
      *VAR NBSH_INT;
      CLASS YR;
      OUTPUT OUT=DJC.GRAPH_STATS
      MEAN()= / AUTONAME AUTOLABEL WAYS INHERIT;
      RUN;

PROC GPLOT DATA=DJC.GRAPH_STATS;
      PLOT NBSH_COUNT_MEAN*YR / AREAS=1 FRAME VAXIS=AXIS1 HAXIS=AXIS2;
      RUN;
```

Manuscript 2 SAS Code (n-BSH and HRQOL)

```
PROC IMPORT OUT=djc.DANIEL_UR1965_WWRP_RESPONSE DATAFILE= "Q:\Daniels_data\UR
1965_WWRP_RESPONSE.xlsx"
     DBMS=xlsx REPLACE;
     SHEET="PCS_MCS_SLP";
     GETNAMES=YES;
RUN;


proc sql;
CREATE TABLE djc.DANIELS_FINALDATA_withWWRPDate AS
SELECT a.*,b.survey_dt
FROM djc.daniels_finaldata as a
LEFT JOIN djc.DANIEL_UR1965_WWRP_RESPONSE as b ON (a.nhrc_id = b.nhrc_id);
QUIT;

libname djc 'P:\AESOP\Daniels_data';

* defining data for paper one.
inclusion criteria:
insomnia diagnosis
combat injury with no death
N-bsh USER;

DATA PAPER2;
      SET djc.paper2_GE30;
      IF NOT (death_dt - inj_date GE 0 and death_dt - inj_date LE 730);
      *WHERE NBSH_tot GE 30;
      WHERE PCS GT 0;
      IF NBSH_TOT LT 90 THEN NBSH_CAT = 3;
      ELSE IF NBSH_TOT GE 90 AND NBSH_TOT LT 180 THEN NBSH_CAT = 2;
      ELSE IF NBSH_TOT GE 180 THEN NBSH_CAT = 1;
      IF NBSH_GRP = "1NBSH_90" THEN NBSH_CAT_CHK = 3;
      ELSE IF NBSH_GRP = "2NBSH_90_179" THEN NBSH_CAT_CHK = 2;
      ELSE IF NBSH_GRP = "3NBSH_180+" THEN NBSH_CAT_CHK = 1;
      IF (PTSD = 1 | DEPRESSION = 1 | ANXIETY = 1) THEN MENT_HLTH=1;
      ELSE MENT_HLTH=0;
      IF TBI_TOT GE 1 THEN TBI_CAT=1;
      ELSE TBI_CAT=0;
      IF NO_DEP = "1_2" | NO_DEP = "2_PLUS" THEN DEP_CAT = 1;
      ELSE DEP_CAT = 0;
      *if calculatedage ge 18 and le 24 then age_new = 0;
      *else if calculatedage ge 25 and le 34 then age_new = 1;
      *else if calculatedage ge 35 and le 44 then age_new = 2;
      *else if calculatedage ge 45 then age_new = 3;
      *if gender = "Male" then gender_new = 0;
      *else if gender = "Female" then gender_new=1;
      *if BOS = "Army" then BOS_new = 0;
      *else if BOS = "Navy" then BOS_new = 1;
      *else if BOS = "Air Force" then BOS_new = 2;
      *if no_dep = " " then no_dep_new = 0;
      *else if no_dep "1_2" then no_dep_new = 1;
      *else if no_dep "2_plus" then no_dep_new = 2;
      *if no_comorb = " " then no_comorb_new = 0;
      *else if no_comorb = "1_2" then no_comorb_new = 1;
```

```
      *else if no_comorb = "2_plus" then no_comorb_new = 2;
      IF diff_surveyDate_injDate LT 730 THEN DELETE; * THIS IS THE ONLY
      PERSON WHO COMPLETED ANOTHER SURVEY BETWEEN 2 YR FOLLOW UP AND SURVEY
      DATE.;
      RUN;

PROC PRINT DATA=PAPER2;
      WHERE diff_surveyDate_injDate <730;
      RUN;
      * ONLY ONE PERSON NOTED. THIS SEEMS LOW, SO I DOUBLE CHECKED WITH JAMES
      AND HE ALSO GOT JUST 1 PERSON.;

