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Central nervous system and musculoskeletal medication profile of a veteran cohort with blast-related injuries

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Abstract—Little is known about the utilization of central nervous system (CNS) and musculoskeletal (MS) medications in Operation Iraqi Freedom/Operation Enduring Freedom (OIF/OEF) veterans with blast-related injuries (BRIs). We followed prescription drug use among a cohort of 133 OIF/OEF veterans with BRIs by using the Joint Theatre Trauma Registry, the Tampa Polytrauma Registry, and electronic medical records. We extracted 12 months of national medication records from the Veterans Health Administration Decision Support System and analyzed them with descriptive statistics. Over the 12-month period (fiscal year 2007), CNS medications comprised 27.9% (4,225/15,143) of total prescriptions dispensed to 90.2% (120/133) of our cohort. Approximately one-half (48.9%) of the 133 patients were treated with opioid analgesics. Nearly 60% received antidepressants. More than one-half (51.1%) of patients were treated with anticonvulsants. Benzodiazepines and antipsychotics were dispensed to 17.3% and 15.8%, respectively. For MS medicines, 804 were prescribed for 48.1% (64/133) of veterans. Nearly one-fourth (24.8%) were treated with skeletal muscle relaxants. The CNS and MS medications, in general, were continuously prescribed over the 12-month study period. This study provides insight into the complex medical management involved in the care of veterans with BRIs.

Key words: blast injuries, central nervous system, medications, musculoskeletal, OIF/OEF, opioids, polytrauma, prescription drug use, rehabilitation, veterans.

INTRODUCTION AND BACKGROUND

Many wounded veterans from combat theaters in Iraq and Afghanistan exhibit severe polytrauma from blast-related injuries (BRIs) sustained via conventional explosives and improvised explosive devices (IEDs). Direct exposure to the blast results in tremendous forces on tissues and organs. Blasts can create flying debris (shrapnel) and displacement of objects, resulting in polytrauma. While not all blast exposure will result in observable injuries (e.g., burn, tissue loss, puncture wounds), the general

Abbreviations: AMA = American Medical Association, BRI = blast-related injury, CDC = Centers for Disease Control and Prevention, CNS = central nervous system, DSS = Decision Support System, FY = fiscal year, IED = improvised explosive device, JTTR = Joint Theater Trauma Registry, MS = musculoskeletal, OIF/OEF = Operation Iraqi Freedom/Operation Enduring Freedom, PRC = Polytrauma Rehabilitation Center, R&D = Research and Development, SD = standard deviation, TPR = Tampa Polytrauma Registry, VA = Department of Veterans Affairs, VHA = Veterans Health Administration.

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exposure to shock waves may damage organs and systems of the body, such as the central nervous system (CNS).

The Centers for Disease Control and Prevention (CDC) provides an overview of blast and explosive type injuries [1]. Many of these types of injuries can affect the digestive system (e.g., bowel perforation, hemorrhage, ruptured liver or spleen, sepsis, mesenteric ischemia from air embolism) and, of course, the nervous system (e.g., concussion, closed and open brain injury, stroke, spinal cord injury, air embolism-induced injury).

The medication management of BRIs is complex, because these patients are prescribed antidepressants, anticonvulsants, benzodiazepines, and analgesics (both opioids and nonopioids) to manage the pain and resulting mental health effects, such as depression, frequently associated with these injuries [1–7]. While treating chronic nonmalignant pain is important, the treatment of depression or cognitive/behavioral symptoms associated with BRIs may necessitate the prolonged use of these multiple drug regimens. These drug combinations merely reflect the complex medication conditions being treated [5–7].

Our previous analysis of CNS medication utilization in 60 patients with combat-related blast injuries treated at the James A. Haley Veteran's Hospital in Tampa, Florida, found that all but one patient (59/60) were prescribed at least one medication from the Department of Veterans Affairs (VA) CNS medication classification and 95.0 percent (57/60) were identified as being on multiple CNS medications [2]. In our cohort, the types of injuries included traumatic brain injuries, fractures, spinal cord injuries, and ocular injuries, which frequently result in chronic pain as evidenced in the civilian population [7]. The most common complications documented in this cohort were skin ulcers, late effects of injuries to the nervous system (e.g., concussion, closed and open brain injury, spinal cord injury, air embolism-induced injury), and bladder disorders. To our knowledge, our previous study is the only one containing benchmark data on CNS drug use for veterans with BRIs [2]. The intent of this article is to provide a more detailed description of the CNS and musculoskeletal (MS) drug utilization profile for a larger cohort of veterans with BRIs identified from additional data.

