Effect of number of deployments on symptom prevalence in Gulf War Veterans

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Abstract

Objectives: This study aims to assess whether number of tours to the Persian Gulf region affected the prevalence of symptoms relevant to Gulf War Illness.

Methods: This retrospective chart review, approved by the institutional human subject committee, collected medical notes of veterans enrolled in the Gulf War Registry between July 2013 and June 2015 (N=364) at the VA San Diego Healthcare System. These veterans were first categorized based on the number(s) of tours (T) served within Gulf War I (1990-1991) and/or Post-Gulf War I (1992-2015), with tour stratifications based on average deployment length (7 months). These tour stratifications were then expanded across all veterans included in the study. Chi-square analysis was used for all categorical data collected, and analysis of variance was used to analyze all continuous data. All analysis was two-tailed, where applicable, with α < 0.05.

Results: Veterans serving a greater number of tours (>2T), when compared to those serving fewer tours (1T; 2T), demonstrated a higher prevalence of overall pain symptoms (p <0.001), as well as a greater number of symptom relevant to Gulf War Illness (p = 0.002). Additionally, those serving more tours demonstrated greater overall NSAIDs usage (p = 0.012) than those serving fewer tours.

Conclusion: These findings suggest that increased number of tours served in the Persian Gulf may be related to with higher NSAIDs usages, prevalence of pain and other comorbid symptoms of Gulf War Illness.

Introduction

In the years following their return from the Persian Gulf region, a significant number of veterans have experienced a wide variety of unexplained symptoms collectively coined as Gulf War Illness. These symptoms include, but are not limited to, persistent fatigue, chronic pain, irritable bowel syndrome, headache, and dermatological issues [1]. The unknown cause of these symptoms, as well as their continued development within the Gulf War veteran population, continues to be a topic of great concern and interest. Due to this concern, the Gulf War Registry (GWR) was established to provide support and treatment for veterans deployed to this region [2]. As part of the enrollment process, veterans are evaluated on the six major symptom categories associated with serving in the Persian Gulf area: neurological, gastrointestinal, respiratory, dermatological problems, pain, and fatigue [3]. Those enrolled and evaluated in the GWR had served either in Gulf War I (Operation Desert Shield: 1990-1991; Operation Desert Storm: 1991), or in a second cohort categorized as Post-Gulf War I (Operation Iraqi Freedom: 2003-2010 and Operation New Dawn: 2010-2011). Though there have been numerous studies which suggest certain environmental or chemical exposures experienced during deployment may contribute to the development of these symptoms, these studies have been unable to determine a definitive causal relationship, necessitating a different approach to exploring the development of these symptoms [4-10]. Few studies have explored how deployment duration or frequency plays a role in symptom development. Knowing these differences may shed some light on important factors which can affect the prevalence of Gulf War Illness-related symptomology and provide references for future

deployment and/or healthcare policies for military personnel. This study aims to address this knowledge gap by assessing the prevalence of Gulf War Illness-related symptomology in terms of number(s) of tours (T) deployed to the Persian Gulf region.

Methods

At the Veterans Affairs San Diego Healthcare System, a list of veterans who had a documented GWR computerized medical record note between July 2013 and June 2015 was compiled for a chart review, performed with institutional human subject committee approval. Due to the nature of the study, informed consent was waived, and data was extracted from the veterans' GWR medical note. Data categories included basic demographic information, dates of active duty in the Persian Gulf, documented health problems, active medication usage, as well as the intensities of pain recorded by providers on a 0-10 Numerical Pain Rating Score (NPRS) [11]. Veterans were only enrolled in the GWR if they served specifically in the Persian Gulf region, thus excluding those who served in Afghanistan during Operation Enduring Freedom from 2001 to 2014.

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Through the information recorded during the Gulf War veterans' GWR visits, veterans were classified based on which deployment period they served under and how long they were deployed. Deployment periods were grouped into three groups: Gulf War I, 1990-1991; Post-Gulf War I, 1992-2015; and both Gulf War I and Post-Gulf War I. Symptom domains were based on the six categories of symptoms found in the electronic GWR note. The six categories are as follows: pain, neurological, fatigue, gastrointestinal (GI), respiratory, and dermatological symptoms, with each symptom recorded categorically as either yes or no. The pain and neurological symptom categories were further classified into three and five subcategories, respectively.

The pain symptoms category incorporated all available pain outcomes: joint pain, muscle pain and chronic pain conditions. The joint pain category included knee, ankle, shoulder, or wrist pain, while the muscle pain category consisted of leg, arm (distal from joints), or back pain categorized as either acute (< 3 months) or chronic (≥ 3 months). Any chronic joint or muscle pain conditions reported in the subject's medical record were included in the category of chronic pain. Neurological symptoms were comprised of the following subcategories: headache, memory and attention, mood, visual and hearing, and neurological sleep. Overall neurological symptoms were calculated from the combined score of these subcategories of each subject. The mood subcategory included mood disorders such as major depressive disorder and general anxiety disorder; the visual and hearing subcategory consisted of visual obstruction complaints and sensorineural hearing loss; and neurological sleep included insomnia or hypersomnia. The fatigue domain encompassed symptoms of fatigue such as chronic fatigue syndrome, sleep apnea, or insomnia. The domains combining headache, muscle, and joint pain were categorized based on subjects' reports. Those who positively indicated for two out of the three symptoms (headache, muscle, or joint pain) were included into the respective combined pain category. Symptoms included in the GI category included constipation, diarrhea, abdominal pain, gastrointestinal esophageal reflux disease, and irritable bowel syndrome. Respiratory symptoms encompassed wheezing, coughing, asthma, bronchitis, and obstructive sleep apnea. The last symptom category, skin problems, encompassed rashes, eczema, psoriasis, and dermatitis. The number of symptom categories were recorded based on the number of the six Gulf War Illness categories that veterans reported during their GWR visit. Those who reported three or more Gulf War Illness symptoms were included into the ≥ 3 / 6 symptom categories. Through a documented Veterans Affairs (VA) clinician's assessment utilizing Clinician-Administered PTSD Scale for DSM-5 (CAPS), diagnoses of post-traumatic stress disorder (PTSD) were recorded and grouped [12]. Medication usage was documented by healthcare professionals and pharmacy technicians into the computerized patient record system for each veteran, documenting the use of analgesics such as tricyclic antidepressants, anticonvulsants, triptans, non- steroidal anti-inflammatory drugs (NSAIDs), and selective serotonin reuptake inhibitors (SSRIs). These medications were subsequently grouped by drug class for statistical analyses.