PROC SORT DATA=PAPER2;
      BY NBSH_CAT;
      RUN;
PROC MEANS MIN MAX MEAN MEDIAN STD DATA=PAPER2;
      VAR diff_surveyDate_injDate;
      *BY NBSH_CAT;
      RUN;


* DESCRIPTIVE STATISTICS FOR TABLE 1 IN PAPER 2;
PROC FREQ DATA=PAPER2;
      TABLE (AGE_GRP GENDER RACE_GRP BOS PAY_GRADE DEP_CAT COMORBID_GRP
      TBI_CAT PTSD DEPRESSION ANXIETY CHRONIC_PAIN ISS_CAT)*ESZOPICLONE_USE /
      chisq;
      RUN;

PROC FREQ DATA=PAPER2
      TABLE (AGE_GRP GENDER RACE_GRP BOS PAY_GRADE DEP_CAT COMORBID_GRP
      TBI_CAT PTSD DEPRESSION ANXIETY CHRONIC_PAIN ISS_CAT)*ZOLEPLON_USE /
      missing chisq;
      RUN;

PROC FREQ DATA=PAPER2;
      TABLE (AGE_GRP GENDER RACE_GRP BOS PAY_GRADE DEP_CAT COMORBID_GRP
      TBI_CAT PTSD DEPRESSION ANXIETY CHRONIC_PAIN ISS_CAT)*ZOLPIDEM_USE /
      missing chisq;
      RUN;

* DESCRIPTIVE STATISTICS FOR TABLE 2 IN PAPER 2;
PROC FREQ DATA=PAPER2;
      TABLE (AGE_GRP GENDER RACE_GRP BOS DEP_CAT COMORBID_GRP TBI_CAT PTSD
      DEPRESSION ANXIETY CHRONIC_PAIN ISS_CAT)*NBSH_CAT / MISSING chisq;
      RUN;

proc freq data=paper2;
      table (age_grp gender bos)*nbsh_cat / missing fisher;
      run;

PROC ANOVA DATA=PAPER2;
      CLASS NBSH_CAT;
      *MODEL PCS = NBSH_CAT;
      MODEL MCS = NBSH_CAT;
      MEANS NBSH_CAT;
      RUN;
```

```
*EXPLORING DATA FURTHER;
proc MEANS MEAN MEDIAN MIN MAX STD data=paper2;
      VAR MCS PCS CALCULATEDAGE;
      run;
      * AGE MIN=18, AGE MAX=58, AGE MEAN=27, AGE MEDIAN=25;

* ANALYSIS FOR PAPER PAPER 2, TABLE 3 (PCS AND MCS SCORE);

*UNADJUSTED MODELS;

PROC GLM DATA=PAPER2;
      class NBSH_CAT;
      MODEL MCS = NBSH_CAT;
      RUN;

PROC glm DATA=PAPER2;
      class NBSH_CAT_CHK;
      MODEL PCS = NBSH_CAT_CHK;
      RUN;
      * overall NBSH use is NOT associated with PCS OR MCS IN unadjusted
      MODELS. ;

PROC SORT DATA=PAPER2;
      BY NBSH_CAT;
      RUN;

PROC UNIVARIATE DATA=PAPER2;
      VAR MCS;
      BY NBSH_CAT;
      HISTOGRAM;
      RUN;

PROC MEANS MEAN STD DATA=PAPER2;
      VAR PCS MCS;
      RUN;

* EXPLORING NBSH USE AS A LINEAR VARIABLE;
PROC REG DATA=PAPER2;
MODEL MCS = NBSH_TOT;
RUN;
* NOT SIG OR ABOVE 1% R2 FOR MCS OR PCS IN LINEAR MODELS;

* ADJUSTED MODELS

* MCS MODELS;

* GENMOD PROCEDURE;
PROC SORT DATA=PAPER2;
      BY MCS;
      RUN;

PROC GENMOD DATA=PAPER2;
      CLASS nbsh_CAT AGE_GRP COMORBID_GRP MENT_HLTH ISS_CAT gender ;
      MODEL MCS = NBSH_CAT AGE_GRP GENDER COMORBID_GRP MENT_HLTH ISS_CAT /
      DIST=NORMAL;
      REPEATED SUBJECT=NHRC_ID / CORRW TYPE=UNSTR;
      BAYES SEED=1 OUTPOST=POSTSURG;
```

```
      RUN;

