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A retrospective description of outpatient medication prescriptions following major limb amputation in the Iraq and Afghanistan conflicts: A brief report on the population

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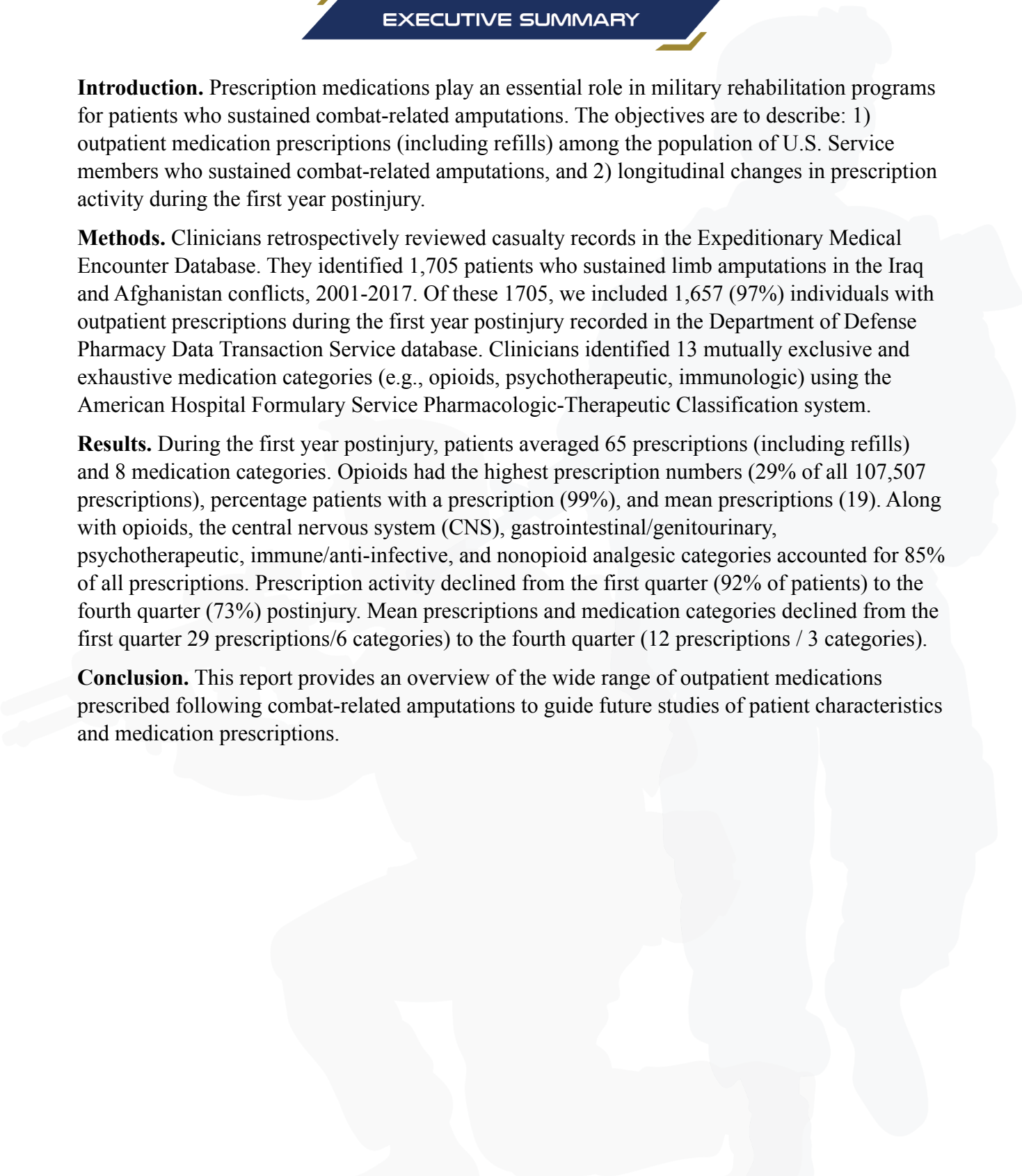
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The study protocol was approved by the Naval Health Research Center (NHRC) Institutional Review Board in compliance with all applicable Federal regulations governing the protection of human subjects. Research data were derived from an approved NHRC, Institutional Review Board protocol number NHRC.2003.0025.



EXECUTIVE SUMMARY

Introduction. Prescription medications play an essential role in military rehabilitation programs for patients who sustained combat-related amputations. The objectives are to describe: 1) outpatient medication prescriptions (including refills) among the population of U.S. Service members who sustained combat-related amputations, and 2) longitudinal changes in prescription activity during the first year postinjury.

