9-1-2018

Associations between Use of Antimalarial Medications and Health among U.S. Veterans of the Wars in Iraq and Afghanistan.

Aaron I. Schneiderman
Veterans Health Administration

Yasmin S. Cypel
Veterans Health Administration

Erin K. Dursa
Veterans Health Administration

Robert M. Bossarte
West Virginia University

Am. J. Trop. Med. Hyg., 99(3), 2018, pp. 638–648
doi:10.4269/ajtmh.18-0107

Associations between Use of Antimalarial Medications and Health among U.S. Veterans of the Wars in Iraq and Afghanistan

Aaron I. Schneiderman,[1]* Yasmin S. Cypel,[1] Erin K. Dursa,[1] and Robert M. Bossarte[2]

[1]*Department of Veterans Affairs, Epidemiology Program, Post Deployment Health Services (10P4Q), Office of Patient Care Services, Veterans Health Administration, Washington, District of Columbia;* [2]*Department of Behavioral Medicine and Psychiatry, West Virginia University Injury Control Research Center, West Virginia University School of Medicine, Morgantown, West Virginia*

Abstract. Mefloquine (Lariam®; Roche Holding AG, Basel, Switzerland) has been linked to acute neuropsychiatric side effects. This is a concern for U.S. veterans who may have used mefloquine during recent Southwest Asia deployments. Using data from the *National Health Study for a New Generation of U.S. Veterans*, a population-based study of U.S. veterans who served between 2001 and 2008, we investigated associations between self-reported use of antimalarial medications and overall physical and mental health (MH) using the twelve-item short form, and with other MH outcomes using the post-traumatic stress disorder Checklist-17 and the Patient Health Questionnaire (anxiety, major depression, and self-harm). Multivariable logistic regression was performed to examine associations between health measures and seven antimalarial drug categories: any antimalarial, mefloquine, chloroquine, doxycycline, primaquine, mefloquine plus any other antimalarial, and any other antimalarial or antimalarial combination while adjusting for the effects of deployment and combat exposure. Data from 19,487 veterans showed that although antimalarial use was generally associated with higher odds of negative health outcomes, once deployment and combat exposure were added to the multivariable models, the associations with each of the MH outcomes became attenuated. A positive trend was observed between combat exposure intensity and prevalence of the five MH outcomes. No significant associations were found between mefloquine and MH measures. These data suggest that the poor physical and MH outcomes reported in this study population are largely because of combat deployment exposure.

INTRODUCTION

The relationship between antimalarial medications used for chemoprophylaxis and a range of adverse outcomes is documented by case reports and survey studies; however, findings and estimates of risk associated with malaria chemoprophylaxis have been inconsistent and frequently poorly defined.[1,2] The adverse outcomes reported and investigated are most notably dermatological, gastrointestinal (GI), and neuropsychiatric (e.g., includes both central and peripheral nervous system disorders such as headache and dizziness, and psychiatric disorders such as anxiety and depression).[3–5] The importance and impact of the possible side effects of antimalarial medication is especially significant for more than 2.7 million U.S. military service members and veterans who served in Southwest Asia and other countries with endemic malaria.[6–8] During this time, recognition of the potential side effects profiles for some medications, specifically mefloquine (Lariam®; Roche Holding AG, Basel, Switzerland), has resulted in changes to U.S. Department of Defense (DoD) policy and prescribing practices.[9,10]

Antimalarial drug profiles, military operational requirements, and the regional presence of drug-resistant malaria strains are all factors that guide policy and practice regarding the use of specific chemoprophylactic agents.[6,11,12] The medications that satisfy policy and prevention requirements may have known side effects that influence prescribing practices and adherence. Doxycycline is well tolerated when used for prophylaxis, but GI complaints and photosensitivity are common side effects,[13–16] and an increased risk for development of irritable bowel syndrome and inflammatory bowel disease has also been suggested[17]; GI tolerability is usually improved with administration of enteric-coated forms of doxycycline hyclate, a main form of doxycycline,[18] or with use of its monohydrate derivative.[13] For chloroquine, the most serious side effects noted include retinopathy,[4,19–22] cardiomyopathy,[4,22] myopathy,[22] and neuromyopathy.[4,22] Primaquine has a long history of use and is effective against the various life stages of the *Plasmodium* species, the malarial parasites, but carries the significant danger of hemolysis in glucose-6-phosphate dehydrogenase–deficient populations.[23] Besides its effect on red blood cell metabolism, another adverse consequence of primaquine use is GI upset.[24]

Mefloquine use has been linked to reports of acute neuropsychiatric side effects in both civilian and military populations,[25–32] particularly in those with a history of psychiatric disorders.[29,33,34] The package insert for mefloquine advises against prescribing it to individuals with a psychiatric disorder or a history of seizures because of product safety concerns based on case reports and clinical studies. This has led to the addition by the manufacturer of a U.S. Food and Drug Administration black-box package warning in 2013 that addresses acute neuropsychiatric effects and the possibility of persistent or permanent neurologic health outcomes.[35] Concerns over acute and potential long-term effects from the use of mefloquine in military personnel have resulted in DoD policy changes prioritizing the selection of other chemoprophylactic agents in place of mefloquine during recent military conflicts.[6,11,12] Mefloquine's neuropsychiatric effects may occur through the inhibition of neurotransmitters such as acetylcholinesterase.[36]

Overall, the burden of mental health (MH) disorders among veterans of the U.S. military engagements in Afghanistan (Operation Enduring Freedom [OEF]) and Iraq (Operation Iraqi Freedom [OIF]) has been a significant concern for Veterans Affair and DoD and a significant driver of health-care

* Address correspondence to Aaron I. Schneiderman, Department of Veterans Affairs, Epidemiology Program, Post Deployment Health (10P4Q), Office of Patient Care Services, Veterans Health Administration, 810 Vermont Ave., NW, Washington, DC 20420. E-mail: aaron.schneiderman@va.gov

utilization.[37–39] Both epidemiological research and health-care utilization figures demonstrate the high level of MH diagnoses and symptoms among these military personnel and veterans that stem from deployment-related exposures. The potential for neuropsychiatric effects from the administration of mefloquine may be related to a concomitant increase in MH concerns, including post-traumatic stress disorder (PTSD), anxiety disorders, depression, and suicide.[40]

This study examines whether the use of mefloquine and other antimalarial medications in a population of OEF/OIF veterans is associated with self-reported MH conditions and measures of functional health status, while considering the independent effects of deployment and combat exposure.

MATERIALS AND METHODS

Study population. The Department of Veterans Affairs (VA) *2009–2011 National Health Study for a New Generation of U.S. Veterans* ("NewGen") study sampled 30,000 OEF/OIF veterans (deployed) and 30,000 non-OEF/OIF veterans who served in the military between October 2001 and June 2008 (nondeployed), including veterans in the reserves or National Guard who had not separated from these military components. The sample (N = 60,000) was selected from a sample frame generated from data files provided by the DoD Defense Manpower Data Center and the VA/DoD Identification Repository database and was stratified by branch of service (Air Force, Army, Marines, and Navy), unit component (active duty, reserve, or National Guard), and gender. A 20% oversample for women was included to achieve adequate panel representation.[41] Survey data were collected between 2009 and 2011 using tailored design methodology for mail, telephone, and web-based modes.[42] The response rate was 34.3% (N = 20,563).[41] The study was approved by the Washington DC VA Medical Center Institutional Review Board.