* GLM PROCEDURE. I used this one;
PROC GLM DATA=PAPER2;
      ODS SELECT ParameterEstimates;
      class nbsh_CAT AGE_GRP COMORBID_GRP MENT_HLTH ISS_CAT gender ;
      MODEL MCS = NBSH_CAT AGE_GRP GENDER MENT_HLTH ISS_CAT  / Solution ;
      ods select FitStatistics;
      RUN;
      *R2 NO ADJUSTMENTS = 0.001
       R2 FOR ALL = 0.10
       R2 WITHOUT GENDER = 0.10
       R2 WITHOUT AGE_GRP = 0.08
       R2 WITHOUT COMORBID_GRP = 0.06
       R2 WITHOUT ISS = 0.05
       R2 WITHOUT MENT_HTLH = 0.05
       R2 with MENT_HLTH as Effect Modifier = 0.10, P values 0.04 (int) and
      0.09 (chronic)

       EMM for variables
       age_grp insig
       gender insig
       ment_hlth insig
       ISS_cat insig


* PCS MEDELS;

* GENMOD PROCEDURE;
PROC SORT DATA=PAPER2;
      BY PCS;
      RUN;

PROC GENMOD DATA=PAPER2;
      CLASS nbsh_CAT AGE_GRP COMORBID_GRP MENT_HLTH ISS_CAT gender ;
      MODEL PCS = NBSH_CAT AGE_GRP GENDER MENT_HLTH ISS_CAT / DIST=NORMAL;
      RUN;

PROC GLM DATA=PAPER2;
      ODS SELECT ParameterEstimates;
      class nbsh_CAT AGE_GRP COMORBID_GRP MENT_HLTH ISS_CAT gender ;
      MODEL PCS = NBSH_CAT AGE_GRP GENDER COMORBID_GRP MENT_HLTH ISS_CAT  /
      Solution ;
      ods select FitStatistics;
      RUN;
      *R2 WITH ALL = 0.05
       R2 WITH NO ADJUSTMENTS = 0.0001
       RW WITHOUT AGE_GRP = 0.03
       R2 WITHOUT GENDER = 0.04
       R2 WITHOUT COMORBID_GRP = 0.05
       R2 WITHOUT MENT_HLTH = 0.05
       RW WITHOUT ISS_CAT = 0.04

       EMM for Variables
       age_grp insig
       gender insig
       ment_hlth insig
```

```
ISS_cat insig;
```

Manuscript 3 CODE (TBI severity and n-BSH use)

```
libname djc 'P:\AESOP\Daniels_data';

* CHANGING THE TBI CODING TO MATCH THE ARMED FORCES HEALTH SURVEILLANCE
      DEFINITIONS TO ALIGN WITH THE MOST CURRENT TBI GUIDELINES. This is
      specifically for paper 3 when I look at TBI in more detail;

PROC SQL;
   CREATE TABLE WORK.QUERY_FOR_TRNSTRANSPOSED AS
   SELECT t1.nhrc_id,
          t1.dx1,
          t2.ICD9,
          t2.Severity,
          t2.LOC,
          t2.tbiMild,
          t2.tbiModerate,
          t2.tbiSevere,
          t2.tbiPenetrating,
          t2.LOCgrp
       FROM WORK.TRNSTRANSPOSED_0001 t1
            INNER JOIN WORK.FINAL_TBI_CD_JAN19 t2 ON (t1.dx1 =
      t2.ICD9);
QUIT;