Methods. Clinicians retrospectively reviewed casualty records in the Expeditionary Medical Encounter Database. They identified 1,705 patients who sustained limb amputations in the Iraq and Afghanistan conflicts, 2001-2017. Of these 1705, we included 1,657 (97%) individuals with outpatient prescriptions during the first year postinjury recorded in the Department of Defense Pharmacy Data Transaction Service database. Clinicians identified 13 mutually exclusive and exhaustive medication categories (e.g., opioids, psychotherapeutic, immunologic) using the American Hospital Formulary Service Pharmacologic-Therapeutic Classification system.

Results. During the first year postinjury, patients averaged 65 prescriptions (including refills) and 8 medication categories. Opioids had the highest prescription numbers (29% of all 107,507 prescriptions), percentage patients with a prescription (99%), and mean prescriptions (19). Along with opioids, the central nervous system (CNS), gastrointestinal/genitourinary, psychotherapeutic, immune/anti-infective, and nonopioid analgesic categories accounted for 85% of all prescriptions. Prescription activity declined from the first quarter (92% of patients) to the fourth quarter (73%) postinjury. Mean prescriptions and medication categories declined from the first quarter 29 prescriptions/6 categories) to the fourth quarter (12 prescriptions / 3 categories).

Conclusion. This report provides an overview of the wide range of outpatient medications prescribed following combat-related amputations to guide future studies of patient characteristics and medication prescriptions.

INTRODUCTION

Prescription medications are an integral part of rehabilitation programs for U.S. Service members who sustained combat-related limb amputations in the Iraq and Afghanistan conflicts.^{1,2} Serious combat trauma, particularly blast-related amputations, may have immediate and lasting secondary impacts on multiple physiological and psychological systems¹⁻⁴ that often require careful medication management.¹ Understanding individual and population prescription practices and requirements can inform military and Department of Veterans Affairs (VA) medical planning and clinical rehabilitation guidelines.^{5,6}

An initial descriptive study of this population is important given the wide range and potentially large numbers of medications prescribed to these patients.^{1,5,6} Service members who sustained amputations in recent conflicts are of special interest because of their high-profile injuries, unique patient characteristics, comorbidities, and postinjury care programs.^{1,2,5-10} Combat related amputations are associated with many complications that may persist, resolve, and/or recur during the first year postinjury (e.g., acute stress, sleep, pain, infections, thrombosis, heterotopic ossification, and psychological disorders).^{1-6,8,9} Managing these conditions effectively can help optimize health outcomes and quality of life.^{1-6,11}

This brief report's objectives were to provide a descriptive overview of outpatient medication prescriptions (including refills) for the population of U.S. Service members who sustained combat related amputations, 2001–2017, and to provide a longitudinal description of changes in medication prescription activity during the first year postinjury.

METHODS

Study Design

The study protocol was approved by the Naval Health Research Center Institutional Review Board in compliance with all applicable Federal regulations governing the protection of human subjects. Research data were derived from an approved Naval Health Research Center, Institutional Review Board protocol number NHRC.2003.0025.

This was a retrospective review of existing Department of Defense (DoD) health and pharmacy data. Clinicians identified 1,705 U.S. Service members who sustained 1 or more major limb amputations in Iraq or Afghanistan, from 2001 through 2017, in the Expeditionary Medical Encounter Database (EMED).^{7,12} The EMED includes virtually all U.S. casualties in the Iraq and Afghanistan conflicts. Of 1,705 patients identified, 1,657 (97%) were included who had at least one outpatient medication prescription record. The remaining 48 patients were excluded because they had no medication prescription records, possibly because the data were missing or they received medications outside the Military Health System.

Data Sources

Injury-specific data. The EMED provides injury-specific data based on clinician review of casualty records from the point of injury through long-term rehabilitative outcome. Military trauma clinicians and expert registered nurse coders at Naval Health Research Center reviewed

casualty records to assign International Classification of Diseases, 9th and 10th Revisions, Clinical Modification (ICD-9-CM and ICD-10-CM) codes and Abbreviated Injury Scale scores for each injury.