Antimalarial use. Respondents were asked whether they ever took medications to prevent malaria during their military service and if "yes," marked the type of antimalarial taken based on the following response options: mefloquine, chloroquine (Aralen®; Sanofi Aventis, Bridgewater, NJ), doxycycline (Vibramycin®; Pfizer, Inc., New York, NY), primaquine, or "other." When possible, "other" responses were recoded into existing options. All responses were then classified depending on whether use of a single drug was reported or if multiple antimalarials were used. The resultant antimalarial classification used for analyses consisted of mefloquine, chloroquine, doxycycline, primaquine, mefloquine used with other antimalarials (a history of using two or three different drugs), and other antimalarials (a single antimalarial and a history of two or three different drugs, excluding mefloquine combinations), and drug type not specified. For any reports of multiple antimalarials (sometimes referred to as "combinations"), no data on whether they were administered together or at different times were collected. Except for reports of four or more antimalarials used, all combinations of mefloquine use were examined (reports of mefloquine and other antimalarials) because of its possible association with neuropsychiatric symptoms.[25–32,40,43–46] Antimalarial drug status was based on the survey questions described previously and defined on three levels: whether an antimalarial drug was taken but not specified ("unknown" type), one or more specific drugs were taken ("known" type), or no drugs were taken. Antimalarial drug use was specified as either used or not used.

Combat exposure. An individual's exposure to military combat was assessed based on a dichotomous response (yes/no) to three survey questions adapted from the DoD Post Deployment Health Assessment form (DD 2796): "Did you ever feel that you were in great danger of being killed?" "Did you see anyone wounded, killed, or dead?" "Were you engaged in direct combat where you discharged your weapon?"[47] Summary scores were created that ranged from 0 to 3 where increasing scores represented increasing combat exposure intensity. The internal consistency of these items was assessed using Cronbach's alpha.[48]

Health outcome measures and indices. Mental and physical health outcomes were based on responses to items included in the NewGen questionnaire. Mental and physical health component scores were determined using the Medical Outcomes Study twelve-item short form (SF-12)[49] to assess overall mental and physical health that can be compared with national U.S. norms having a mean (± standard deviation) of 50 (±10). A positive outcome for PTSD was determined based on scores from the 17-item PTSD checklist (PCL-C).[50] A PCL cutoff of 50 or higher was used to identify those screening positive for PTSD.[37,51] Scales from the self-administered version of the Patient Health Questionnaire (PHQ),[52] were scored for major depression, thoughts of death or self-harm, and other anxiety disorders. Six health indices were examined in total (SF-12 Composite Mental Health Score, SF-12 Composite Physical Health Score, PTSD, thoughts of death/self-harm, other anxiety disorders, and major depression).

Deployment status and other individual characteristics. Sociodemographic and military service characteristics were included in statistical models. Self-reported deployment to OEF/OIF (deployed/not deployed) and sample frame data for branch of service (Army, Air Force, Marine Corps, and Navy) and service component (active duty, reserve, National Guard) were examined. The sociodemographic characteristics were gender, age group (24–34, 35–44, 45–54, and ≥ 55), education (high school/General Equivalency Diploma, some college/associate's degree, bachelor's degree, or higher), race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, Asian, American Indian or Alaska native, native Hawaiian/Pacific Islander, other), current household income (< $35,000, $35,000–49,999, $50,000–74,999, $75,000–99,999, $100,000–149,999, and ≥ $150,000), current employment status (yes/no), and marital status (married, separated/divorced, widowed, and never married/single). All the sociodemographic data, except for age, were based on self-reports; age data were obtained from the sample frame.

Statistical analyses. SAS® software version 9.4 (SAS Institute, Inc., Cary, NC) was used to generate all statistical output.[53] Cross-tabulations for each of the sociodemographic and military service characteristics with antimalarial drug status were completed to describe sample characteristics and preliminary associations among deployment status, antimalarial use, and health outcomes. χ^2 statistics were generated to check for statistical significance of these associations. Means and their standard errors were computed for the SF-12 composite mental and physical health scores by deployment status and within deployment status by all categories of antimalarial drug use. Dichotomous outcome variables were created; individuals' SF-12 composite scores were coded as either 1 (above U.S. mean) or 0 (below mean).

Multivariable logistic regression was used to examine associations between each of the six health indices (dependent

variables) and seven antimalarial drug categories (any antimalarial, mefloquine, chloroquine, doxycycline, primaquine, mefloquine plus any other antimalarial, and any other antimalarial or combination of antimalarials; "type not specified" was excluded) while controlling for sociodemographic and military service characteristics. Three models were examined to better understand the independent effects of deployment and combat exposure on the association between health outcome and antimalarial drug use. Model 1 ("demographic") examined the relationship between health outcome and antimalarial drug use while controlling for gender, age group, education, race/ethnicity, income, employment status, marital status, component, and branch of service. Model 2 ("deployment") examined the relationship between health outcome and antimalarial drug use but added deployment as an independent variable and a first-order interaction term (deployment × antimalarial). Model 3 ("combat exposure") paralleled model 2 except that combat exposure was added. Interaction terms were tested for significance and dropped from models if found not to be statistically significant; if associations between health outcome and antimalarial drug differed significantly when stratified by deployment status, they were reported separately. Adjusted odds ratios (AORs) and 95% confidence intervals (CIs) are reported for each of the three models by outcome and antimalarial drug. Each of these three regressions modeled the odds of having SF-12 composite scores fall below the U.S. mean versus the odds of having scores above the U.S. mean. When PTSD, suicide, other anxiety, and major depression were used as outcome variables, we modeled the odds of having the condition versus the odds of not having the condition.

To extend interpretation of selected regression findings, bivariate analyses were performed among the deployed to further examine the relationship between combat intensity score and health outcomes among those who reported antimalarial use and those who did not.

Survey responses were weighted to account for nonresponse. The resultant weights were modified using a poststratification approach to reduce bias resulting from the misclassification of deployment in the sampling frame.[54,55] All statistics reported, except for counts, were weighted.

RESULTS

Of 20,563 respondents, a total of 1,076 individuals were excluded from analysis based on responses to antimalarial medication use during military service: "don't know" ($N = 150$), failure to endorse any selection ($N = 818$), endorsement of four or more antimalarials ($N = 91$), and self-reporting nonantimalarial drugs ($N = 17$). The final analytical sample contained 19,487 individuals.

Table 1 provides descriptive statistics on demographic and service characteristics by reported antimalarial use. A majority ($N = 11,100$; 61.4%) of veterans reported receiving no antimalarial drugs, whereas 23.5% ($N = 4,952$) reported receiving these medications but did not provide medication information. Another 3,435 participants (15.1%) reported receiving an antimalarial and could identify the medication. Of those endorsing one or more antimalarials, doxycycline (45.2%), mefloquine (alone or reported with other antimalarials, 23.3%), and chloroquine (10.4%) were the most frequently reported (not shown in tables).

Chi-square tests of association for each respondent characteristic by antimalarial drug status were statistically significant ($P < 0.0001$) (Table 1). Use of antimalarial medication was more frequently reported by males than by females and was more prevalent among participants aged 35 years and older when compared with those who did not report receiving antimalarial medications. Participants who reported receiving one or more specific antimalarial medications were more likely to report their race as non-Hispanic white (76.2%) when compared with those who reported no antimalarial use (70.0%) or an unknown type of antimalarial medication (70.5%). Antimalarial use (i.e., known or unknown type) was more prevalent among those who served in the Army (56.9%) than among those who served in the Marine Corps (15.3%), Air Force (15.1%), or Navy (12.7%) (not reported in tables). Those who deployed to Iraq or Afghanistan were more likely to report receiving some form of antimalarial medication (known or unknown type) than those who were not deployed (76.1% and 23.9%, respectively) (not reported in tables).