PROC SQL;
      CREATE VIEW WORK.SORTTempTableSorted AS
            SELECT T.ICD9_1, T.ICD9_2, T.ICD9_3, T.ICD9_4, T.ICD9_5,
      T.ICD9_6, T.ICD9_7, T.ICD9_8, T.ICD9_9, T.ICD9_10, T.ICD9_11,
      T.ICD9_12, T.ICD9_13, T.ICD9_14, T.ICD9_15, T.ICD9_16, T.ICD9_17,
      T.ICD9_18, T.ICD9_19, T.ICD9_20, T.ICD9_21, T.ICD9_22
                , T.ICD9_23, T.ICD9_24, T.ICD9_25, T.ICD9_26,
      T.ICD9_27, T.ICD9_28, T.ICD9_29, T.ICD9_30, T.ICD9_31, T.ICD9_32,
      T.ICD9_33, T.ICD9_34, T.ICD9_35, T.ICD9_36, T.ICD9_37, T.ICD9_38,
      T.ICD9_39, T.ICD9_40, T.ICD9_41, T.ICD9_42
                , T.ICD9_43, T.ICD9_44, T.ICD9_45, T.ICD9_46,
      T.ICD9_47, T.ICD9_48, T.ICD9_49, T.ICD9_50, T.ICD9_51, T.ICD9_52,
      T.ICD9_53, T.ICD9_54, T.ICD9_55, T.ICD9_56, T.ICD9_57, T.ICD9_58,
      T.ICD9_59, T.ICD9_60, T.ICD9_61, T.ICD9_62
                , T.ICD9_63, T.nhrc_id
      FROM WORK.QUERY_FOR_EMED_FINAL_WITH_T_0001 as T
;
QUIT;
PROC TRANSPOSE DATA=WORK.SORTTempTableSorted
      OUT=WORK.TRNSTRANSPOSED 0001(LABEL="Transposed
      WORK.QUERY_FOR_EMED_FINAL_WITH_T_0001")
      PREFIX=dx
      NAME=Source
      LABEL=Label
```

```
;
      BY nhrc_id;
      VAR ICD9_1 ICD9_2 ICD9_3 ICD9_4 ICD9_5 ICD9_6 ICD9_7 ICD9_8
      ICD9_9 ICD9_10 ICD9_11 ICD9_12 ICD9_13 ICD9_14 ICD9_15 ICD9_16
      ICD9_17 ICD9_18 ICD9_19 ICD9_20 ICD9_21 ICD9_22 ICD9_23 ICD9_24
      ICD9_25 ICD9_26 ICD9_27 ICD9_28 ICD9_29 ICD9_30 ICD9_31 ICD9_32
        ICD9_33 ICD9_34 ICD9_35 ICD9_36 ICD9_37 ICD9_38 ICD9_39 ICD9_40
      ICD9_41 ICD9_42 ICD9_43 ICD9_44 ICD9_45 ICD9_46 ICD9_47 ICD9_48
      ICD9_49 ICD9_50 ICD9_51 ICD9_52 ICD9_53 ICD9_54 ICD9_55 ICD9_56
      ICD9_57 ICD9_58 ICD9_59 ICD9_60 ICD9_61 ICD9_62
        ICD9_63;

/* ---------------------------------------------------------------------
   End of task code
   ---------------------------------------------------------------------
      */
RUN;


PROC SORT DATA=WORK.QUERY FOR TRNSTRANSPOSED
      OUT=WORK.SORTSORTED_0009(LABEL="Sorted
      WORK.QUERY_FOR_TRNSTRANSPOSED")
      NODUPKEY
      ;
      BY nhrc_id tbiMild tbiModerate tbiSevere tbiPenetrating;

RUN;


PROC FREQ DATA = WORK.SORTTempTableSorted
      NOPRINT
      ORDER=INTERNAL
;
      TABLES Severity * nhrc_id * LOC /
            NOROW
            NOPERCENT
            NOCUM
            SCORES=TABLE
            ALPHA=0.05
            OUT=WORK.F001TabAnalysisTableSORTSORTED_0(LABEL="Cell
      statistics for nhrc_id by LOC for each combination of Severity
      for WORK.SORTSORTED_0009")
;
/* ---------------------------------------------------------------------
   End of task code
   ---------------------------------------------------------------------
      */
RUN; QUIT;
```

```
PROC SQL;
   CREATE TABLE WORK.QUERY_FOR_PAPER3 AS
   SELECT t1.nhrc_id,
          t2.Mild,
          t2.Moderate,
          t2.Penetrating,
          t2.Severe,
          t2.Unclassified,
          t2.LOC,
          t1.tot_inj,
          t1.max_cont,
          t1.med tot,
          t1.age_grp,
          t1.gender,
          t1.race_grp,
          t1.BOS,
          t1.no_dep,
          t1.No comorbid,
          t1.Comorbid_grp,
          t1.PTSD,
          t1.ISS_CAT,
          t1.nbsh,
          t1.bzd,
          t1.mra,
          t1.antihist,
          t1.antidep,
          t1.Zaleplon_dose,
          t1.Eszopiclone_dose,
          t1.Zolpidem_dose,
          t1.inj_date,
          t1.death_dt,
          t1.Doxepin_use,
          t1.Estazolam_use,
          t1.Eszopiclone_use,
          t1.Flurazepam_use,
          t1.Hydroxyzine_use,
          t1.Mirtazapine_use,
          t1.Ramelteon_use,
          t1.Temazepam_use,
          t1.Trazadone_use,
          t1.Triazolam_use,
          t1.Zaleplon_use,
          t1.Zolpidem use,
          t1.AntiDep_use2,
          t1.antihist use2,
          t1.bzd_use2,
          t1.MRA_use2,
          t1.NBSH use2,
          t1.depression,
          t1.chronic pain,
          t1.Anxiety,
          t1.Insomnia,
```