Pharmacy prescriptions. Medication prescription data came from the Pharmacy Data Transaction Service (PDTs), which maintains outpatient prescription records for DoD beneficiaries worldwide. The PDTs records all new and refill prescriptions dispensed based on DoD benefits at military treatment facilities (MTFs), some VA facilities, retail, and mail order to active duty Service members, retirees, and dependents.¹³

Medications were classified according to the American Hospital Formulary Service (AHFS) Pharmacologic-Therapeutic Classification system,¹⁴ which includes over 200 medication classes and subclasses (e.g., the central nervous system [CNS] medications class has subclassifications for analgesics and psychotherapeutics). Specific AHFS classes were identified or combined to provide a manageable number of 13 categories for analysis and presentation. The categories were also selected because of their relevance for the medical issues of patients with combat-related amputations. Clinicians identified AHFS classes (CNS, gastrointestinal/genitourinary [GI/GU], electrolytic/caloric, cardiovascular, respiratory) or subclasses (psychotherapeutic, analgesic opioid, analgesic nonopioid) as categories. The CNS category excluded psychotherapeutics and analgesics (opioid and nonopioid). The remaining medication categories (immune/anti-infective, autonomic, blood formation/thrombosis, hormone/metabolic, miscellaneous) consisted of combined or condensed AHFS classes. We included over-the-counter medications (e.g., vitamins, creams/washes) and other items containing a chemical compound. We excluded devices and pharmaceutical aids (e.g., stockings, syringes, and bandages). A prior publication supplement provides a complete description of medications and AHFS classifications.¹⁵

Statistical Analyses

The primary unit of analysis was the individual prescription per previous studies,^{16,17} including all new and refill prescriptions. We calculated: (1) percent of patients with a medication prescription, (2) overall number of outpatient medication prescriptions, (3) total number of prescriptions within the 13 medication categories, and (4) mean and median prescriptions per patient (based on patients with at least 1 prescription).

Measures were summarized for the first year postinjury and during each 4 consecutive quarterly intervals (91 days) during that year (i.e., quarters 1–4). A separate longitudinal measure was calculated, labeled as “continued prescriptions,” and defined as individuals with at least 1 prescription from a single category (e.g., opioid) or combination of categories (e.g., opioid, CNS, psychotherapeutic) during the last 3 consecutive quarters (i.e., quarters 2–4). Continued prescriptions are relevant for opioid, psychotherapeutic, and other CNS medications because of their potential for adverse events (e.g., addiction).¹⁸

RESULTS

Overall, 97% of patients (1,657 of 1,705) had at least 1 outpatient medication prescription recorded in PDTs (not shown). These 1,657 patients had a total of 107,507 medication

prescriptions (new or refills; see Table 1). During the first 12 months postinjury, patients averaged 65 prescriptions (SD = 43.4; interquartile range, 33-86). Patients averaged 8 different medication categories during the first year (not shown). The delivery source listed for over 97% of all prescriptions was MTF direct care or MTF clinician (not shown). Inpatient medication prescription records, which usually account for the first weeks postinjury, were unavailable. Thirty-nine percent of patients had their first outpatient prescription record within 30 days postinjury, 80% within 60 days, and 92% within 90 days.

1.