All subjects were grouped into the following tour-based stratifications based on war period served:

a) Gulf War I comparison conducted between ≤ 1T (≤ 7 months) and > 1T (> 7 months); b) Post-Gulf War I comparison conducted between ≤ 2T (≤ 14 months) and > 2T (> 14 months); and c) Both war periods comparison conducted between ≤ 3T (≤ 21 months) and > 3T (> 21 months). Stratification groups were based on the reported average single tour deployment which was 7 months [13-14]. Veterans deployed in Gulf War I, Post-Gulf War I, and both war periods served a reported average number(s) of tours (T) at 1.0, 1.6, and 2.9, respectively [15]. Additional analyses were then conducted, expanding the stratification groups across all subjects, irrespective of war period, with the following tour-based stratifications: 1T, 2T, and > 2T. The raw data were organized and imported into SPSS version 27 for analysis.

Statistical Analysis

These groups were compared using chi-squared for categorical data and analysis of variance (ANOVA) with pairwise test using the Tukey method to control for Type I error. All data and variables were analyzed for predictability using a logistic regression method. Furthermore, groups were compared on subjects' characteristics using chi-squared or ANOVA. These characteristics included age, gender, race, ethnicity, PTSD, military branch, military occupational specialty, number of deployments, alcohol usage, and body mass index (BMI). Categorical variables were coded as follows: gender as male or female; race as Caucasian, African American, Asian, or other; ethnicity as Hispanic or non-Hispanic; PTSD as yes or no; military branch as the Navy, Marines, Army, or other; and military occupation specialty as combat or non-combat. Alcohol usage was measured as the number of drinks consumed per day and arranged into subcategories based on that usage: none for zero drinks consumed per day, light for one drink, moderate for two drinks, and heavy for three drinks consumed per day. Significant variables were added to the model when there was a sufficient number of subjects available per group. Where there were statistical differences found between covariates, sub-analyses were conducted on symptom prevalence and medication usage to adjust for these covariates between groups. Data was analyzed using SPSS version 27 (IBM Corp. Released 2020. IBM SPSS Statistics for Windows, Version 27.0. Armonk, NY: IBM Corp.) All analysis was two- tailed, where applicable, with α < 0.05.

Results

A) Analytical results based on the number(s) of tours within each war period category are listed as follows:

Demographic Information

Gulf War I, Post-Gulf War I, and both war periods consisted of 163, 155, and 46 veterans, respectively (Table 1). There were no significant differences between number of tours within the three war periods for gender, ethnicity, race, military branch, and military occupational specialty. The distribution for average alcohol usage demonstrated an overall significance (p < 0.05) between ≤ 2T and > 2T groups serving in Post-Gulf War I, with none (0.0%) qualifying as a moderate or heavy drinker in the ≤ 2T group compared to 3.6% as moderate and 3.6% as a heavy alcohol consumer in the > 2T group (Table 1).

Symptom Prevalence

The prevalence of overall pain symptoms was significantly (p < 0.05) higher in the group who served more tours within the Gulf War I group (Table 2). 62.6% of veterans serving ≤ 1T reported overall pain symptoms compared to 79.2% of the > 1T group. Further analyses into pain outcomes showed a significant (p < 0.01) difference in muscle pain between the ≤ 1T and > 1T groups, with a prevalence of 42.9% and 66.7%, respectively. Examining the other symptom categories, those who served > 1T in Gulf War I had a significantly (p < 0.05) higher prevalence of veterans rating positive for ≥ 3 / 6 symptom categories than veterans who served ≤ 1T, at 70.8% compared to 52.7%, respectively. Analysis of the joint pain category, overall neurological symptoms, headache, mood, visual and hearing symptoms, neurological sleep,

combined symptomology of the three categories (headache, muscle, and joint pain), fatigue, GI, respiratory, skin symptoms, number of symptoms categories, PTSD, and NPRS did not yield any significant differences between the two tour durations within Gulf War I.

In the Post-Gulf War I group, 92.9% in the > 2T group reported significantly different (p < 0.05) overall pain symptoms compared to 77.8% of the ≤ 2T group (Table 2). In the chronic pain category, ≤ 2T (58.6%) and > 2T (83.9%) groups were found to be significantly (p < 0.01) different (Table 2). Memory and attention symptoms also displayed significant (p < 0.05) results, reporting a higher prevalence of symptoms in 16.1% of the > 2T group compared to 6.1% of the ≤ 2T group. Joint pain, muscle pain, neurological symptoms and its subcategories (headache, memory and attention, mood, visual and hearing, neurological sleep), combined symptomology of the three categories (headache, muscle, and joint pain), fatigue, GI, respiratory, skin symptoms, and the other symptoms subcategories (number of

symptoms categories, PTSD, and NPRS) did not yield any significant results.

For those who served in both Gulf War I and Post-Gulf War I, none of the evaluated symptom categories demonstrated any significance between the ≤ 3 T and > 3 T groups (Table 2).