Statistics on the prevalence of participants reporting poor physical and MH (SF-12), endorsement of thoughts of death or self-harm or positive screens for PTSD, other anxiety disorders, and major depression are in Table 2. Among deployed participants, those who received an antimalarial were more likely than those who did not use an antimalarial to report higher prevalence of all six health outcomes included in this study. Specifically, 53.6% of the deployed sample who reported antimalarial use had an SF-12 MH component score below the U.S. mean (no use = 47.3%), 43.5% had an SF-12 physical health component score below the U.S. mean (no use = 36.2%), 18.5% screened positive for symptoms of PTSD (no use = 11.3%), 11.7% endorsed thoughts of death or self-harm (no use = 8.8%), 12.5% screened positive for symptoms of other anxiety disorders (no use = 8.2%), and 11.5% screened positive for major depression (no use = 8.1%). There was little variability in the prevalence of outcomes across specific antimalarial agents, except for primaquine which had the lowest reported prevalence across measured health indices.

When comparing across outcomes (Table 2) among the deployed, participants who reported receiving chloroquine reported the highest prevalence of poor physical health and MH (SF-12); those who reported receiving mefloquine and any other antimalarial (chloroquine, doxycycline, or primaquine) had the highest prevalence of positive screens for PTSD, other anxiety disorders, and major depression. The one exception to this pattern was for those who reported taking primaquine alone, which had the lowest reporting for both use (1.4%) and reported mental and physical health outcomes (SF-12 MH component score, 41.0%; SF-12 physical health component score, 28.7%; PTSD, 6.9%; thoughts of death/self-harm, 6.3%; other anxiety disorders, 1.4%; and major depression, 3.3%).

Relationships between prevalence of adverse outcomes and antimalarial use status among the nondeployed sample were not consistent with those observed among the deployed (Table 2). The nondeployed sample who endorsed antimalarial use reported higher prevalence of poor physical health (53.9% versus 40.3% with no use), screened positive for other anxiety disorders (9.8% versus 8.6% with no use) and major depression (8.9% versus 8.6%). Further comparison of the nondeployed reporting no antimalarial use to those reporting antimalarial use showed nonusers had higher prevalence of

TABLE 1

Sociodemographic and military service characteristics of survey respondents by antimalarial drug status (N = 19,487): National Health Study for a New Generation of U.S. Veterans

	Antimalarial drug status‡		
	Reported receiving drug(s), but none specified (N = 4,952; 23.5%)	Reported receiving one or more drugs (N = 3,435; 15.1%)	Reported receiving no drugs (N = 11,100; 61.4%)
Characteristic*†	----n§ (%‖)----		
Gender‡			
Males	4,233 (90.6)	2,837 (89.5)	8,288 (79.9)
Females	719 (9.4)	598 (10.5)	2,812 (20.1)
Age group¶			
24–34	1,719 (46.0)	1,215 (46.8)	5,541 (64.1)
35–44	1,247 (23.4)	1,000 (26.7)	2,489 (18.2)
45–54	1,461 (23.8)	928 (21.2)	2,280 (14.1)
≥ 55	525 (6.8)	292 (5.3)	790 (3.6)
Education‡			
High school/GED	787 (18.3)	350 (12.6)	1,744 (19.4)
Some college/AA**	2,443 (53.2)	1,529 (50.6)	5,585 (54.3)
College or more	1,705 (28.5)	1,550 (36.8)	3,744 (26.3)
Race/ethnicity‡#			
Non-Hispanic white	3,438 (70.5)	2,596 (76.2)	7,730 (70.0)
Non-Hispanic black	638 (12.2)	336 (9.3)	1,476 (12.7)
Hispanic	486 (9.8)	228 (6.8)	973 (9.1)
Asian	90 (1.9)	63 (1.9)	223 (2.0)
American Indian or Alaska native	40 (0.8)	24 (0.8)	73 (0.8)
Native Hawaiian or Pacific Islander	38 (0.8)	16 (0.5)	70 (0.6)
Other	186 (4.0)	151 (4.7)	501 (4.9)
Current household income‡			
< $35,000	1,072 (26.6)	599 (22.2)	3,119 (35.3)
$35,000–49,999	834 (17.9)	515 (16.9)	1,936 (18.4)
$50,000–74,999	1,152 (23.0)	810 (24.5)	2,449 (20.8)
$75,000–99,999	746 (13.9)	549 (14.1)	1,519 (11.7)
$100,000–149,999	764 (13.3)	600 (14.9)	1,346 (9.8)
≥ $150,000	318 (5.3)	330 (7.3)	588 (4.0)
Currently used for wages‡ (% yes)	3,141 (62.2)	1,999 (56.8)	6,604 (58.1)
Marital status‡			
Married	3,525 (68.6)	2,426 (68.9)	7,130 (60.7)
Separated/divorced	694 (13.6)	504 (13.9)	1,640 (14.2)
Widowed	21 (0.3)	7 (0.2)	32 (0.2)
Never married/single	698 (17.4)	489 (16.9)	2,261 (24.9)
Service component¶			
Active duty	2,035 (55.3)	1,223 (50.0)	4,184 (53.7)
Reserve	1,586 (22.1)	1,289 (25.1)	3,875 (26.4)
National guard	1,331 (22.6)	923 (24.8)	3,041 (20.0)
Branch of service¶			
Army	2,915 (55.3)	2,117 (59.3)	5,540 (45.0)
Air Force	823 (14.9)	605 (15.4)	2,702 (22.8)
Marine Corps	579 (15.5)	385 (15.0)	886 (10.7)
Navy	635 (14.4)	328 (10.2)	1,972 (21.5)
Deployment to OEF/OIF‡ (% yes)	3,706 (71.6)	2,944 (83.3)	5,806 (42.8)
Combat exposure intensity††			
0	1,072 (23.4)	576 (16.9)	4,316 (56.2)
1	977 (21.3)	709 (20.6)	1,811 (21.3)
2	1,202 (27.1)	1,001 (29.6)	1,193 (13.7)
3	1,062 (28.2)	899 (33.0)	677 (8.9)

OEF = Operation Enduring Freedom (Afghanistan); OIF = Operation Iraqi Freedom (Iraq).
* Sum of counts may not always equal total because of missing values.
† Association between each of the sociodemographic and antimalarial drug status is statistically significant ($P < 0.0001$) based on the χ^2 test statistic.
‡ Self-reported.
§ Sample size (unweighted).
‖ Percent (weighted).
¶ Obtained from sampling frame.
# "Other" race/ethnicity represents those who reported themselves as some combination of race and/or ethnicity or undefined.
** Associate of Arts Degree.
†† Combat exposure intensity is the sum of a positive response on 3 questionnaire items (ever felt in great danger of being killed; ever seen anyone wounded, killed or dead; ever engaged in direct combat where you discharged your weapon). Scores range from 0 (not exposed) to 3 (most exposed).

poor MH (SF-12; 45.2%, no use versus 42.5%, use), positive PTSD screen (12.7% versus 10.1%), or reported thoughts of death or self-harm (10.3% versus 10.1%). The highest prevalence of poor SF-12 MH Composite Score among the nondeployed was reported by those who did not endorse antimalarial use. Participants who were unable to provide information on the antimalarial used had the highest prevalence of positive screens for PTSD compared with other singly used antimalarials or antimalarial combinations.