```
t1.sleep_apnea,
t1.caseid,
t1.calculatedAge,
t1.Pay_Grade,
t1.episodeid,
t1.Trauma_Code,
t1.Wounded_Date,
t1.DEP_BGN_CDT,
t1.DEP_END_CDT,
t1.duty_DOD_OCC_CD,
t1.BGN_PRI_DOD_OCC_CD,
t1.LOC_CTRY_CD,
t1.Mounted_Dismounted,
t1.fr_id,
t1.Arrival_Date,
t1.Disposition Date,
t1.final_disposition,
t1.Disposition,
t1.class_1,
t1.MOI 1,
t1.Treatment_Type,
t1.mtf location,
t1.Death_Date,
t1.ISS,
t1.Doxepin_cont,
t1.Estazolam_cont,
t1.Eszopiclone_cont,
t1.Flurazepam_cont,
t1.Hydroxyzine_cont,
t1.Mirtazapine_cont,
t1.Ramelteon_cont,
t1.Temazepam_cont,
t1.Trazadone_cont,
t1.Triazolam_cont,
t1.Zaleplon_cont,
t1.Zolpidem_cont,
t1.MRA_cont,
t1.AntiDep_tot,
t1.NBSH_tot,
t1.bzd_tot,
t1.MRA_tot,
t1.antihist_tot,
t1.PCS,
t1.MCS,
t1.PHQ8,
t1.PHQ8YN,
t1.PCL5,
t1.PCL5YN,
t1.SLPDURA,
t1.SLPHRS,
t1.SLPQUAL,
t1.INSOMNIA_wwrp,
```

```
          t1.yr,
          t1.nbsh_count,
          t1.diff,
          t1.Paper1,
          t1.NBSH_CAT,
          t1.MENT_HLTH,
          t1.TBI_CLASS_CAT,
          t1.age_CAT,
          t1.ZALEPLON_LOW,
          t1.ESZOPICLONE_LOW,
          t1.ZOLPIDEM_LOW,
          t1.NBSH DOSE,
          t1.NBSH_USER_TYPE,
          t1.OTHER MED,
          t1.DEP_CAT
      FROM TMP00002.paper3 t1
           LEFT JOIN WORK.TBI_CASES_NEW t2 ON (t1.nhrc_id =
     t2.nhrc_id);
QUIT;

PROC TABULATE
DATA=WORK.F001TABANALYSISTABLESORTSORTED_0

     OUT=WORK.STABSUMMARYTABLES_0002(LABEL="Summary Tables  for
     WORK.F001TABANALYSISTABLESORTSORTED_0")

     ;

     VAR LOC;
     CLASS Severity /ORDER=UNFORMATTED MISSING;
     CLASS nhrc_id /  ORDER=UNFORMATTED MISSING;
     TABLE /* Row Dimension */
nhrc_id,
/* Column Dimension */
Severity*
  N
LOC*
  Sum           ;
     ;
     WEIGHT COUNT;

RUN;
/* -------------

/* CODE FOR PAPER 3 NOW THAT TBI IS UPDATED TO AFHS DEFINITIONS;


DATA djc.Paper3;
     SET djc.paper3_wtbi_new;
     *SET djc.daniels_finaldata_addnewtbi;
     IF NOT (death_dt - inj_date GE 0 and death_dt - inj_date LE 730);
     WHERE INSOMNIA=1;
     *WHERE INSOMNIA=1 and NBSH_tot GE 28;
```