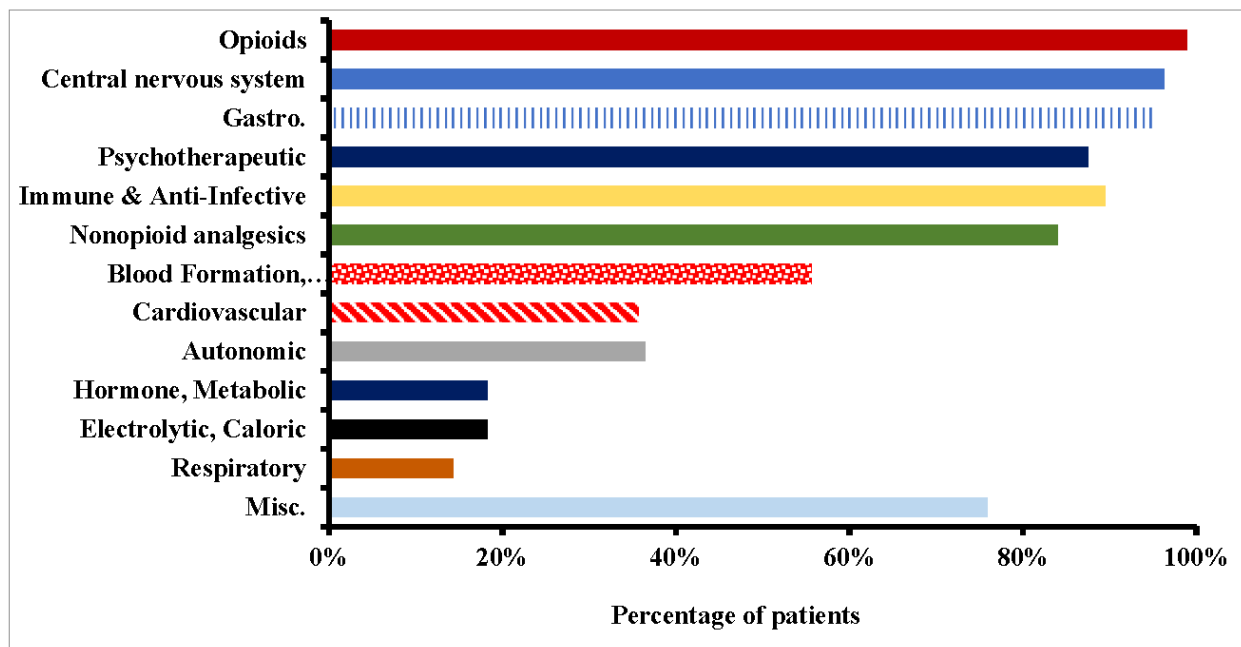
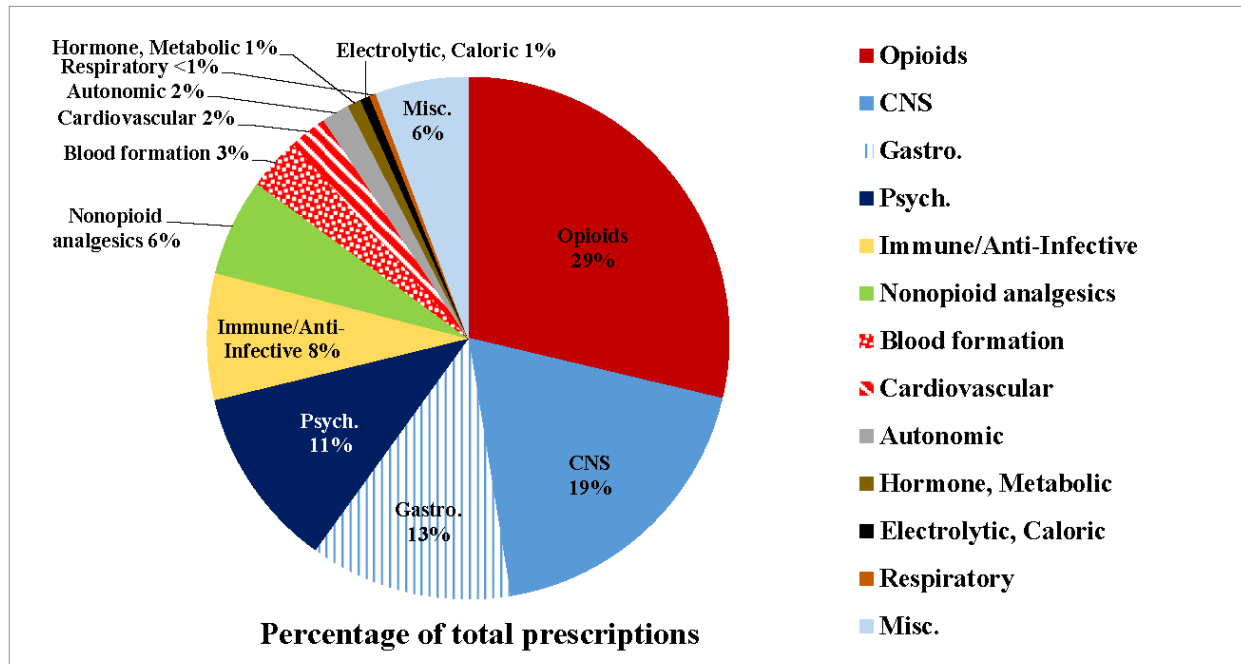
Outpatient Prescriptions (Including All New and Refill Prescriptions) by Medication Category During the First Year Postinjury for Patients With Combat-Related Amputations (N = 1657).