Comparisons of study outcomes provide evidence of relationships between antimalarial use and deployment. When all those who reported antimalarial use were compared on deployment status, the deployed reported higher prevalence than the nondeployed for poor MH (SF-12; 53.6% versus

TABLE 2

OEF/OIF deployment status and antimalarial drug use (N = 19,487) for selected health outcomes: National Health Study for a New Generation of U.S. Veterans

OEF/OIF deployment status, antimalarial drugs received during military service*	All (N = 19,487)	Selected health outcomes*							
		SF-12 mental health score (below U.S. mean)		SF-12 physical health score (below U.S. mean)		PTSD	Thoughts of death/self-harm	Other anxiety	Major depression
	n (%)	(%)	Mean (SEM)†	(%)	Mean (SEM)†	(%)	(%)	(%)	(%)
Deployed	12,456 (55.7)	50.7	46.7 (0.13)	40.0	49.5 (0.11)	15.1	10.3	10.5	9.9
Antimalarial drug use	6,650 (52.8)	53.6	45.8 (0.18)	43.5	48.8 (0.15)	18.5	11.7	12.5	11.5
Mefloquine	307 (4.4)	51.5	45.6 (0.90)	38.1	51.0 (0.58)	14.2	14.0	10.8	9.3
Chloroquine	274 (3.5)	57.7	46.1 (0.73)	51.8	46.4 (0.79)	18.9	12.8	10.4	11.4
Doxycycline	1,315 (20.5)	53.3	46.1 (0.39)	39.3	49.8 (0.30)	17.9	10.9	11.2	9.8
Primaquine	98 (1.4)	41.0	49.0 (1.15)	28.7	51.0 (0.99)	6.9	6.3	1.4	3.3
Mefloquine + "X"‡	425 (6.0)	53.0	45.0 (0.80)	44.1	48.4 (0.65)	20.0	10.7	15.3	12.5
Other antimalarials	525 (7.0)	47.2	47.6 (0.61)	44.6	48.3 (0.55)	17.8	10.9	12.1	12.0
Type not specified	3,706 (57.2)	54.8	45.5 (0.24)	45.1	48.4 (0.20)	19.3	12.1	13.3	12.4
No use	5,806 (47.2)	47.3	47.6 (0.18)	36.2	50.2 (0.15)	11.3	8.8	8.2	8.1
Nondeployed	7,031 (44.3)	44.6	48.3 (0.17)	43.2	48.6 (0.15)	10.6	10.3	8.9	8.6
Antimalarial drug use	1,737 (20.8)	42.5	48.7 (0.35)	53.9	46.1 (0.32)	10.1	10.1	9.8	8.9
Mefloquine	39 (2.2)	33.9	52.2 (2.04)	49.0	48.8 (1.67)	7.5	7.0	5.7	3.3
Chloroquine	110 (5.8)	37.2	50.6 (1.06)	47.7	47.8 (1.23)	7.4	9.2	2.5	4.5
Doxycycline	141 (8.8)	41.4	49.1 (1.07)	40.9	49.3 (1.16)	11.1	10.5	7.1	9.1
Primaquine	35 (1.6)	40.7	50.8 (2.06)	42.8	47.6 (2.39)	3.0	5.9	11.0	3.2
Mefloquine + "X"‡	52 (2.8)	36.8	49.9 (1.65)	51.2	45.7 (1.57)	9.7	7.5	7.3	4.3
Other antimalarials	114 (6.3)	41.0	48.7 (1.56)	58.6	46.0 (1.14)	13.3	15.0	11.2	11.2
Type not specified	1,246 (72.5)	43.7	48.4 (0.43)	56.1	45.5 (0.38)	13.7	9.9	10.8	9.4
No use	5,294 (79.2)	45.2	48.1 (0.19)	40.3	49.2 (0.17)	12.7	10.3	8.6	8.6

OEF = Operation Enduring Freedom (Afghanistan); OIF = Operation Iraqi Freedom (Iraq); PTSD = post-traumatic stress disorder.
* Self-reported; n (unweighted), % (weighted).
† Standard error of the mean.
‡ X = 1 or 2 other antimalarials reported.

42.5%), thoughts of death or self-harm (11.7% versus 10.1%), positive screens for PTSD (18.5% versus 10.1%), other anxiety disorders (12.5% versus 9.8%), and major depression (11.5% versus 8.9%). Relationships between outcome prevalence and deployment were less clear for those reporting no antimalarial use.

Table 3 contains the AORs obtained from the logistic regression models that had no significant first-order interaction terms, whereas Table 4 contains the AORs based on models that did. When controlling for demographic and military service characteristics alone (model 1, "demographics"), the odds are elevated for finding a negative health outcome among those taking any antimalarial medications compared with the odds for those not taking any antimalarial medications. Statistically significant elevated odds ratios (ORs) were found for poor MH (AOR = 1.39, 95% CI: 1.29–1.49), poor physical health (AOR = 1.23, 95% CI: 1.14–1.32), positive screen for PTSD (AOR = 1.83, 95% CI: 1.64–2.04), thoughts of death or self-harm (AOR = 1.31, 95% CI: 1.16–1.47), or positive screens for other anxiety disorders (AOR = 1.56, 95% CI: 1.38–1.76) and major depression (AOR = 1.45, 95% CI: 1.28–1.65). The addition of deployment as an independent variable had little effect on estimates. However, the addition of combat exposure resulted in the loss of statistical significance for all observed relationships.

Chloroquine showed significant elevated ORs for poor overall MH (SF-12) in models 1 and 2 (demographic and deployment, respectively: AOR = 1.33, 95% CI: 1.05–1.70; AOR = 1.30, 95% CI: 1.03–1.66) for users versus nonusers. These relationships were no longer significant when combat exposure was added in model 3 (AOR = 1.15, 95% CI: 0.88–1.50).

Significant elevated associations between doxycycline use and poor MH outcome were shown in the demographic model (AOR = 1.21, 95% CI: 1.07–1.37) and with a positive screen for PTSD in the demographic (AOR = 1.38, 95% CI: 1.15–1.65) and deployment models (AOR = 1.22, 95% CI: 1.02–1.47). In model 3, the AORs for poor overall MH and PTSD weakened and lost statistical significance (AOR = 0.96, 95% CI: 0.83–1.09 and AOR = 0.96, 95% CI: 0.79–1.15, respectively).

No significant associations were found for mefloquine use for the MH and physical health outcomes, a finding that continued across the three models. Adjusted odds ratios ranged for model 1 from 0.86 (95% CI: 0.54–1.36—major depression) to 1.36 (95% CI: 0.92–2.01—thoughts of death/self-harm), whereas for model 3, ORs dropped with no change in significance. Reported mefloquine and any other antimalarial use resulted in significant, elevated associations with a positive screen for PTSD and other anxiety disorders in the demographic (PTSD: AOR = 1.63, 95% CI: 1.20–2.20; other anxiety: AOR = 1.63, 95% CI: 1.17–2.27) and deployment models (PTSD: AOR = 1.45, 95% CI: 1.07–1.97; other anxiety: AOR = 1.53, 95% CI: 1.10–2.14), whereas adjustment for combat exposure in model 3 resulted in further decreases and nonsignificance in the AORs (PTSD: AOR = 1.09, 95% CI: 0.79–1.50 (Table 3); other anxiety, among deployed: AOR = 1.26, 95% CI: 0.88–1.81) (Table 4).