Medication Usage Based on Number(s) of Tours Within Each War Period Category

Medication usage of SSRIs in the > 1T Gulf War I group were significantly (p < 0.05) more prevalent (16.7%) than the medication usage of veterans who served ≤ 1T (6.6%) (Table 3). GI medication usage was significantly (p < 0.05) more prevalent in those who served > 3T (0.0%) compared to those who served ≤ 3T (18.5%) in both war periods. Other unrelated medications were also significantly (p < 0.01) more prevalent in those who served in both war periods for > 3T (66.7%) than those who served in ≤ 3T (26.3%). No other medications

Table 1. Demographic Information of Groups Based on Number(s) of Tours (T) Within Three War Period Categories

	Gulf War I N = 163 (100%)		P - Value	Post – Gulf War I N = 155 (100%)		P- Value	Gulf War I & Post- Gulf War I N = 46 (100%)		P - Value
	≤ 1 T N = 91 (55.8%)	> 1 T N = 72 (44.2%)		≤ 2 T N = 99 (63.9%)	> 2 T N = 56 (36.1%)		≤ 3 T N = 19 (41.3%)	> 3 T N = 27 (58.7%)	
Gender			-			-			-
Male	83 (91.2%)	70 (97.2%)	-	83 (83.8%)	46 (82.1%)	-	18 (94.7%)	26 (59.1%)	-
Female	8 (8.8%)	2 (2.8%)	-	16 (16.2%)	10 (17.9%)	-	1 (5.3%)	1 (3.7%)	-
Average Age (SD)	52.35 (6.58)	52.58 (7.66)	-	41.05 (8.39)	39.98 (8.38)	-	51.95 (6.46)	51.85 (6.07)	-
Ethnicity			-			-			-
Hispanic	14 (15.4%)	10 (13.9%)	-	32 (32.3%)	15 (26.8%)	-	2 (10.5%)	6 (22.2%)	-
Non-Hispanic	68 (54.4%)	57 (45.6%)	-	61 (20.6%)	39 (9.7%)	-	17 (4.3%)	19 (13.0%)	-
Unknown	9 (9.9%)	5 (6.9%)	-	6 (6.1%)	2 (3.6%)	-	0 (0.0%)	2 (7.4%)	-
Race			-			-			-
Caucasian	37 (40.7%)	31 (43.1%)	-	58 (58.6%)	32 (57.1%)	-	7 (36.8%)	12 (44.4%)	-
African American	23 (25.3%)	13 (18.1%)	-	12 (12.1%)	9 (16.1%)	-	7 (36.8%)	3 (11.1%)	-
Asian	10 (11.0%)	11 (15.3%)	-	10 (10.1%)	5 (8.9%)	-	5 (26.3%)	5 (18.5%)	-
Other	6 (6.6%)	7 (9.7%)	-	4 (4.0%)	5 (8.9%)	-	0 (0.0%)	2 (7.4%)	-
Unknown	15 (16.5%)	10 (13.9%)	-	15 (15.2%)	5 (8.9%)	-	0 (0.0%)	5 (18.5%)	-
Military Branch			-			-			-
Navy	25 (27.5%)	28 (38.9%)	-	43 (43.4%)	26 (46.4%)	-	12 (66.7%)	20 (74.1%)	-
Marines	44 (48.4%)	33 (45.8%)	-	35 (35.4%)	15 (26.8%)	-	4 (22.2%)	5 (18.5%)	-
Army	19 (20.9%)	9 (12.5%)	-	18 (18.2%)	13 (23.2%)	-	2 (11.1%)	1 (3.7%)	-
Other	3 (3.3%)	2 (2.8%)	-	3 (3.0%)	2 (3.6%)	-	0 (0.0%)	1 (3.7%)	-
Military Occupational Specialty (MOS)			-			-			-
Non-Combat	67 (73.6%)	54 (77.1%)	-	78 (80.4%)	45 (83.3%)	-	15 (83.3%)	24 (88.9%)	-
Combat	24 (26.4%)	16 (22.9%)	-	19 (19.6%)	9 (16.7%)	-	3 (16.7%)	3 (11.1%)	-
Average BMI (SD)	30.44 (4.98)	30.91 (5.74)	-	30.15 (4.90)	30.26 (6.25)	-	29.64 (5.51)	32.28 (8.63)	-
Alcohol Usage			-			0.031			-
None	80 (87.9%)	60 (83.3%)	-	96 (97.0%)	48 (85.7%)	-	16 (84.2%)	25 (92.6%)	-
Light	5 (5.5%)	6 (8.3%)	-	3 (3.0%)	4 (7.1%)	-	0 (0.0%)	1 (3.7%)	-
Moderate	5 (5.5%)	5 (6.9%)	-	0 (0.0%)	2 (3.6%)	-	1 (5.3%)	1 (3.7%)	-
Heavy	1 (1.1%)	1 (1.4%)	-	0 (0.0%)	2 (3.6%)	-	2 (10.5%)	0 (0.0%)	-

"-" indicates not statistically significant; T: Number of Tour(s); BMI: Body Mass Index;

Table 2. Symptom Prevalence and Severity Based on Number(s) of Tours (T) Within Three Different War Period Categories