```
      *IF NBSH_GRP = "1NBSH_90" THEN NBSH_CAT_CHK = 1;
      *ELSE IF NBSH_GRP = "2NBSH_90_179" THEN NBSH_CAT_CHK = 2;
      *ELSE IF NBSH_GRP = "3NBSH_180+" THEN NBSH_CAT_CHK = 3;
      IF (PTSD = 1 | DEPRESSION = 1 | ANXIETY = 1) THEN MENT_HLTH=1;
      ELSE MENT_HLTH=0;
      * TBI with Barell matrix;
      *IF TBI_CLASS = " " THEN TBI_CLASS_CAT = 0;
      *IF TBI_CLASS = "TBI_I" THEN TBI_CLASS_CAT = 1;
      *IF TBI_CLASS = "TBI_2" THEN TBI_CLASS_CAT = 2;
      *IF TBI_CLASS = "TBI_3" THEN TBI_CLASS_CAT = 3;
      * TBI with Armed Forces Database Definition;
      IF (MILD = 1 AND LOCgrp = 0) THEN TBI_FINAL = 1;
      IF (MILD = 1 AND LOCgrp = 1) THEN TBI_FINAL = 2;
      IF (MODERATE = 1 | SEVERE = 1) THEN TBI_FINAL = 3;
      IF (MILD LT 1 & MODERATE LT 1 & SEVERE LT 1 & PENETRATING LT 1) THEN
      TBI_FINAL = 0;
      IF TBI_FINAL GE 1 THEN TBI_FINAL_CAT = 1;
      IF TBI_FINAL = 0 THEN TBI_FINAL_CAT = 0;
      IF (PENETRATING = 1 AND LOCgrp = 0) THEN TBI_PEN = 1;
      IF (PENETRATING = 1 AND LOCgrp = 1) THEN TBI_PEN = 2;
      ELSE TBI_PEN = 0;
      if calculatedage ge 18 and calculatedage le 24 then age_CAT = 0;
      else if calculatedage ge 25 and calculatedage le 34 then age_CAT = 1;
      else if calculatedage ge 35 and calculatedage le 44 then age_CAT = 2;
      else if calculatedage ge 45 then age_CAT = 3;
      if iss ge 1 and iss lt 9 then iss_cat=1;
      else if iss ge 9 then iss_cat=2;
      *IF (ZALEPLON_DOSE = "Zaleplon_high" | Eszopiclone_dose =
      "Eszopiclone_high" | Zolpidem_dose = "Zolpideom_high" ) THEN NBSH_DOSE
      = 1;
      *ELSE NBSH_DOSE = 0;
      IF (ZALEPLON_DOSE=ZALEPLON_LOW |  ESZOPICLONE_DOSE=ESZOPICLONE_LOW |
      ZOLPIDEM_DOSE=ZOLPIDEM_LOW) THEN NBSH_DOSE=1;
      ELSE NBSH_DOSE=0;
      IF (MRA_TOT GE 1 | ANTIDEP_TOT GE 1 | BZD_TOT GE 1 | ANTIHIST_TOT GE 1)
      & Missing(NBSH_TOT) THEN NBSH_USER_TYPE=0; * non n-BSH user;
      IF (MRA_TOT GE 1 | ANTIDEP_TOT GE 1 | BZD_TOT GE 1 | ANTIHIST_TOT GE 1)
      & NBSH_TOT >= 1 THEN NBSH_USER_TYPE=1; * combo user;
      IF (MRA_TOT=" " & ANTIDEP_TOT=" " & BZD_TOT=" " & ANTIHIST_TOT=" ") &
      NBSH_TOT >= 1 THEN NBSH_USER_TYPE=2; * n-BSH only user;
      IF (NBSH_USER_TYPE = 0 | NBSH_USER_TYPE = 1) THEN OTHER_MED = 1;
      ELSE OTHER_MED = 0;
      *IF (NBSH_USER_TYPE=0 | NBSH_TOT LT 28) THEN NBSH_CAT = 0;
      IF NBSH_TOT GE 30 AND NBSH_TOT LT 90 THEN NBSH_CAT = 1;
      else if nbsh_tot ge 90 and nbsh_tot lt 180 then nbsh_cat = 2;
      ELSE IF NBSH_TOT GE 180 THEN NBSH_CAT = 3;
      IF (NO_DEP = "1_2" | NO_DEP = "2_plus") THEN DEP_CAT = 1;
      ELSE DEP_CAT = 0;
      IF ISS GE 1 AND ISS LE 3 THEN ISS_NEW_CAT = 0;
      IF ISS GE 4 AND ISS LE 8 THEN ISS_NEW_CAT = 1;
      IF ISS GE 9 THEN ISS_NEW_CAT = 2;
      RUN;