METHODS

Polytrauma patients were identified from two sources: (1) the Joint Theater Trauma Registry (JTTR) based at the U.S. Army Institute of Surgical Research at Fort Sam Houston, Texas, and (2) the Tampa Polytrauma Registry (TPR) maintained and housed at the Level 1 Polytrauma/Blast-Related Injury Center at the Tampa VA. The JTTR provided us with a current list of Operation Iraqi Freedom/Operation Enduring Freedom (OIF/OEF) veterans treated at the Tampa and Orlando Florida Veterans Health Administration (VHA) medical clinics for complications from BRIs in combat theaters [8]. Both registries contain information on the mechanism of injury and a unique patient identifier but do not have information on injury severity or injury date. BRIs in combat theaters are usually caused by direct fire from IEDs and by indirect fire, such as mortar attacks.

Cohort Identification

We performed manual chart reviews of the Computerized Patient Record System at the Tampa VA to confirm blast exposure by using text from the medical record including, but not limited to, the words "blast," "bomb," "explosion," "grenade/rocket propelled grenade," "improvised explosive device," "land mine," "mortar," "shrapnel," and "vehicle improvised explosive device." Cohort identification and verification of BRIs are critical in a study of this nature, because both registries contain many non-combat-related (primarily motor vehicle accidents) and nonblast (generally gunshot wound) patients. We retained only patients we could confirm by crosswalking the registry data with the electronic medical record data for a definitive cohort of 210 veterans with BRIs as of April 1, 2008.

We converted the 210 patient Social Security numbers to a scrambled Social Security number format to track inpatient and outpatient pharmacy service use via national VHA data sets. We were unable to identify scrambled Social Security numbers for 2 patients, resulting in a potential study cohort of 208 patients. In order to enable our analysis using existing data, we further limited our cohort of 208 patients to those who received VHA care in fiscal year (FY) 2007 (October 1, 2006–September 30, 2007), resulting in 148 unique patients.

National medication records for this cohort were extracted from the VHA Decision Support System (DSS). The DSS allowed tracking of all VHA medications dispensed from any VHA clinic or hospital for this cohort at any VA facility in the United States. We obtained pharmacy data for FY 2007 by using the scrambled Social Security numbers for the cohort. The DSS did

not contain the medication records for 15 of the 148 patients. Hence, our final study cohort consisted of 133 BRI patients who received medications during FY 2007.

Statistical Analysis

We used descriptive statistics to analyze inpatient and outpatient medication utilization categorized according to VHA CNS and MS drug classes, similar to the American Hospital Formulary Service Pharmacologic-Therapeutic Classification System [9]. To assess the duration of use of these medications over the study period, we used the variable "day supply" within the individual pharmacy claims and structured query language (SAS, Proc SQL) to calculate the total days of CNS or MS medication use per patient. All analyses were conducted with SAS version 9.1 (SAS Institute Inc; Cary, North Carolina). This study was approved by the James A. Haley Veterans' Hospital Research and Development (R&D) Committee and approved by University of South Florida Institutional Review Board (IRB 104159) for human subject protection standards.

RESULTS

The average age of our study cohort (N = 133) was 30 (standard deviation [SD] = 8.0, range 20–52) and all were male. Female soldiers are prohibited from deployment in combat units but do sustain BRIs, albeit infrequently, via indirect fire. **Table 1** summarizes the

Table 1.
Inpatient and outpatient utilization by major Veterans Health Administration (VHA) drug class headings for patients with blast-related injury (N = 133).

Major VHA Drug Class Heading	Pharmacy Claims			No. of Patients
	Inpatient	Outpatient	Total	
Antidotes, Deterrents, and Poison Control (AD)	35	16	51	13
Antihistamines (AH)	229	67	296	48
Antimicrobials (AM)	780	95	875	54
Autonomic Medications (AN)	521	17	538	13
Blood Products/Modifiers/Volume Expanders (BL)	791	55	846	35
Cardiovascular Medications (CV)	358	151	509	48
Central Nervous System Medications (CN)	3,122	1,103	4,225	120
Dental and Oral Agents, Topical (OR)	21	10	31	8
Dermatological Agents (DE)	431	139	570	64
Diagnostics Agents (DX)	5	6	11	6
Gastrointestinal Agents (GA)	2,082	107	2,189	57
Genitourinary Drugs (GU)	55	57	112	18
Hormones/Synthetics/Modifiers (HS)	256	32	288	23
Immunological Agents (IM)	17	1	18	8
Irrigation/Dialysis Solutions (IR)	2	6	8	5
Musculoskeletal Medications (MS)	627	177	804	68
Nasal and Throat Agents, Topical (NT)	65	11	76	21
New Drugs, Not Classified (NC)	1,099	191	1,290	64
Ophthalmic Agents (OP)	198	26	224	21
Otic Agents (OT)	1	3	4	4
Pharmaceutical Aids/Reagents (PH)	128	11	139	18
Prosthetics/Supplies/Devices (XA)	25	166	191	31
Rectal, Local (RS)	58	18	76	14
Respiratory Tract Medications (RE)	215	54	269	24
Therapeutic Nutrients/Minerals/Electrolytes (TN)	1,118	34	1,152	37
Vitamins (VT)	305	46	351	29
Total	12,544	2,599	15,143	133*