Reports of any other antimalarial or antimalarials showed significant elevated associations with poor physical health (AOR = 1.23, 95% CI: 1.02–1.49), positive screens for PTSD (AOR = 1.63, 95% CI: 1.24–2.13), thoughts of death or self-harm (AOR = 1.42, 95% CI: 1.03–1.96), or positive screens for other anxiety disorders (AOR = 1.53, 95% CI: 1.12–2.10) and major depression (AOR = 1.63, 95% CI: 1.19–2.22) in demographic models with similar levels in the deployment models but generally failed to retain statistical significance with the addition of combat exposure in model 3 (poor physical health: AOR = 1.07, 95% CI: 0.87–1.31; PTSD: AOR = 1.14,

TABLE 3

Results of multivariable regression relationship between each of six health outcomes and antimalarial use while controlling for sociodemographic and military service variables

	Health outcomes†					
Antimalarial, model*	SF12—composite mental health score	SF12—composite physical health score	PTSD	Thoughts of death/ self-harm	Other anxiety	Major depression
Any antimalarial						
Model 1: demographics	1.39 (1.29–1.49)‡	1.23 (1.14–1.32)‡	1.83 (1.64–2.04)‡	1.31 (1.16–1.47)‡	1.56 (1.38–1.76)‡	1.45 (1.28–1.65)‡
Model 2: demographics + deployment	1.30 (1.14–1.33)‡	1.32 (1.22–1.42)‡	1.69 (1.51–1.90)‡	1.35 (1.19–1.53)‡	1.51 (1.33–1.73)‡	1.43 (1.25–1.63)‡
Model 3: demographics, deployment + combat exposure	1.02 (0.94–1.11)	1.08 (0.99–1.18)	1.07 (0.94–1.22)	0.97 (0.85–1.12)	1.04 (0.90–1.20)	–
Chloroquine						
Model 1: demographics	1.33 (1.05–1.70)‡	1.20 (0.94–1.53)	1.23 (0.86–1.76)	1.24 (0.84–1.83)	0.80 (0.52–1.23)	0.98 (0.64–1.50)
Model 2: demographics + deployment	1.30 (1.03–1.66)‡	1.22 (0.95–1.55)	1.18 (0.82–1.68)	1.24 (0.84–1.82)	–	0.96 (0.63–1.47)
Model 3: demographics, deployment + combat exposure	1.15 (0.88–1.50)	1.15 (0.88–1.50)	0.89 (0.60–1.33)	0.94 (0.62–1.42)	0.66 (0.40–1.06)	–
Doxycycline						
Model 1: demographics	1.21 (1.07–1.37)‡	0.96 (0.84–1.09)	1.38 (1.15–1.65)‡	1.13 (0.91–1.40)	1.10 (0.88–1.36)	1.10 (0.88–1.38)
Model 2: demographics + deployment	1.11 (0.98–1.26)	1.00 (0.87–1.14)	1.22 (1.02–1.47)‡	1.13 (0.91–1.40)	1.02 (0.82–1.28)	1.04 (0.83–1.31)
Model 3: demographics, deployment + combat exposure	0.96 (0.83–1.09)	0.91 (0.79–1.04)	0.96 (0.79–1.15)	0.87 (0.69–1.09)	0.85 (0.67–1.07)	0.84 (0.66–1.06)
Mefloquine						
Model 1: demographics	1.06 (0.82–1.36)	0.93 (0.72–1.22)	0.97 (0.66–1.44)	1.36 (0.92–2.01)	0.97 (0.64–1.48)	0.86 (0.54–1.36)
Model 2: demographics + deployment	0.97 (0.75–1.25)	0.97 (0.74–1.27)	0.86 (0.58–1.27)	1.36 (0.92–2.01)	0.91 (0.59–1.38)	0.81 (0.51–1.29)
Model 3: demographics, deployment + combat exposure	0.87 (0.66–1.14)	0.96 (0.73–1.26)	–	1.21 (0.80–1.82)	0.77 (0.49–1.22)	0.74 (0.46–1.20)
Primaquine						
Model 1: demographics	0.98 (0.64–1.49)	0.63 (0.42–0.95)‡	0.61 (0.27–1.35)	0.87 (0.35–2.09)	0.34 (0.12–0.99)‡	0.52 (0.20–1.34)
Model 2: demographics + deployment	0.93 (0.61–1.43)	0.64 (0.43–0.97)‡	0.56 (0.25–1.24)	0.87 (0.36–2.08)	–	0.50 (0.19–1.29)
Model 3: demographics, deployment + combat exposure	0.74 (0.46–1.18)	0.56 (0.35–0.87)‡	0.48 (0.21–1.10)	0.78 (0.31–1.98)	0.19 (0.06–0.67)‡	0.46 (0.17–1.21)
Mefloquine + any other antimalarial						
Model 1: demographics	1.22 (0.99–1.51)	1.09 (0.88–1.36)	1.63 (1.20–2.20)‡	1.11 (0.77–1.59)	1.63 (1.17–2.27)‡	1.36 (0.95–1.95)
Model 2: demographics + deployment	1.13 (0.91–1.40)	1.13 (0.91–1.41)	1.45 (1.07–1.97)‡	1.10 (0.77–1.59)	1.53 (1.10–2.14)‡	1.30 (0.90–1.85)
Model 3: demographics, deployment + combat exposure	0.92 (0.73–1.15)	1.00 (0.80–1.26)	1.09 (0.79–1.50)	0.91 (0.62–1.33)	–	–
Any other antimalarial (s)						
Model 1: demographics	1.12 (0.93–1.34)	1.23 (1.02–1.49)‡	1.63 (1.24–2.13)‡	1.42 (1.03–1.96)‡	1.53 (1.12–2.10)‡	1.63 (1.19–2.22)‡
Model 2: demographics + deployment	1.06 (0.87–1.27)	1.26 (1.04–1.53)‡	1.51 (1.15–1.98)‡	1.42 (1.03–1.96)‡	1.47 (1.07–2.01)‡	1.57 (1.15–2.16)‡

(continued)

TABLE 3
Continued

Antimalarial, model*	Health outcomes†					
	SF12—composite mental health score	SF12—composite physical health score	PTSD	Thoughts of death/ self-harm	Other anxiety	Major depression
Model 3: demographics, deployment + combat exposure	0.92 (0.75–1.13)	1.07 (0.87–1.31)	1.14 (0.86–1.52)	–	1.09 (0.78–1.52)	1.20 (0.86–1.68)

CI = confidence interval; PTSD = post-traumatic stress disorder; SF-12 = twelve-item short form.
* Adjusted odds ratios (95% CI); (–) = interaction.
† Model 1 = all independent variables except deployment and combat intensity; model 2 = all independent variables except combat intensity; model 3 = all independent variables (includes deployment and combat intensity). We modeled the odds of having a score fall below the U.S. mean vs. the odds of having a score above the U.S. mean when the SF-12 composite scores were used as outcome variables. When PTSD, thoughts of death/self-harm, other anxiety, and major depression were used as outcome variables, we modeled the odds of having the condition vs. the odds of not having the condition. *N*'s for the logistic regressions ranged from 14,813 to 19,106 depending on which outcomes and sets of independent variables were being examined.
‡ 95% CI does not contain 1.0.