	Gulf War I N = 163			Post – Gulf War I N = 155			Gulf War I & Post- Gulf War I N = 46		
	≤ 1 T N = 91	> 1 T N = 72	P - Value	≤ 2 T N = 99	> 2 T N = 56	P - Value	≤ 3 T N = 19	> 3 T N = 27	P - Value
Pain Symptoms	57 (62.6%)	57 (79.2%)	0.022	77 (77.8%)	52 (92.9%)	0.016	17 (89.5%)	25 (92.6%)	-
Joint Pain	43 (47.3%)	35 (48.6%)	-	58 (58.6%)	37 (66.1%)	-	13 (68.4%)	20 (74.1%)	-
Muscle Pain	39 (42.9%)	48 (66.7%)	0.002	55 (55.6%)	38 (67.9%)	-	13 (68.4%)	17 (63.0%)	-
Chronic Pain	50 (54.9%)	48 (66.7%)	-	58 (58.6%)	47 (83.9%)	0.001	11 (57.9%)	20 (74.1%)	-
Neurological Symptoms	55 (60.4%)	50 (69.4%)	-	75 (75.8%)	43 (78.2%)	-	14 (73.7%)	18 (66.7%)	-
Headache	30 (33.0%)	24 (33.3%)	-	44 (44.4%)	24 (42.9%)	-	9 (47.4%)	7 (25.9%)	-
Memory + Attention	9 (9.9%)	8 (11.1%)	-	6 (6.1%)	9 (16.1%)	0.043	1 (5.3%)	6 (22.2%)	-
Mood	27 (29.7%)	25 (34.7%)	-	45 (45.5%)	23 (41.1%)	-	6 (31.6%)	11 (40.7%)	-
Visual + Hearing	18 (19.8%)	16 (22.2%)	-	22 (22.2%)	12 (21.4%)	-	4 (21.1%)	8 (29.6%)	-
Neurological Sleep	10 (11.1%)	7 (9.7%)	-	16 (16.2%)	12 (21.4%)	-	1 (5.3%)	2 (7.4%)	-
Headache and Joint	18 (19.8%)	11 (15.3%)	-	25 (25.3%)	16 (28.6%)	-	6 (31.6%)	7 (25.9%)	-
Headache and Muscle	12 (16.2%)	12 (24.0%)	-	25 (25.3%)	15 (26.8%)	-	4 (21.1%)	5 (18.5%)	-
Joint and Muscle	27 (29.7%)	28 (38.9%)	-	39 (39.4%)	24 (42.9%)	-	9 (47.4%)	12 (44.4%)	-
Fatigue Symptoms	42 (46.2%)	40 (56.3%)	-	48 (48.5%)	24 (42.9%)	-	10 (52.6%)	19 (70.4%)	-
Gastrointestinal Symptoms	28 (30.8%)	28 (38.9%)	-	30 (30.3%)	24 (42.9%)	-	3 (15.8%)	10 (37.0%)	-
Respiratory Symptoms	40 (44.0%)	40 (55.6%)	-	47 (47.5%)	19 (33.9%)	-	7 (36.8%)	16 (59.3%)	-
Skin Problems	12 (13.2%)	16 (22.2%)	-	17 (17.2%)	10 (17.9%)	-	3 (15.8%)	3 (11.1%)	-
Other									
# of Symptom Categories	2.57 (1.47)	3.22 (1.45)	-	2.98 (1.38)	3.07 (1.35)	-	2.84 (1.17)	3.37 (0.93)	-
≥ 3 / 6 Symptom Categories	48 (52.7%)	51 (70.8%)	0.019	63 (63.6%)	35 (62.5%)	-	11 (57.9%)	21 (77.8%)	-
PTSD	24 (26.4%)	23 (31.9%)	-	38 (38.4%)	28 (50.0%)	-	4 (21.1%)	9 (33.3%)	-
NPRS (SD)	3.35 (2.98)	3.87 (2.99)	-	3.33 (2.95)	3.79 (2.78)	-	3.42 (3.35)	2.94 (3.19)	-

"–" indicates not statistically significant; T: Number of Tour(s); PTSD: Post-Traumatic Stress Disorder; NPRS: Numerical Pain Rating Scale

Table 3. Medication Usage Based on Number(s) of Tours (T) Within Three Different War Period Categories

	Gulf War I N = 163			Post – Gulf War I N = 155			Gulf War I & Post- Gulf War I N = 46		
	≤ 1 T N = 91	> 1 T N = 72	P - Value	≤ 2 T N = 99	> 2 T N = 56	P - Value	≤ 3 T N = 19	> 3 T N = 27	P - Value
Analgesics	33 (36.3%)	31 (43.1%)	-	38 (38.4%)	27 (48.2%)	-	6 (31.6%)	15 (55.6%)	-
Narcotics	3 (3.3%)	6 (8.3%)	-	7 (7.1%)	4 (7.1%)	-	0 (0.0%)	1 (3.7%)	-
NSAIDs	22 (24.2%)	24 (33.3%)	-	23 (23.2%)	21 (37.5%)	-	5 (26.3%)	13 (48.1%)	-
Tricyclics	3 (3.3%)	1 (1.4%)	-	2 (2.0%)	4 (7.1%)	-	0 (0.0%)	1 (3.7%)	-
SSRI	6 (6.6%)	12 (16.7%)	0.042	19 (19.2%)	11 (19.6%)	-	2 (10.5%)	7 (25.9%)	-
Triptan	6 (6.6%)	1 (1.4%)	-	11 (11.1%)	5 (8.9%)	-	1 (5.3%)	2 (7.4%)	-
Mood/Sleep	18 (19.8%)	20 (27.8%)	-	31 (31.3%)	17 (30.4%)	-	4 (21.1%)	7 (25.9%)	-
GI	16 (17.6%)	16 (22.2%)	-	13 (13.1%)	13 (23.2%)	-	0 (0.0%)	5 (18.5%)	0.047
Respiratory	7 (7.7%)	7 (9.7%)	-	10 (10.1%)	2 (3.6%)	-	0 (0.0%)	1 (3.7%)	-
Dermatological	1 (1.1%)	2 (2.8%)	-	3 (3.0%)	2 (3.6%)	-	1 (5.3%)	3 (11.1%)	-
Unrelated	37 (40.7%)	31 (43.1%)	-	41 (41.4%)	21 (37.5%)	-	5 (26.3%)	18 (66.7%)	0.007

"–" indicates not statistically significant; T: Number of Tour(s); NSAIDs: Nonsteroidal anti-inflammatory drugs; SSRI: Selective serotonin reuptake inhibitor; GI: Gastrointestinal

(analgesics, tricyclics, triptan, for mood/sleep, respiratory, and dermatological) were found to be significant within these stratifications.

B) Analytic results based on number(s) of tours across all war period categories are discussed as follows:

Demographic Information

Those who served 1T, 2T, and > 2T consisted of 138, 132, and 94 veterans, respectively (Table 4). Analysis of the average age demonstrated a significant (p < 0.01) difference across number of tours served. Those who served > 2T were, on average, significantly (p < 0.01) younger than those who served 1T, reporting an average age of 44.90 (9.64) compared to 49.01 (9.13). Differences in military branches were significant (p < 0.05) overall. Veterans serving 1T and 2T were significantly (p <

0.01 and p < 0.05, respectively) different from the > 2T group, with a significantly (p < 0.001) greater portion (45.3%) of those serving 1T from the Marine Corps compared to 23.4% of those serving > 2T. No other statistically significant differences between groups in ethnicity, gender, ethnicity, race, military occupational specialty, alcohol usage, or BMI were found.