Note: For complete list of all 570 VHA drug classes and 97,763 medications by generic, trade, and manufacturer names that comprise VHA drug classes, please refer to freely downloadable VHA National Drug File (Microsoft Access Database): http://www.pbm.va.gov/NationalFormulary.aspx/.
*Patients used multiple drug classes and numbers do not add up.

inpatient and outpatient pharmacy claims by the major VHA drug classes. Over the 12-month period (FY 2007), a total of 15,143 pharmacy claims were found across various drug classes, averaging 9.5 pharmacy claims per patient per month. The top five major VHA drug classes accounted for more than 64 percent of the total pharmacy claims. In descending order, these were CNS medications (27.9%), gastrointestinal medications (14.5%), new drugs not yet classified (8.5%), therapeutic nutrients (7.6%), and blood products (6.0%).

Of the 15,143 pharmacy claims, 82.8 percent were related to inpatient treatment (12,544/15,143) and 17.2 percent to outpatient treatment (2,599/15,143). The 12,544 inpatient claims involved 44.4 percent (59/133) of our study population, while the 2,599 outpatient claims included 85.0 percent (113/133). The average day supply related to inpatient and outpatient pharmacy claims was 11.2 days (SD = 4.7 days) and 42.3 days (SD = 26.6 days), respectively.

The CNS medications comprised 27.9 percent (4,225/15,143) of the total pharmacy claims and were dispensed to 90.2 percent (120/133) of our cohort. Of the 4,225 CNS pharmacy claims, 73.9 percent (3,122/4,225) were for inpatient treatment and 26.1 percent (1,103/4,225) were for outpatient treatment (**Table 1**). Among BRI patients, the CNS medications were generally prescribed for the entire FY. Of the 120 patients taking CNS medications, 78.3 percent (94/120) had been dispensed multiple CNS medications.

Table 2 presents the CNS medication profile for the cohort and examples of the most commonly prescribed CNS medications. Approximately one-half (48.9%) of the patients were treated with opioid analgesics (e.g., morphine, oxycodone, fentanyl). Nearly 60 percent received antidepressants (e.g., buproprion, citalopram, fluoxetine, mirtazepine, sertraline). More than one-half were given anticonvulsants (e.g., gabepentin, oxcarbazepine, topiramate). Finally, benzodiazepines (e.g., alprazolam, diazepam, temazepam) and antipsychotics (e.g., quetiapine, risperidone) were prescribed to 17.3 and 15.8 percent, respectively.

For MS medications (nonopioid analgesics and skeletal muscle relaxants), we found 804 pharmacy claims for 48.1 percent (64/133) of patients. **Table 3** presents the MS medication profile and examples of the most commonly prescribed medications. Nearly one-fourth (24.8%) of the

Table 2.
Central nervous system (CNS) drug utilization for patients with blast-related injury (*N* = 133).

VHA CNS Drug Classes	Pharmacy Claims	No. of Patients	Claims per Patient	% of Patients
CN101 Analgesics (e.g., morphine, oxycodone, fentanyl)	532	65	8.2	48.9
CN102 Opioid Antagonist Analgesics (e.g., naloxone)	1	1	1.0	0.75
CN103 Nonopioid Analgesics (e.g., acetaminophen, aspirin)	145	41	3.5	30.8
CN104 Nonsteroidal Anti-Inflammatory Analgesics (e.g., etodalac)	22	9	2.4	6.8
CN105 Antimigraine Agents (e.g., zolmitriptan)	25	7	3.6	5.3
CN204 Local Anesthetics, Injections (e.g., bupivacaine, lidocaine)	6	2	3.0	1.5
CN302 Benzodiazepine-Derivative Sedative Hypnotic (e.g., alprazolam, diazepam, temazepam)	144	23	6.3	17.3
CN309 Sedative Hypnotics, Other (e.g., bupirone, chloral hydrate, zolpidem)	55	14	3.9	10.5
CN400 Anticonvulsants (e.g., gabepentin, oxcarbazepine, topiramate)	1704	68	25.1	51.1
CN500 Antiparkinson Agents (e.g., pramipexole)	53	2	26.5	1.5
CN550 Antivertigo Agents (e.g., meclizine)	171	9	19.0	6.8
CN601 Tricyclic Antidepressants (e.g., amitriptyline, nortriptyline)	90	19	4.7	14.3
CN609 Antidepressants, Other (e.g., buproprion, citalopram, fluoxetine, mirtazepine, sertraline)	784	79	9.9	59.4
CN709 Antipsychotics (e.g., quetiapine, risperidone)	120	21	5.7	15.8
CN802 Amphetamine-like Stimulants (e.g., methylphenidate)	156	5	31.2	3.8
CN809 CNS Stimulants, Other (e.g., modafinil)	206	5	41.2	3.8
CN900 CNS Medication, Other (e.g., donepezil, strattera)	11	2	5.5	1.5