Medication category	No. patients	% (of 1657)*	No. prescriptions	Mean no. prescriptions**	Median	Interquartile range
Opioids	1638	99%	30 872	19	14	8, 26
Nervous System	1595	96%	20 111	13	10	5, 17
Gastro & Genitourinary	1574	95%	13 486	9	7	3, 11
Psychotherapeutic	1450	88%	12 081	8	6	3, 12
Immune & Anti-Infective	1483	89%	8417	6	4	2, 8
Nonopioid Analgesics	1391	84%	6488	5	4	2, 6
Blood Formation, Thrombosis	922	56%	3537	4	2	1, 5
Cardiovascular	591	36%	2514	4	2	1, 5
Autonomic	604	36%	1852	3	2	1, 4
Hormone, Metabolic	302	18%	898	3	2	1, 4
Electrolytic, Caloric	302	18%	655	2	1	1, 2
Respiratory	237	14%	427	2	1	1, 2
Misc.	1258	76%	6169	5	3	2, 6
Total	1657	100%	107 507	65	55	33, 86

*1657 of 1704 (97%) amputation patients were included with at least one prescription. **Based on patients with at least one prescription for the medication category. Gastro = gastrointestinal.

Opioids had the highest totals among the 13 medication categories on all measures, including total prescriptions (30,872; 29% of 107,507 prescriptions), percentage of patients with at least 1 prescription (99%) and mean/median prescriptions per patient (19/14; see Table 1 and Figure 1). The next 5 highest totals by patient percentages were the CNS, GI/GU, psychotherapeutic, immune/anti-infective, and nonopioid analgesic categories (with 84% to 96% of patients). The CNS and GI/GU had the highest numbers of prescriptions among these 5 categories, with 20,111

and 13,486 prescriptions, respectively, and the highest mean prescriptions per patient (12.6 and 8.6, respectively). These 5 categories, along with the opioids, accounted for 85% of all prescriptions (91,455 of 107,507). Finally, blood formation/thrombosis was the only other medication category for which over half of patients (55.6%) had at least 1 prescription although these medications accounted for only 3.3% (3537 of 107,507) of all prescriptions. The majority of patients (76%) also had a miscellaneous prescription during the first year postinjury.



1. Percentage of 107,507 total prescriptions (top) and percentage of 1,657 patients (bottom) by medication category during the first 12 months postinjury. CNS = central nervous system, psych = psychotherapeutic, gastro = gastrointestinal/genitourinary, Cardio = cardiovascular.

Table 2 shows the leading 2 subcategories of medications prescribed by patient percentages for each category. For example, the leading opioid subcategories were combination analgesics (e.g., oxycodone/acetaminophen) and semisynthetics (oxycodone).

2. Leading Subcategories by Patient Percentages for the 13 Major Medication Categories During the First 12 Months Postinjury

Medication category	% Patients with prescription (n = 1657)*	No. patients (n = 1,657)
Opioids		
Combination analgesics	78	1290
Semisynthetics	71	1173
Nervous system		
Anticonvulsants	93	1546
Anxiolytics, sedatives, hypnotics	67	1117
Gastro and Genitourinary		
Cathartics/laxatives	92	1531
Antiemetics, misc.	25	422
Psychotherapeutic		
Antidepressants	81	1350
Antipsychotics	43	720
Immune and anti-infective		
Antibacterials	77	1284
Antihistamines	26	428
Nonopioid analgesics		
Nonsteroidal anti-inflammatory agents	76	1261
Analgesics and antipyretics, miscellaneous	45	753
Blood formation, thrombosis		
Anticoagulants (Enoxaparin sodium)	43	711
Antianemia drugs, iron preparations	20	332
Cardiovascular		
Central alpha-agonists (clonidine)	12	204
Alpha-adrenergic blocking agents (prazosin)	10	161
Autonomic		
Centrally acting skeletal muscle relaxants	19	318
Alpha and beta adrenergic agonists	7	114
Hormone, metabolic		

Medication category	% Patients with prescription (n = 1657)*	No. patients (n = 1,657)
Adrenals	10	165
Androgens	7	109
Electrolytic, caloric		
Replacement preparations	12	207
Phosphate-removing agents	3	44
Respiratory		
Expectorants	8	128
Antitussives	6	93
Misc.		
Skin and mucous membrane agents	55	907
Vitamins	40	666

*The study sample consisted of 1,657 patients had at least one outpatient medication prescription recorded in PDTS during first 12 months postinjury. Gastro = gastrointestinal.

The percentage of patients who had medication prescriptions recorded generally declined from the first quarter (92%) and second quarter (91%) to the fourth quarter (73%; see Table 3). The total mean prescriptions declined steadily across quarters—from 29 during the first quarter to 12 during the fourth quarter. Also, the mean medication categories prescribed per patient declined across quarters (see bottom of Table 3). Nonetheless, the majority of patients had medication prescriptions recorded during all 4 quarters, including 73% during the fourth quarter. For specific categories, prescriptions for opioid, CNS, or psychotherapeutic medications ranged from 32% to 51% of patients during the fourth quarter, averaging between 3.3 and 5.0 prescriptions (see Table 3). For opioids, the patient percentages and mean prescriptions remained substantially higher than nonopioid analgesics during all 4 quarters. Notably, the patient percentages for blood formation/thrombosis prescriptions decreased by more than half between the first quarter (48%) and the second quarter (19%). For cardiovascular and autonomic categories, patient percentages were 20% or less and patients averaged 2 prescriptions during each of the 4 quarters.