PROC FREQ DATA=DJC.PAPER3;
      TABLE NBSH_TOT; RUN;

*VERIFYING CODING;
```

```
PROC FREQ DATA=DJC.PAPER3;
      *TABLE TBI_CLASS_CAT*TBI_CLASS / MISSING; * CHECK, THIS WORKS;
      *TABLE (ZALEPLON_DOSE Eszopiclone_dose Zolpidem_dose )*NBSH_DOSE /
      MISSING; * CHECK, THIS WORKS;
      *TABLE NBSH_DOSE;
      *table nbsh_user_type;
      TABLE NBSH_CAT TBI_FINAL;
      RUN;

PROC FREQ DATA=DJC.PAPER3;
      TABLE TBI_FINAL NBSH_DOSE / MISSING ;
      *TABLE TBI_CLASS_CAT TBI_FINAL_CAT;
      *TABLE MILD MODERATE SEVERE PENETRATING LOCGRP;
      *TABLE TBI_FINAL*(MILD MODERATE SEVERE PENETRATING LOCGRP);
      RUN;
      * MOST OF OUR DATA IS CONCUSIONS FROM BLAST INJURIES (850.XX) RATHER
      THAN FRACTURES (800, 801, 803);

* DESCRIPTIVE STATISTICS: TABLE 1;
PROC FREQ DATA=DJC.PAPER3;
      *TABLE (AGE_CAT GENDER RACE_GRP BOS DEP_CAT PTSD DEPRESSION ANXIETY
      CHRONIC_PAIN COMORBID_GRP ISS_CAT)*TBI_CLASS_CAT / missing chisq;
      TABLE (AGE_CAT GENDER RACE_GRP BOS DEP_CAT PTSD DEPRESSION ANXIETY
      CHRONIC_PAIN COMORBID_GRP ISS_CAT NBSH_DOSE NBSH_CAT)*TBI_FINAL /
      chisq;
      RUN;

PROC SORT DATA=DJC.PAPER3;
      BY TBI_FINAL;
      RUN;

*SWITCHING AGE TO LINEAR DUE TO MODEL PARAMETERIZATION;
PROC MEANS MEAN STD DATA=DJC.PAPER3;
      VAR CALCULATEDAGE;
      BY TBI_FINAL;
      RUN;


PROC ANOVA DATA=DJC.PAPER3;
      CLASS TBI_FINAL;
      MODEL CALCULATEDAGE = TBI_FINAL;
      RUN;

* seeing if there are issues with ISS coding.;
PROC FREQ DATA=DJC.PAPER3;
      TABLE ISS_NEW_CAT*(ISS_CAT ISS);
      RUN;

PROC PRINT DATA=DJC.PAPER3;
      WHERE TBI_FINAL = 2 AND ISS_NEW_CAT = 0;
      *TABLE ISS_NEW_CAT*TBI_FINAL;
      RUN;
      * verified with EMED original dataset. all is correct.


*** ANALYSIS FOR DOSEAGE OF N-BSH USE (NORMAL VS HIGH); ***;
PROC LOGISTIC DATA=DJC.PAPER3;
```

```
      CLASS NBSH_DOSE (ref = "1") TBI_CLASS_CAT (REF = "0") AGE_CAT GENDER
      CHRONIC_PAIN ISS_CAT MENT_HLTH OTHER_MED;  *BOS (REF = "Air Force");
      MODEL NBSH_DOSE = TBI_CLASS_CAT AGE_CAT GENDER CHRONIC_PAIN ISS_CAT
      MENT_HLTH OTHER_MED;
      RUN;

* WITH NEW TBI VARIABLE;
PROC LOGISTIC DATA=DJC.PAPER3;
      CLASS NBSH_DOSE (ref = "0") TBI_FINAL_CAT GENDER CHRONIC_PAIN ISS_CAT
      MENT_HLTH OTHER_MED;
      MODEL NBSH_DOSE = TBI_FINAL_CAT CALCULATEDAGE GENDER CHRONIC_PAIN
      ISS_CAT MENT_HLTH OTHER_MED;
      RUN;


*** ANALYSIS FOR DURATION OF USE (ORDINAL / POLYCHOTOMOUS); ***;
PROC SORT DATA=DJC.PAPER3;
      BY NBSH_CAT;
      RUN;