Symptom Prevalence

Overall pain symptom comparisons based on number of tours demonstrated significantly (p < 0.001) higher overall prevalence with the > 2T (92.6%) group reporting significantly (p < 0.001) more overall pain than both 1T (68.8%) and 2T (78.0%) groups (Table 5, Figure 1). Further comparisons of other pain categories showed a significant (p <

Table 4. Demographic Comparisons Based on Number(s) of Tours (T) Across All War Period Categories

	1 T N = 138 (100%)	2 T N = 132 (100%)	> 2 T N = 94 (100%)	All Groups P- Value	1 T vs 2 T P-Value	1 T vs > 2 T P-Value	2 T vs > 2 T P-Value
Gender				-	-	-	-
Male	121 (87.7%)	122 (92.4%)	83 (88.3%)	-	-	-	-
Female	17 (12.3%)	10 (7.6%)	11 (11.7%)	-	-	-	-
Average Age (SD)	49.01(9.13)	47.39 (9.54)	44.90 (9.64)	0.005	-	0.003	-
Ethnicity				-	-	-	-
Hispanic	27 (19.6%)	31 (23.5%)	21 (22.3%)	-	-	-	-
Non-Hispanic	100 (72.5%)	92 (69.7%)	69 (73.4%)	-	-	-	-
Unknown	11 (8.0%)	9 (6.8%)	4 (4.3%)	-	-	-	-
Race				-	-	-	-
Caucasian	66 (47.8%)	65 (49.2%)	46 (48.9%)	-	-	-	-
African American	27 (19.6%)	24 (18.2%)	16 (17%)	-	-	-	-
Asian	16 (11.6%)	16 (12.1%)	14 (14.9%)	-	-	-	-
Other	9 (6.5%)	7 (5.3%)	8 (8.5%)	-	-	-	-
Unknown	20 (14.5%)	20 (15.2%)	10 (10.6%	-	-	-	-
Military Branch				0.023	-	0.003	0.0496
Navy	47 (34.3%)	53 (40.2%)	54 (57.4%	-	-	-	-
Marines	62 (45.3%)	52 (39.4%)	22 (23.4%)	-	-	< 0.001	< 0.001
Army	24 (17.5%)	23 (17.4%)	15 (16.0%)	-	-	-	-
Other	4 (2.9%)	4 (3.0%)	3 (3.2%)	-	-	-	-
Military Occupational Specialty (MOS)				-	-	-	-
Non-Combat	103 (75.2%)	101 (78.9%)	79 (85.9%)	-	-	-	-
Combat	34 (24.8%)	27 (21.1%)	13 (14.1%)	-	-	-	-
Average BMI (SD)	30.31 (5.11)	30.47 (5.22)	30.88 (6.97)	-	-	-	-
Alcohol Usage				-	-	-	-
None	125 (90.6%)	117 (88.6%)	83 (88.3%)	-	-	-	-
Light	7 (5.1%)	7 (5.3%)	5 (5.3%)	-	-	-	-
Moderate	5 (3.6%)	5 (3.8%)	4 (4.3%)	-	-	-	-
Heavy	1 (0.7%)	3 (2.3%)	2 (2.1%)	-	-	-	-

"-" indicates not statistically significant; BMI: Body Mass Index

0.05) difference in joint pain across all tour groups (Figure 2). Veterans serving > 2T (68.1%) reported significantly ($p < 0.05$) more joint pain than both 1T (52.2%) and 2T (53.0%) groups. Across all number of tours, muscle pain demonstrated more significance ($p < 0.05$), with 1T reporting significantly ($p < 0.01$) less prevalence (49.3%) than > 2T (68.1%) (Figure 3). Analysis of the chronic pain category demonstrated a significant difference across all groups ($p < 0.01$) (Figure 4). Further analysis into the chronic pain category showed a significantly ($p < 0.01$) higher prevalence of chronic pain symptoms (78.7%) in those who served > 2T than those who served 1T (58.7%) and 2T (59.8%).

All other neurological symptom categories (overall neurological, headache, visual and hearing, and neurological sleep) did not demonstrate any significant difference among group comparisons based on number of tours. Within the other Gulf War Illness categories: memory and attention, GI, respiratory, skin problems, there was no significance found. There was also no significant difference observed between the other combined symptomologies: headache and joint; headache and muscle pain; muscle and joint pain.

The number of symptom categories showed significant ($p < 0.01$) differences across all tour categories (Table 5). Those in the 1T group reported a significantly ($p < 0.01$) lower average number of reported symptoms (± SD) than those in the 2T group (2.63 ± 1.46 vs. 3.17 ± 1.38 respectively) (Figure 5). The 1T group also reported a significantly ($p < 0.05$) lower average number of reported symptoms than the > 2T group (3.16 ± 1.20). Overall comparisons between the groups showed a significant ($p < 0.05$) difference for the prevalence of ≥ 3 / 6 symptom

categories. Veterans serving 1T demonstrated a significantly ($p < 0.01$ and $p < 0.05$) lower prevalence of Gulf War Illness symptoms with 53.6% reporting ≥ 3/6 symptom categories.

Medication Usage Based on Number(s) of Tours Within Each War Period Category

Overall NSAID usage was found to be significantly ($p < 0.05$) different (Table 6) across number of tours served. Those serving more tours, 2T (32.6%) and > 2T (38.3%), reported significantly ($p < 0.05$ and $p < 0.01$, respectively) higher NSAID usage compared to 1T (21.0%) (Figure 6). All other medications, general analgesics (including narcotics), tricyclics, SSRIs, triptan, mood/sleep, GI, respiratory, dermatological, and unrelated medications, did not yield any significant difference among the different tour groups.