95% CI: 0.86–1.52; other anxiety: AOR = 1.09, 95% CI: 0.78–1.52; major depression: AOR = 1.20, 95% CI: 0.86–1.68) (Table 3). Thoughts of self-harm and death were an exception to this pattern for the nondeployed where the odds of self-harm/death among users were more than three times the odds among nonusers in model 3 (AOR = 3.14, 95% CI: 1.24–7.94) (Table 4).

Primaquine use was weakly, but significantly, associated with poor physical health (SF-12; AOR = 0.63, 95% CI: 0.42–0.95) and with a positive screen for other anxiety disorders (AOR = 0.34, 95% CI: 0.12–0.99) (Table 3). Generally, similar reductions to estimates with concomitant losses in significance for primaquine were found for models 2 and 3 after adjusting for deployment and combat exposure. Exceptions included the estimate for models 2 and 3 for overall physical health (AOR = 0.64, 95% CI: 0.43–0.97 and AOR = 0.56, 95% CI: 0.35–0.87, respectively); model 3, other anxiety (AOR = 0.19, 95% CI: 0.06–0.67) (Table 3); and the AOR representing the association between primaquine use and anxiety among the deployed in model 2 (AOR = 0.14, 95% CI: 0.03–0.60) (Table 4).

Associations between health outcome and antimalarial drug differed significantly when stratified by deployment (Table 4). The AORs found among the nondeployed were far lower than those found for veterans deployed to Iraq or Afghanistan for major depression and its association with antimalarial use (chloroquine, AOR = 0.13, 95% CI: 0.18–0.88; any antimalarial use, AOR = 0.62, 95% CI: 0.42–0.90) (model 3), and for anxiety and chloroquine use (AOR = 0.26, 95% CI: 0.08–0.86) (model 2).

Table 5 provides weighted prevalence estimates of each of the six outcomes stratified by combat exposure intensity score (0, 1, 2, or 3) among the deployed. The prevalence of each outcome increases among antimalarial users with increasing combat intensity score. For the overall MH score, the prevalence of a score below the U.S. mean among users with a combat exposure intensity score of 0 (lowest intensity) was 32.5 that increased to 65.8 for those with a score of 3 (highest intensity). Prevalence of a score below the U.S. mean ranged from 31.3 to 49.7 for the overall physical health score, from 3.1 to 32.5 for PTSD, from 4.6 to 17.7 for thoughts of death/self-harm, from 2.7 to 20.4 for other anxiety, and from 3.8 to 18.0 for depression. This positive trend was also observed among those who did not report antimalarial use.

DISCUSSION

This study surveyed a large population-based sample of deployed and nondeployed veterans about use of antimalarial agents and assessed health indices vulnerable to medication side effects. The findings suggest that there is a burden of MH symptoms across the surveyed population, with a greater burden among the OEF/OIF deployed, regardless of the antimalarial medication reported. Although there appeared to be significant elevated odds of poor mental and physical health outcomes among those who reported antimalarial use relative to nonusers, once the effect of combat exposure was adjusted for, significant relationships generally diminished, implying that in this large population-based sample, it is the effect of combat exposure that is driving the MH burden, not the exposure to antimalarial medication.

The highest prevalence of PTSD and other anxiety disorders was reported by deployed veterans who endorsed use of mefloquine plus other antimalarials. The highest prevalence of thoughts of death or self-harm among the deployed was reported by the mefloquine group. Other anecdotal reports and research indicated that neuropsychiatric side effects of mefloquine are a risk,[3,25–32,40,43–46,56] but more so for those with prior MH issues,[29,33,34] first-time users,[31] and women[1,27,31,33,57–59] that is probably because of their lower

TABLE 4
Interactions from multivariable logistic regression, stratified by deployment status

Antimalarial/outcome association, model	Deployed*	Nondeployed*
Any antimalarial use/major depression, model 3†	1.09 (0.93–1.28)	0.62 (0.42–0.90)‡
Chloroquine/anxiety, model 2†	0.97 (0.60–1.55)	0.26 (0.08–0.86)‡
Chloroquine/major depression, model 3†	0.95 (0.59–1.54)	0.13 (0.18–0.88)‡
Primaquine/anxiety, model 2†	0.14 (0.03–0.60)‡	1.45 (0.35–6.08)
Mefloquine/post-traumatic stress disorder, model 3†	0.74 (0.49–1.10)	–
Mefloquine plus§/anxiety, model 3	1.26 (0.88–1.81)	–
Mefloquine plus§/major depression, model 3†	1.11 (0.76–1.64)	–
Other antimalarial(s)/ thoughts of death/self-harm, model 3†	1.06 (0.75–1.50)	3.14 (1.24–7.94)‡

CI = confidence interval.
* Adjusted odds ratios (95% CI); (–) = estimates not reported because odds ratios and associated 95% CIs are smaller than 0.001.
† Model 2 = all independent variables except combat intensity; model 3 = all independent variables (includes deployment and combat intensity).
‡ 95% CI does not contain 1.0.
§ Mefloquine and other antimalarial(s) reported.

TABLE 5

OEF/OIF combat exposure intensity and antimalarial drug use among veterans who were deployed (N = 12,456), selected health outcomes: National Health Study for a New Generation of U.S. Veterans

		Selected health outcomes*					
OEF/OIF CE,*† antimalarial drugs received during military service*	All (N = 12,456)‡	SF-12 mental health score (below U.S. mean)	SF-12 physical health score (below U.S. mean)	PTSD	Thoughts of death/ self-harm	Other anxiety	Major depression
	(%)	(%)	(%)	(%)	(%)	(%)	(%)
CE = 0	3,736 (28.7)	35.7	30.8	3.6	4.3	3.3	4.0
Antimalarial drug use	1,244 (16.7)	32.5	31.3	3.1	4.6	2.7	3.8
Mefloquine	61 (4.6)	27.3	29.4	6.9	1.6	2.1	3.4
Chloroquine	47 (3.0)	47.3	32.4	3.3	6.3	1.6	6.5
Doxycycline	222 (18.6)	34.8	26.6	3.8	5.8	3.7	3.8
Primaquine	18 (1.3)	39.9	37.3	–§	–	–	–
Mefloquine + "*X*"‖	48 (3.8)	34.7	26.5	6.7	10.9	9.8	9.8
Other antimalarials	85 (6.3)	16.0	37.1	0.6	3.0	0.6	1.7
Type not specified	763 (62.4)	32.8	32.3	2.7	4.2	2.4	3.6
No use	2,492 (42.3)	37.2	30.6	3.8	4.2	3.6	4.1
CE = 1	2,913 (22.6)	45.6	37.1	8.2	7.0	6.3	6.3
Antimalarial Drug Use	1,438 (20.0)	43.3	38.3	7.2	6.9	5.0	5.9
Mefloquine	73 (4.5)	49.4	36.8	2.7	14.8	9.6	8.4
Chloroquine	59 (3.8)	48.1	49.5	3.3	3.2	4.4	1.8
Doxycycline	271 (19.6)	40.9	34.1	6.3	7.4	4.5	5.2
Primaquine	18 (1.3)	17.0	12.1	6.7	2.2	–	–
Mefloquine + "*X*"	76 (4.6)	36.1	38.5	6.6	3.8	5.6	6.0
Other antimalarials	129 (8.0)	37.1	30.7	1.0	2.2	0.7	3.4
Type not specified	812 (58.3)	45.4	40.7	9.0	7.3	5.6	6.6
No use	1,475 (25.4)	47.7	36.0	9.1	7.2	7.4	6.7
CE = 2	3,128 (24.7)	59.1	45.3	18.7	12.6	13.3	12.1
Antimalarial drug use	2,049 (29.8)	59.0	47.1	19.3	12.2	14.4	12.7
Mefloquine	93 (3.8)	56.5	32.3	10.1	14.4	9.9	8.4
Chloroquine	88 (3.8)	54.0	51.6	17.9	8.0	10.7	9.3
Doxycycline	430 (20.8)	59.1	42.8	16.1	10.2	12.8	10.1
Primaquine	35 (4.5)	51.2	41.5	6.2	2.1	3.7	9.0
Mefloquine + "*X*"	149 (6.5)	59.4	43.0	12.7	7.8	12.5	10.7
Other antimalarials	158 (6.8)	48.4	47.6	16.6	9.2	12.4	9.8
Type not specified	1,096 (55.8)	60.9	50.3	22.8	14.2	16.4	14.9
No use	1,079 (18.9)	59.3	42.1	17.8	13.3	11.5	11.0
CE = 3	2,513 (24.0)	64.7	48.4	31.9	18.2	20.2	18.3
Antimalarial drug use	1,869 (33.5)	65.8	49.7	32.5	17.7	20.4	18.0
Mefloquine	78 (4.2)	61.6	50.1	29.8	18.9	16.2	14.2
Chloroquine	76 (3.4)	72.6	60.6	37.2	26.1	17.6	21.8
Doxycycline	387 (21.9)	62.8	44.8	31.7	15.1	16.9	14.7
Primaquine	27 (1.2)	45.2	19.8	11.5	17.6	–	–
Mefloquine + "*X*"	152 (7.7)	58.4	50.9	33.5	15.3	22.2	16.9
Other antimalarials	152 (6.9)	67.8	55.5	38.3	21.8	25.0	24.5
Type not specified	997 (54.6)	68.2	50.7	32.4	18.0	21.9	19.1
No use	644 (13.3)	61.6	44.8	30.1	19.5	19.5	19.2