3.

Percentage of Patients and Mean Number of Outpatient Prescriptions by Category and Quarter (91 Days) During the First Year Postinjury (N = 1657).

Medication category	Postinjury quarter (91 days)							
	1		2		3		4	
	% Patients/mean prescriptions							
Opioids	90%	8	75%	7	62%	6	51%	5

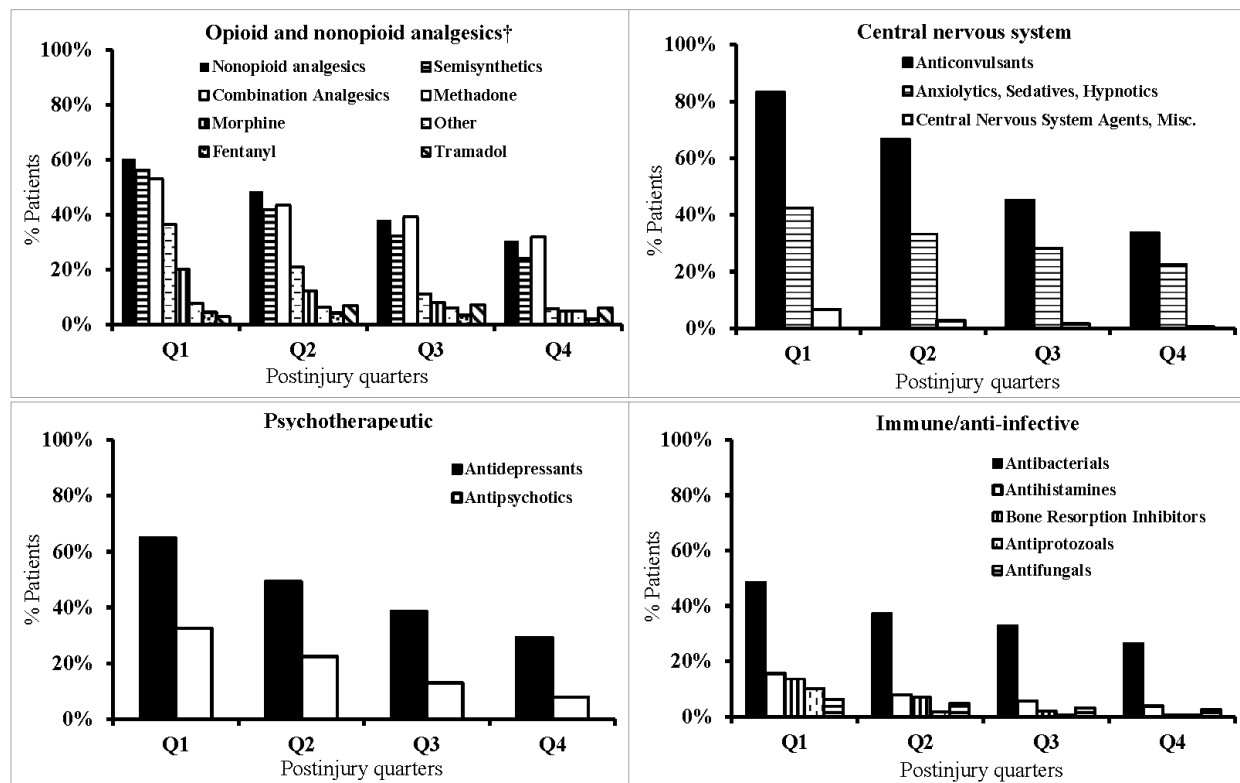
Medication category	Postinjury quarter (91 days)							
	1		2		3		4	
	% Patients/mean prescriptions							
Central nervous system	86%	6	74%	5	55%	4	43%	4
Gastro and genitourinary	84%	5	51%	4	41%	3	29%	2
Psychotherapeutic	73%	4	56%	4	43%	3	32%	3
Immunologic and anti-infective	67%	3	50%	3	43%	2	34%	2
Nonopioid analgesics	60%	3	49%	2	38%	2	30%	2
Blood formation, thrombosis	48%	3	19%	3	8%	2	4%	2
Cardiovascular	20%	2	17%	2	16%	2	13%	2
Autonomic	18%	2	15%	2	13%	2	10%	2
Hormone, metabolic	7%	2	8%	2	9%	2	6%	2
Electrolytic, caloric	10%	2	6%	2	5%	2	4%	1
Respiratory	5%	1	4%	1	5%	2	4%	2
Miscellaneous	52%	3	38%	3	31%	2	24%	2
Combination prescriptions								
Opioid and benzodiazepine	36%	—	18%	—	11%	—	8%	—
Opioid, CNS and psychotherapeutic	70%	—	46%	—	31%	—	21%	—
Total of 13 categories	92%	29	91%	19	83%	15	73%	12
Mean categories per patient	—	6	—	5	—	4	—	3