C) Analytic Results adjusting for Covariates

Secondary analysis was conducted when significant differences in military branches were found among the groups. There were no significant differences found when adjusting for Navy only. When adjusting for Marines only, two categories remained significant: pain symptoms and joint pain. When comparing between Marines deployed for 1T vs 2T, more Marines deployed for 2T reported pain symptoms ($p < 0.05$). Comparing those who deployed for 1T with those deployed for > 2T, a higher prevalence of pain symptoms was recorded, with 95.5% of those deployed > 2T reporting pain symptoms compared to 67.7% ($p < 0.05$). Overall, there was a significant difference ($p < 0.01$), across all three tour deployment categories, with 90.0% of Marines deployed

Table 5. Symptom Prevalence and Severity Comparisons Based on Number(s) of Tours Across All War Period Categories

	1 T N = 138	2 T N = 132	> 2 T N = 94	All Groups P- Value	1 T vs 2 T P- Value	1 T vs > 2 T P- Value	2 T vs > 2 T P- Value
Pain Symptoms	95 (68.8%)	103 (78.0%)	87 (92.6%)	< 0.001	-	< 0.001	0.003
Joint Pain	72 (52.2%)	70 (53.0%)	64 (68.1%)	0.033	-	0.016	0.023
Muscle Pain	68 (49.3%)	78 (59.1%)	64 (68.1%)	0.016	-	0.005	-
Chronic Pain	81 (58.7%)	79 (59.8%)	74 (78.7%)	0.003	-	0.001	0.003
Neurological Symptoms	90 (65.2%)	94 (71.2%)	71 (76.3%)	-	-	-	-
Headache	52 (37.7%)	47 (35.6%)	39 (41.5%)	-	-	-	-
Memory + Attention	10 (7.2%)	14 (10.6%)	15 (16.0%)	-	-	-	-
Mood	48 (34.8%)	51 (38.6%)	38 (40.4%)	-	-	-	-
Visual + Hearing	32 (23.2%)	25 (18.9%)	23 (24.5%)	-	-	-	-
Neurological Sleep	18 (13.1%)	15 (11.4%)	15 (16.0%)	-	-	-	-
Headache and Joint	31 (22.5%)	24 (18.2%)	28 (29.8%)	-	-	-	-
Headache and Muscle	28 (23.1%)	20 (17.9%)	25 (27.2%)	-	-	-	-
Joint and Muscle	48 (34.8%)	49 (37.1%)	42 (44.7%)	-	-	-	-
Fatigue Symptoms	61 (44.2%)	74 (56.5%)	48 (51.1%)	-	-	-	-
Gastrointestinal Symptoms	42 (30.4%)	45 (34.1%)	36 (38.3%)	-	-	-	-
Respiratory Symptoms	57 (41.3%)	71 (53.8%)	41 (43.6%)	-	-	-	-
Skin Problems	18 (13.0%)	29 (22.0%)	14 (14.9%)	-	-	-	-
Other							
# of Symptom Categories	2.63 (1.46)	3.17 (1.38)	3.16 (1.20)	0.002	0.004	0.011	-
≥ 3 / 6 Symptom Categories	74 (53.6%)	92 (69.7%)	63 (67.0%)	0.015	0.007	0.042	-
PTSD	42 (30.4%)	45 (34.1%)	39 (41.5%)	-	-	-	-
NPRS (SD)	3.40 (2.94)	3.46 (3.07)	3.66 (2.91)	-	-	-	-

"–" indicates not statistically significant; T: Number of Tour(s); PTSD: Post-Traumatic Stress Disorder; NPRS: Numerical Pain Rating Scale

Table 6. Medication Usage Comparisons Based on Number(s) of Tours (T) Across All War Period Categories

	1 T N = 138	2T N = 132	> 2 T N = 94	All Groups P- Value	1 T vs 2 T P- Value	1 T vs > 2 T P- Value	2 T vs > 2 T P- Value
Analgesics	47 (34.1%)	59 (44.7%)	44 (46.8%)	-	-	-	-
Narcotics	6 (4.3%)	10 (7.6%)	5 (5.3%)	-	-	-	-
NSAIDs	29 (21.0%)	43 (32.6%)	36 (38.3%)	0.012	0.032	0.004	-
Tricyclics	4 (2.9%)	1 (0.8%)	6 (6.4%)	-	-	-	-
SSRI	17 (12.3%)	21 (15.9%)	19 (20.2%)	-	-	-	-
Triptan	10 (7.2%)	9 (6.8%)	7 (7.4%)	-	-	-	-
Mood/Sleep	34 (24.6%)	36 (27.3%)	27 (28.7%)	-	-	-	-
GI	24 (17.4%)	20 (15.2%)	19 (20.2%)	-	-	-	-
Respiratory	11 (8.0%)	12 (9.1%)	4 (4.3%)	-	-	-	-
Dermatological	2 (1.4%)	4 (3.0%)	6 (6.4%)	-	-	-	-
Unrelated	53 (38.4%)	57 (43.2%)	43 (45.7%)	-	-	-	-

"–" indicates not statistically significant; T: Number of Tour(s); NSAIDs: Nonsteroidal anti-inflammatory drugs; SSRI: Selective serotonin reuptake inhibitor; GI: Gastrointestinal

Table 7. Adjusted Symptom Prevalence and Medication Usage Comparisons Based on Number(s) of Tours (T) Across All War Period Categories

	1 T	2 T	> 2 T	All Groups P- Value	1 T vs 2 T P- Value	1 T vs > 2 T P- Value	2 T vs > 2 T P- Value
Marines Only N = 136 (100%)							
Pain Symptoms	42 (67.7%)	45 (86.5%)	21 (95.5%)	0.006	0.019	0.010	-
Joint Pain	33 (53.2%)	33 (63.5%)	20 (90.9%)	0.007	-	0.002	0.017
Army Only N = 62 (100%)							
Pain Symptoms	13 (54.2%)	17 (73.9%)	14 (93.3%)	0.030	-	0.010	-
Chronic Pain	11 (45.8%)	10 (43.5%)	13 (86.7%)	0.017	-	0.011	0.008
Memory + Attention	0 (0.0%)	3 (13.0%)	4 (26.7%)	0.036	-	0.008	-
Fatigue	7 (29.2%)	15 (65.2%)	8 (53.3%)	0.043	0.013	-	-
PTSD	7 (29.2%)	12 (52.2%)	11 (73.3%)	0.024	-	0.007	-