CE = combat exposure; PTSD = post-traumatic stress disorder; OEF = Operation Enduring Freedom (Afghanistan); OIF = Operation Iraqi Freedom (Iraq); SF-12 = twelve-item short form.

* Self-reported.

† Combat exposure intensity, defined from 0 (no combat exposure) to 3 (highest intensity) and was based on responses to three questions from the study questionnaire: 1) "Did you ever feel that you were in great danger of being killed?" 2) "Did you see anyone wounded, killed, or dead?" 3) "Were you engaged in directed combat where you discharged your weapon?".

‡ Of the 19,487 respondents in analytical sample, 12,456 were deployed. Of these, 166 had missing on combat exposure.

§ Cell count is 0.

‖ X = 1 or 2 other antimalarials reported.

body weight[60]; still some contend that serious side effects from mefloquine are rare.[2,61–64]

Other than the categories of any antimalarials and other antimalarials in our analysis, only doxycycline and mefloquine plus any other antimalarial showed the greatest associations with PTSD and with PTSD and other anxiety disorders, respectively, before the addition of combat exposure to the models. However, with the inclusion of deployment and combat exposure to regression models, the ORs associated with antimalarial use became attenuated for all health outcomes. Consistent across most health outcomes and all antimalarial medications included in the study was the absence of statistically significant elevated associations when combat exposure was included in the model. This suggests that combat and deployment experiences are potent factors associated with MH outcomes, even in the presence of other recognized hazards such as medication side effects that may contribute to morbidity. The positive trend that was observed when the mental and physical health outcomes were stratified by combat score intensity supports this finding. These findings do not invalidate the previous anecdotal reports or studies that indicate that neuropsychiatric side effects of mefloquine are a risk. Although these findings suggest that veterans' MH morbidity is not a result of mefloquine or other chemoprophylactic agents, further research is warranted to better understand this relationship.

The associations identified for many of the other antimalarial agents in this analysis were not followed by primaquine. It generally had the lowest prevalence of all health indices and the lowest association with any of the health outcomes. Although primaquine had the second highest prevalence for other anxiety disorders among the nondeployed, we were

unable to confirm the existence of other studies that supported this finding. Primaquine also had the lowest prevalence for PTSD, thoughts of self-harm, and major depression among both the deployed and nondeployed compared with the other medications examined. This finding is consistent with other studies supporting its limited impact on neuropsychiatric function.[23] Kolifarhood et al.[65] conducted a meta-analysis and concluded that primaquine had generally equivalent or lesser neuropsychiatric effects than other antimalarial medications. A study of 203 Australian military personnel[66] showed no signs of neuropsychiatric effects, except for headache that was reported to be mild in severity and transient. A study of leisure travelers to Ethiopia included 106 people who were prescribed primaquine, one participant withdrew because of GI complaints.[67] However, in a randomized, placebo-controlled trial, the risk of headache (relative risk = 0.62, $P < 0.05$) was significantly higher among those treated with primaquine than for those given a placebo.[68]

The association between reported use of other antimalarial(s) and thoughts of death/self-harm among the nondeployed is interesting, both in magnitude and significance (AOR = 3.14, 95% CI: 1.24–7.94). We did not expect to find this. Although these individuals did not deploy to OEF/OIF, they may have been stationed in other places where malaria is endemic (Africa, Central America, and South America), requiring the use of antimalarial medication. Although our survey asked about common antimalarial medications, the list was not exhaustive. There are three common antimalarial medications that were not specifically queried in our survey, including Qualaquin® (quinine) (Mutual Pharmaceutical Company, Inc., Philadelphia, PA), Plaquenil® (hydroxychloroquine) (Concordia Pharmaceuticals Inc., Oakville, Ontario, Canada), and Malarone® (atovaquone and proguanil) (GlaxoSmithKline, Philadelphia, PA), all of which have psychiatric side effects.[46,69] It is possible that nondeployed servicemembers serving in other malaria-endemic parts of the world took these antimalarials and experienced psychiatric side effects, or experienced other events during their time in the military that would have resulted in a poor MH outcome.

The study has several strengths including the use of validated scales measuring health outcomes of concern.[49,50,52] This is the first population-based study of OEF/OIF veterans to examine the long-term effects of antimalarial use on mental and physical health outcomes. The stratified sample design was used to obtain representative estimates of several population subgroups of major interest that included the branches of the military; the reserve, National Guard and active duty; and deployed and nondeployed service personnel. Survey responses were weighted to reduce bias resulting from nonresponse and misclassification of deployment status[54] and women were oversampled to maximize their inclusion in the study.[41] The stratified complex survey design served to reduce variance (increase precision) of the point estimates generated for subgroups of this population.

The study relies on self-reported data for type of antimalarial medication, which is acknowledged as a weakness. The number of individuals reporting specific medications was sufficient to conduct robust analyses, but 23.5% of individuals reported use of antimalarials without specifying type and 61.4% comprised individuals who reported no use. Health indices only measured current symptoms, not symptoms experienced historically or potentially related to medications. The absence of data regarding side effects related to medication use is a shortcoming; however, the objective of this study was to assess chronic impact on neuropsychiatric symptoms, not all the side effects of medication use, most of which are acute in nature.[35] Moreover, we have no data on drug compliance, so we are unable to determine whether outcomes assessed result from taking medications as prescribed. There is no measure of deployment duration among the deployed group to ascertain if multiple opportunities to use antimalarials was associated with reporting multiple drugs and increased exposure to both combat and traumatic events. We also did not collect information on antimalarial administration, so we have no data on whether reports of "combinations" involved medications being taken separately or at the same time.