Note: Means based on patients with at least one prescription for the medication category. Miscellaneous medication prescriptions not included in any other category.

The patient percentages for prescription combinations (e.g., both benzodiazepine and opioids) during the same quarter generally declined across quarters (see Table 3). Nonetheless, substantial percentages of patients had prescriptions for CNS, opioid, and psychotherapeutic (all 3 medications) during the third (31%) and fourth quarters (21%). Overall, 47% of patients (782 of 1,657) had a prescription for benzodiazepines (not shown). Finally, 56% had prescriptions for opioids, CNS, and psychotherapeutic medications during at least 1 of quarters 2, 3, or 4 (not shown).

Patient percentages generally declined across quarters for most subcategories within the analgesic, CNS, psychotherapeutic, and immunologic categories (see Figure 2). Nonetheless, the highest subcategories by patient percentages ranged from 26% to 34% during the fourth quarter (e.g., anticonvulsants 34%, antibacterials 26%). For analgesics, the most prevalent subcategories were nonopioid, semisynthetic (e.g., oxycodone hydrochloride), and combination analgesics

(oxycodone/acetaminophen) during all 4 quarters. Notably, 20% of patients still had prescriptions for a semisynthetic during the fourth quarter.



- Percentage of patients with prescriptions for subclasses of analgesic, central nervous system, psychotherapeutic, and immunologic categories by postinjury quarters. Combination analgesics = hydrocodone/acetaminophen, semisynthetics = oxycodone; non-opioids = nonsteroidal anti-inflammatory drugs (e.g., celecoxib).

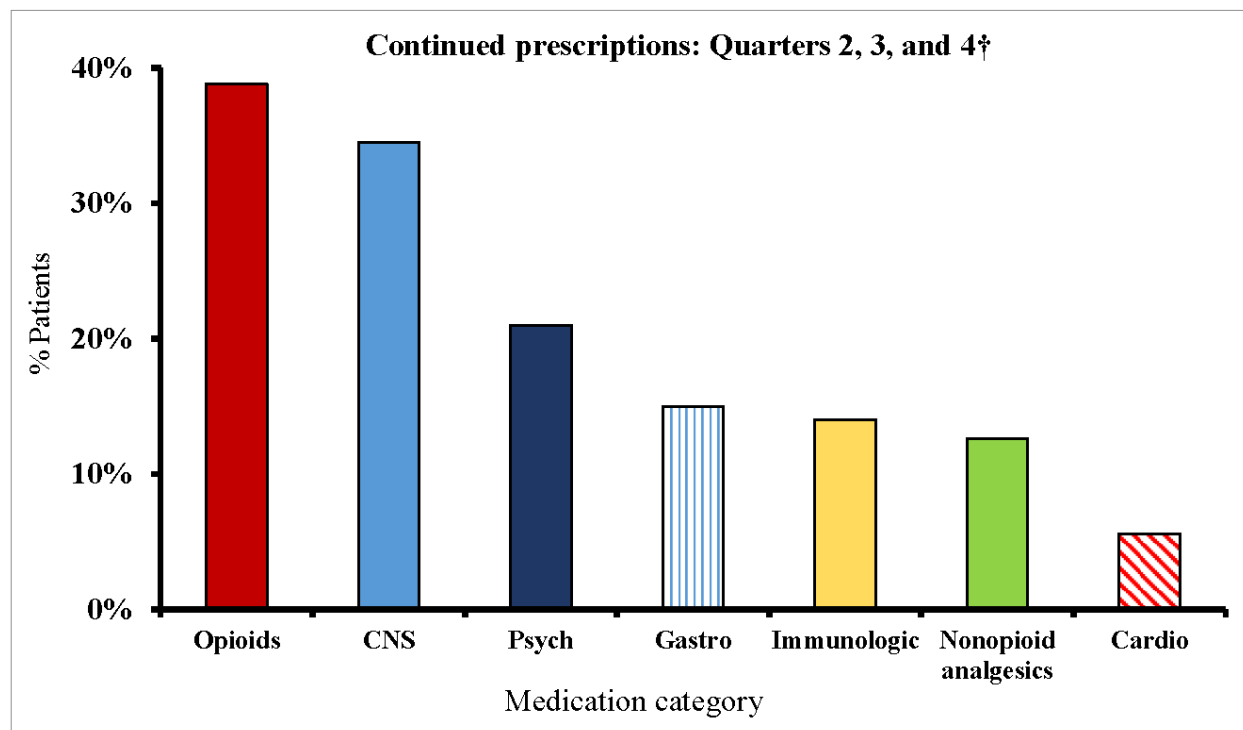
†Analgesic subcategory examples.