"–" indicates not statistically significant; T: Number of Tour(s); PTSD: Post-Traumatic Stress Disorder
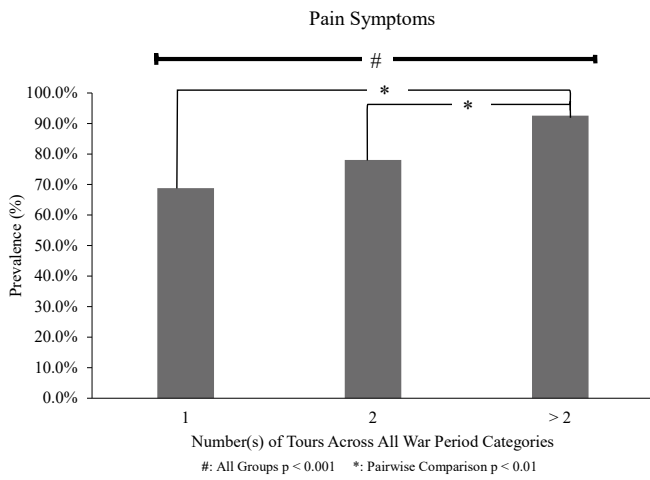
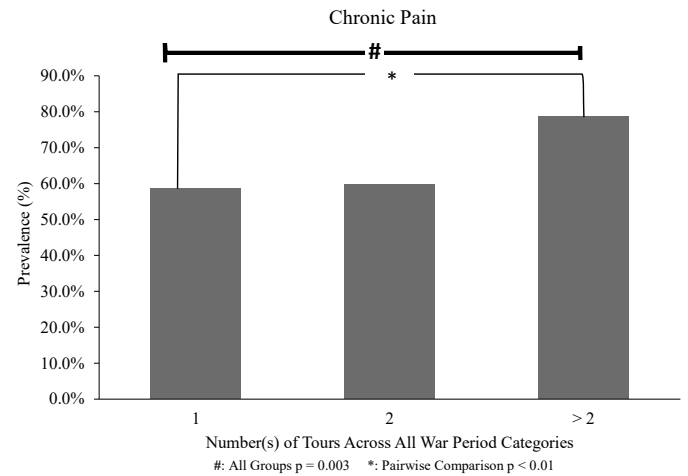**Figure 1.** Prevalence (%) of pain symptoms among Gulf War veterans.

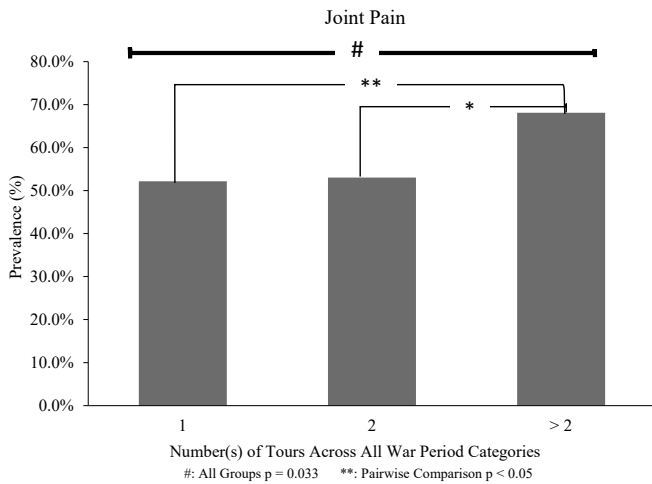**Figure 2.** Prevalence (%) of Gulf War veterans with documented joint pain symptoms.

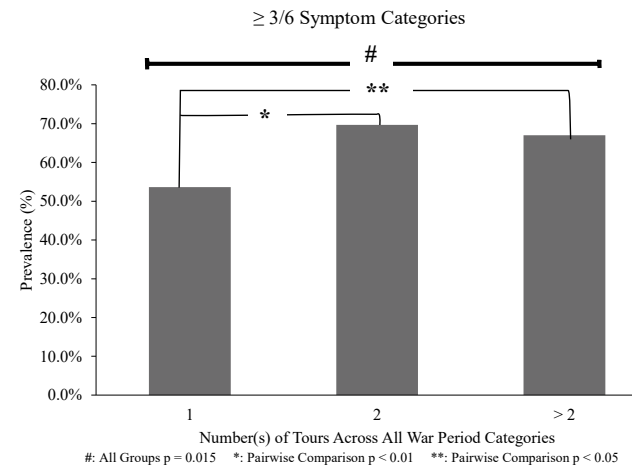**Figure 3.** Prevalence (%) of Gulf War veterans with documented muscle pain symptoms

Figure 4. Prevalence (%) of Gulf War veterans with documented chronic pain symptoms.

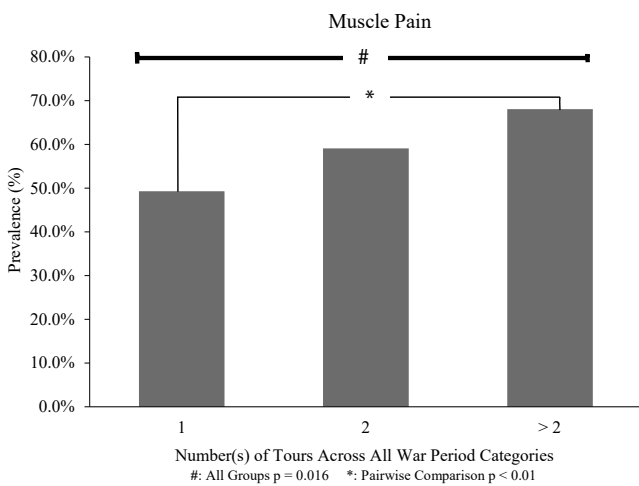**Figure 5.** Prevalence (%) of Gulf War veterans who reported at least 3 symptom categories of Gulf War Illness.
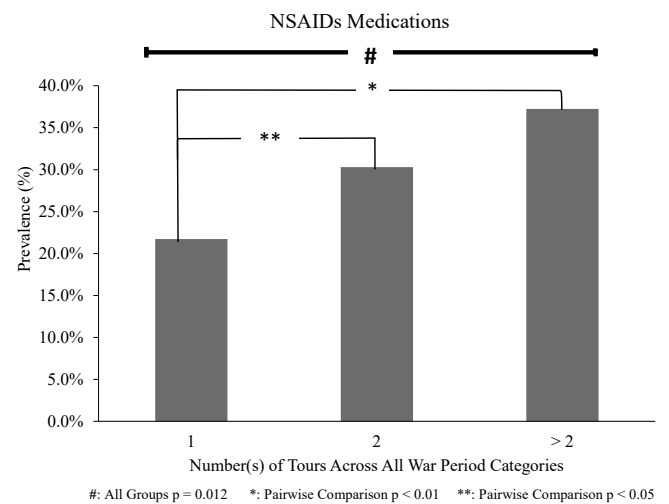
Figure 6. Prevalence (%) of NSAIDs usage among Gulf War veterans