Note: For complete list of all 570 Veterans Health Administration (VHA) drug classes and 97,763 medications by generic, trade, and manufacturer names that comprise VHA drug classes, please refer to freely downloadable VHA National Drug File (Microsoft Access Database): http://www.pbm.va.gov/NationalFormulary.aspx/.

Table 3.
Musculoskeletal (MS) drug utilization for patients with blast-related injury (*N* = 133).

VHA MS Drug Classes	Pharmacy Claims	No. of Patients	Claims per Patient	% of Patients
MS110 Salicylates (e.g., salsalate)	32	4	8.0	3.0
MS120 Nonsalicylates, Nonsteroidal Anti-Inflammatory Drugs (e.g., ibuprofen, indomethacin, naproxen)	234	50	4.7	37.6
MS200 Skeletal Muscle Relaxants (e.g., baclofen, cyclobenzaprine, dantrolene, methocarbamol, tizanidine)	538	33	16.3	24.8

Note: For complete list of all 570 Veterans Health Administration (VHA) drug classes and 97,763 medications by generic, trade, and manufacturer names that comprise VHA drug classes, please refer to freely downloadable VHA National Drug File (Microsoft Access Database): http://www.pbm.va.gov/NationalFormulary.aspx/.

cohort was treated with skeletal muscle relaxants (e.g., baclofen, cyclobenzaprine, dantrolene, methocarbamol, tizanidine), and similar to the duration of CNS medication, the use encompassed the entire FY. All patients using MS medication also used CNS medications at some time during the study period.

DISCUSSION

This study updates a previous study that describes CNS (including opioids) and MS medication use in OIF/OEF veterans with BRIs. Compared with our earlier study, we found similar overall use of CNS and MS drugs. However, in this study, we found lower use of opioids: approximately 48.8 percent compared with 81.6 percent [2].

Several potential reasons exist for this difference in opioid use. Although we had no information on the types and severity of injuries for these patients, the pain center at the Tampa Polytrauma Rehabilitation Center (PRC) has greatly expanded its pain management services, which include alternatives to medication [3].

The types of injuries for our cohort upon receiving care in the VHA included traumatic brain injuries, fractures, spinal cord injuries, and ocular injuries. Main complications for this cohort were skin ulcers, late effects of injuries to the nervous system (e.g., concussion, closed and open brain injury, spinal cord injury, air embolism-induced injury), and bladder disorders. The injuries sustained in our cohort were consistent with our previous study and were similar to those described by the CDC [1]. While we could not quantify the severity of the BRIs sustained in our cohort, the medication profiles of these patients suggests a high degree of medical complexity.

A retrospective analysis primarily of pharmacy data has limitations. We used the electronic medical record only to confirm BRIs. We also could not determine from the JTTR or the TPR registries the onset or severity of BRIs for individual patients. Therefore, we could not determine whether medication use varied by injury severity or time since injury. Furthermore, we do not know the specific reasons why the medications were prescribed or which providers prescribed these medications. No physician profiling of board certification or treating specialty type exists in VHA data sets to evaluate individual provider prescribing behaviors, information that is available in the American Medical Association (AMA) Physician Master File [10]. However, care for OIF/OEF polytrauma patients involves a multidisciplinary team of physiatrists, psychologists, trauma surgeons, pharmacists, and physical and occupational therapists. The specialized and multidisciplinary care provided at PRCs was highlighted by Dr. Steven G. Scott, MD, Director of the Tampa PRC, in a statement before the House Committee on Veterans' Affairs at a "Roundtable Discussion of Issues Concerning our Veterans" on November 19, 2008 [11]. Regardless, future research in this subject matter may benefit from the purchasing of the AMA Physician Masterfile and a merging with the various Austin Automation Center databases for future descriptive and outcome-based studies.

CONCLUSIONS

This study is exploratory and provides benchmark data on the medication use of a vulnerable population. This study provides insight into the complex medical management involved in the care of veterans with BRIs. By providing some benchmark data on the medication profiles of patients with BRIs as they transition from inpatient rehabilitation to the community, we may help guide clinicians' medical decision-making related to CNS and MS medication usage.

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Provided JTTR *data*: K. Siddharthan.
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