For selected opioid prescriptions, the mean prescriptions and median days' supply per quarter (91 days) are summarized here. Oxycodone/acetaminophen mean prescriptions decreased slightly from the second quarter (2.9, n = 665) to the fourth quarter (2.7, n = 449), and median days' supply decreased from the second quarter (13.7 days) to the fourth quarter (12.4 days). The semisynthetic opioid oxycodone mean prescriptions decreased from the second quarter (5.0, n = 610) to fourth quarter (4.1, n = 332), and median days' supply increased slightly from the second quarter (14.2 days) to the fourth quarter (15.0 days). Methadone mean prescriptions per quarter decreased from the second quarter (3.5, n = 348) to the fourth quarter (3.2, n = 96), and median days' supply increased slightly from the second quarter (18.9 days) to the fourth (20.8 days; not shown).

The most prevalent CNS medication subcategories prescribed during all quarters were anticonvulsants and anxiolytics/sedatives (e.g., benzodiazepine; see Figure 2). The most prevalent psychotherapeutic medication subcategories were antidepressants during all 4 quarters (65% to 29% of patients). Antipsychotic medication prescriptions declined from 32% to 8% of patients during the 4 quarters. For immunologic medications, antibacterial prescriptions were the most prevalent subcategories, declining from 48% (first quarter) to 26% (fourth quarter). During

the first quarter, antihistamine (16%) and bone resorption inhibitors (14%) were most prevalent. By the fourth quarter, patient percentages were less than 5% for all other immunologic subcategories besides antibacterial.

Figure 3 shows that 39% to 21% of patients received continued prescriptions for either opioid, CNS, or psychotherapeutic medications during the last 3 consecutive quarters (quarters 2–4). Similarly, 13% to 15% had continued prescriptions for gastrointestinal, nonopioid analgesic, or immunologic medications.



3. Percentage of patients with continued prescriptions† by selected prescription medication categories (N = 1,657). CNS = central nervous system, Psych = psychotherapeutic, Gastro = gastrointestinal/genitourinary, Cardio = cardiovascular.
 †Continued prescriptions = Patients with at least one prescription from the same medication category during each of consecutive postinjury quarters 2, 3, and 4.

DISCUSSION

To our knowledge, this brief report provides the first descriptive overview of outpatient medication prescriptions for patients who sustained combat-related amputations in the Iraq and Afghanistan conflicts. The results quantify the substantial prescription numbers, a wide range of medications, and variation in prescription activity by various medication categories and postinjury time.

The present results indicate that medication prescriptions are an essential and complicated factor for medical planning and rehabilitation throughout the first year postinjury.^{5,6} There is substantial diversity among this patient population in the levels, numbers, and postinjury timing of amputations,⁷ other serious injuries, and complications that may affect prescription activity.^{1-6,8,9,19,20} These complex analyses are beyond the scope of this report. Our results do

provide a foundation for future analytic studies to inform DoD/VA guidelines for amputation care and prescription medications.

The strength of this report is the expert casualty record review¹² to identify the population of Service members with amputations combined with the PDTS.¹³ The present results were limited to outpatient medication prescriptions dispensed primarily at military facilities. Importantly, military facilities are primary medical providers for amputation patients during most, if not all, of the first year postinjury.^{1,2,19,20} The therapeutic purpose(s) of the prescriptions was not identified. Inpatient prescription medication records were unavailable, lowering numbers of first quarter (first 90 days) prescriptions. Patients may or may not have consumed the medications and/or received other medications (e.g., private, VA care) not recorded in military databases.

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