>2T reporting joint pain symptoms compared to the 53.2% of Marines deployed 1T (p < 0.01), and 63.5% of Marines deployed 2T (p < 0.05) who reported joint pain.

After adjusting for veterans who served in the Army only, four symptoms lost significances: overall joint, muscle, number of symptom categories, and ≥ 3/6 symptom categories. After the sub-analysis was performed, three categories gained significance: memory and attention problems (p < 0.05), fatigue (p < 0.05), and PTSD (p < 0.05). Pain symptoms (p < 0.05) and chronic pain (p < 0.05) remained significant. A significantly larger percentage of those who served > 2T experienced pain symptoms (p < 0.05), chronic pain (p < 0.05), memory and attention problems (p < 0.01), and PTSD (p < 0.01) than their counterparts who were deployed for 1T. Additionally, there was a significant difference (p < 0.01) between those in the Army who served 2T and > 2T, with 43.5% of those deployed for 2T reporting chronic pain symptoms compared to the 86.7% who were deployed for > 2T and also reported chronic pain. Significantly more (p< 0.05) veterans deployed 2T also experienced fatigue compared to those who had served 1T (Table 7).

Discussion

With Gulf War Veterans demonstrating increasing prevalence of poorer health than their nondeployed counterparts, it is imperative to understand and explore the possible causes [14]. As most study findings are unable to conclusively determine if certain environmental or chemical factors were the causes for these veterans' symptoms, other potential causal factors should be explored [15]. Comparing the different Gulf War periods in addition to deployment duration, our initial study found that those who served ≥12 months in the Persian Gulf Region, regardless of war period, reported a higher prevalence of overall pain symptoms and NSAIDs usage than those who served ≤ 7 months [16]. Prompted by these earlier findings, further analyses of deployment duration were explored in the current study. The current study's cutoff for number of tours was based on the average tour duration, 7 months, making three tour length groups encompassing ≤ 7 months (1T), 8-14 months (2T), ≥ 15 months (> 2T) [17]. First, our primary analyses demonstrated that those who served a greater number of tours within the war periods, especially in the Gulf War I and Post-Gulf War I groups, exhibited more pain symptoms, neurological symptoms, and more medication usage.

The secondary analysis expanded the groups to encompass all subjects irrespective of war period and was conducted to determine the effect the number of tours deployed to the Persian Gulf had on Gulf War Illness symptomology. Those who served more tours, specifically those serving >2T when compared to 1 T and 2T, exhibited differences across all measured pain symptoms. Joint pain was also found to be significantly worse in the >2T group, which was not shown in the primary analyses. The analyses based solely on the number of tours also demonstrated greater prevalence of Gulf War Illness symptoms such as fatigue and respiratory issues and reported more medication usage to treat these symptoms (NSAIDs, Tricyclics, and dermatological medications). Those who served more tours in the Persian Gulf Region demonstrated increased Gulf War Illness symptoms, which was further supported by regression analysis.

Of note, the demographic categories of average age and military branch were found to be significantly different among the groups. Due to analysis performed in the previous study demonstrating that younger veterans demonstrated more pain than older veterans, further analyses with age adjustment were not performed in the current study.

To account for these differences in covariates, regression analysis was performed for military branch. When the subjects were grouped solely on these military branch differences, there was a significant difference in the prevalence of pain symptoms of those in the Marines and Army, with those in the Army reporting more Gulf War Illness associated symptoms in addition to pain. Overall, these differences are most likely related to the different roles these branches served during their deployment, with those in the Marine Corps and Army serving on the ground, whereas those in the other branches may have served in waters or the air above the region.

The limitations to this study lie in the singular VA Healthcare location the data was collected from as well as the relatively small sample size of 364 subjects. This subject pool is also not representative of the entire Gulf War veteran population, as it reflects more Naval and Marine Corps veteran data than other branches due to the types of military bases located in San Diego County. Expansion of this study's analyses to other VA Healthcare facilities in regions serving a more diverse veteran population in addition to increasing the sample size would ameliorate these issues by increasing statistical power and exploring the external validity on the entire Gulf War veteran population. Another area of weakness in this study could be bias from only obtaining data from veterans who had registered for the GWR. Veterans who register may experience a higher incidence of Gulf War Illness symptoms due to the very nature of signing up to be evaluated for placement into the registry. Further studies should evaluate Gulf War veterans who have not enrolled in the registry in combination with those who already have, to gain a better sense of the Gulf War veteran population.

Gulf War Illness is defined by a wide array of symptoms which do not have a singular identifiable cause [18]. However, veterans deployed to this region continue to report poorer health than those who were not [14]. Many studies have focused on the unique environmental factors that these veterans were exposed to during their service, yet few have focused on how the number of deployments may play a role in symptom development. This study proposes that Gulf War veterans who served more tours than their peers experienced a higher incidence of pain symptoms such as overall pain, joint, muscle and chronic pain. With veterans who served more tours demonstrating a higher prevalence of Gulf War Illness related symptoms, focusing on number of deployments in conjunction the existing information on environmental and chemical exposures may be a worthwhile approach to exploring the myriad of causes for these symptoms. This insight may also be helpful in the process of establishing future deployment policies to mitigate potential health complications experienced by veterans. Further analyses would expand upon these issues, allowing for greater specificity in future deployment policies

Conflicts of Interest

There are no conflicts of interest to report.

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