      * CHECKING CELLS FOR MISSING OR EXTREMELY SMALL COUNTS;
PROC FREQ DATA=DJC.PAPER3;
      TABLES NBSH_CAT*TBI_CLASS_CAT / NOPERCENT NOROW NOCOL MISSPRINT;
      TABLES NBSH_CAT*AGE_CAT / NOPERCENT NOROW NOCOL MISSPRINT;
      TABLES NBSH_CAT*GENDER / NOPERCENT NOROW NOCOL MISSPRINT;
      TABLES NBSH_CAT*MENT_HLTH / NOPERCENT NOROW NOCOL MISSPRINT;
      TABLES NBSH_CAT*ISS_CAT / NOPERCENT NOROW NOCOL MISSPRINT;
      RUN;
      * NONE NOTED;

* ORDINAL REGRESSION MODEL (P=0.15, THEREFORE ASSUMPTION IS MET FOR PROP ODDS
      ASSUMP, P=0.33 IN THE MODEL WITH NON USERS AS A REF GROUP);
PROC LOGISTIC DATA=DJC.PAPER3 ORDER=INTERNAL;
      CLASS NBSH_CAT (ref = "0") TBI_FINAL (REF = "0") AGE_CAT GENDER
      CHRONIC_PAIN ISS_CAT MENT_HLTH OTHER_MED / PARAM = REF; *;
      MODEL NBSH_CAT = TBI_FINAL AGE_CAT GENDER MENT_HLTH CHRONIC_PAIN
      ISS_CAT OTHER_MED;* / link = logit ;
      RUN;

PROC LOGISTIC DATA=DJC.PAPER3 ORDER=INTERNAL;
      CLASS NBSH_CAT (ref = "0") TBI_FINAL (REF = "0") GENDER CHRONIC_PAIN
      ISS_CAT MENT_HLTH OTHER_MED / PARAM = REF; *;
      MODEL NBSH_CAT = TBI_FINAL_CAT CALCULATEDAGE GENDER MENT_HLTH
      CHRONIC_PAIN ISS_CAT OTHER_MED / link = logit ;
      RUN;

* SENSITIVITY ANALYSIS - LOOKING AT OUTCOME AS A LINEAR REG;
PROC GLM DATA=DJC.PAPER3;
      CLASS NBSH_CAT (ref = "1") TBI_final (REF = "0") AGE_CAT GENDER
      CHRONIC_PAIN ISS_CAT MENT_HLTH OTHER_MED ; *;
      MODEL NBSH_TOT = TBI_final AGE_CAT GENDER MENT_HLTH CHRONIC_PAIN
      ISS_CAT OTHER_MED / SOLUTION;
      MEANS TBI_final;
      RUN;
      * SIMILAR RESULTS;
```

```
*FOR NUMBERS AND PERCENTAGES OF EXP AND OUTCOME;
PROC FREQ DATA=DJC.PAPER3;
      *TABLE NBSH_CAT*TBI_CLASS_CAT / CHISQ MEASURES;
      TABLE NBSH_CAT*TBI_FINAL / CHISQ MEASURES;
      RUN;

* NEW REGRESSION ANALYSIS FOR TBI AND N-BSH USE with multinomial reg;
PROC FREQ DATA=DJC.PAPER3;
      TABLE NBSH_CAT*(NBSH_CATMID NBSH_CATLONG);
      RUN;

PROC LOGISTIC DATA=DJC.PAPER3;
      CLASS NBSH_CAT (ref = "0") TBI_FINAL (REF = "0") AGE_CAT GENDER
      CHRONIC_PAIN ISS_CAT MENT_HLTH OTHER_MED / PARAM = REF; *;
      MODEL NBSH_CAT = TBI_FINAL CALCULATEDAGE GENDER MENT_HLTH CHRONIC_PAIN
      ISS_CAT OTHER_MED / link = glogit ;
      RUN;

PROC CATMOD DATA=DJC.PAPER3;
      DIRECT TBI_FINAL AGE_CAT CHRONIC_PAIN ISS_CAT MENT_HLTH OTHER_MED ; *;
      RESPONSE LOGITS;
      MODEL NBSH_CAT = TBI_FINAL AGE_CAT GENDER MENT_HLTH CHRONIC_PAIN
      ISS_CAT OTHER_MED ;
      RUN;
```