Another limitation of this analysis relates to the time period of the questions used to assess exposure and outcomes. Exposure to antimalarial medication was queried during military service and not specific to an OEF/OIF deployment. Therefore, it is not possible to determine if the exposure to antimalarial medication occurred before exposure to combat. Post-traumatic stress disorder was assessed in the past 4 weeks (from date the survey was filled out), as was anxiety. Major depressive disorder and self-harm were assessed in the past 2 weeks. The physical and mental component of the SF-12 assesses experiences in the past 4 weeks. Combat intensity was assessed during any of a respondent's deployments, and not specifically to OEF/OIF deployments (as servicemembers often have multiple deployments during multiple wars). In addition, although the MH outcomes are measured in the past 2 or 4 weeks, it is not possible to determine when the respondents began experiencing the MH outcomes and if it was before or after exposure to antimalarial medication. While these analyses can determine association, temporality cannot be established.

These findings do not invalidate the risks associated with mefloquine use, including the potential for acute or long-term neuropsychiatric effects in certain individuals, such as those with a history of psychiatric illness. Health-care providers, those serving veterans, and those serving the general population need to carefully consider the potential antecedent factors and precipitating events, including combat exposure, when seeking to understand and diagnose psychiatric morbidity or neuropsychiatric effects known to be associated with mefloquine use. Careful assessment of deployment history and medication administration should accompany the patient history during clinical evaluation.

Received February 5, 2018. Accepted for publication May 8, 2018.

Published online June 25, 2018.

Authors' addresses: Aaron I. Schneiderman, Yasmin S. Cypel, and Erin K. Dursa, Department of Veterans Affairs, Epidemiology Program, Post Deployment Health Services (10P4Q), Office of Patient Care Services, Veterans Health Administration, Washington, DC, E-mails: aaron.schneiderman@va.gov, yasmin.cypel@va.gov, and erin.dursa2@va.gov. Robert Bossarte, Department of Behavioral Medicine and Psychiatry, West Virginia University Injury Control Research Center, West Virginia University School of Medicine, Morgantown, WV, E-mail: rbossarte@hsc.wvu.edu.

REFERENCES

1. Chen LH, Wilson ME, Schlagenhauf P, 2007. Controversies and misconceptions in malaria chemoprophylaxis for travelers. *JAMA 297:* 2251–2263.
2. Tickell-Painter M, Saunders R, Maayan N, Lutje V, Mateo-Urdiales A, Garner P, 2017. Deaths and parasuicides associated with

mefloquine chemoprophylaxis: a systematic review. *Travel Med Infect Dis 20:* 5–14.
3. Korhonen C, Petersen K, Bruder C, Jung P, 2007. Self-reported adverse events associated with antimalarial chemoprophylaxis in Peace Corps volunteers. *Am J Prev Med 33:* 194–199.
4. Alkadi HO, 2007. Antimalarial drug toxicity: a review. *Chemotherapy 53:* 385–391.
5. Taylor WR, White NJ, 2004. Antimalarial drug toxicity: a review. *Drug Saf 27:* 25–61.
6. Fukuda M, Raczniak GA, Riddle MS, Forgione M, Magill AJ, 2017. *Special Considerations for US Military Deployments*. Available at: https://wwwnc.cdc.gov/travel/yellowbook/2018/advising-travelers-with-specific-needs/special-considerations-for-us-military-deployments/. Accessed November 17, 2017.
7. Brisson M, Brisson P, 2012. Compliance with antimalarial chemoprophylaxis in a combat zone. *Am J Trop Med Hyg 86:* 587–590.
8. Department of Veterans Affairs, Epidemiology Program, Post-Deployment Health Group, 2017. *Analysis of VA Health Care Utilization among Operation Enduring Freedom (OEF), Operation Iraqi Freedom (OIF), and Operation New Dawn (OND) Veterans: Cumulative from 1st Qtr FY 2002 through 3rd Qtr FY 2015 (October 1, 2001–June 30, 2015)*. Available at: https://www.publichealth.va.gov/epidemiology/reports/oefoifond/health-care-utilization. Accessed January 24, 2018.
9. Office of the Assistant Secretary of Defense for Health Affairs, 2009. *Memorandum: Policy Memorandum on the Use of Mefloquine (Lariam®) in Malaria Prophylaxis*. Available at: http://www.lariaminfo.org/pdfs/policy-memo-secy-defense%20malaria-prophylaxis.pdf. Accessed September 8, 2017.
10. Office of the Assistant Secretary of Defense for Health Affairs, 2013. *Memorandum: Guidance on Medications for Prophylaxis of Malaria*. Available at: https://health.mil/Policies/2013/04/15/Guidance-on-Medications-for-Prophylaxis-of-Malaria.pdf. Accessed November 20, 2017.
11. Armed Forces Epidemiological Board, 2003. *Memorandum: Antimalarials and Current Practice in the Military 2003–13*. Available at: http://facadatabase.gov/committee/historyreportdocuments.aspx?flr=3515&cid=354&fy=2003. Accessed November 27, 2017.
12. Armed Forces Epidemiological Board, 2004. *Memorandum: Armed Forces Epidemiological Board (AFEB) Select Subcommittee to Develop Mefloquine Study Options*. Available at: http://facadatabase.gov/committee/historyreportdocuments.aspx?flr=3528&cid=354&fy=2004. Accessed November 27, 2017.
13. Tan KR, Magill AJ, Parise ME, Arguin PM, 2011. Doxycycline for malaria chemoprophylaxis and treatment: report from the CDC expert meeting on malaria chemoprophylaxis. *Am J Trop Med Hyg 84:* 517–531.
14. Saunders DL, Garges E, Manning JE, Bennett K, Schaffer S, Kosmowski AJ, Magill AJ, 2015. Safety, tolerability, and compliance with long-term antimalarial chemoprophylaxis in American soldiers in Afghanistan. *Am J Trop Med Hyg 93:* 584–590.
15. Sonmez A, Harlak A, Kilic S, Polat Z, Hayat L, Keskin O, Dogru T, Yilmaz MI, Acikel CH, Kocar IH, 2005. The efficacy and tolerability of doxycycline and mefloquine in malaria prophylaxis of the ISAF troops in Afghanistan. *J Infect 51:* 253–258.
16. Pagès F, Boutin JP, Meynard JB, Keundjian A, Ryfer S, Giurato L, Baudon D, 2002. Tolerability of doxycycline monohydrate salt vs. chloroquine-proguanil in malaria chemoprophylaxis. *Trop Med Int Health 7:* 919–924.
17. Lee TW, Russell L, Deng M, Gibson PR, 2013. Association of doxycycline use with the development of gastroenteritis, irritable bowel syndrome and inflammatory bowel disease in Australians deployed abroad. *Intern Med J 43:* 919–926.
18. Sloan B, Scheinfeld N, 2008. The use and safety of doxycycline hyclate and other second-generation tetracyclines. *Expert Opin Drug Saf 7:* 571–577.
19. Melles RB, Marmor MF, 2015. Pericentral retinopathy and racial differences in hydroxychloroquine toxicity. *Ophthalmology 122:* 110–116.
20. Jong EC, Nothdurft HD, 2001. Current drugs for antimalarial chemoprophylaxis: a review of efficacy and safety. *J Travel Med 8 (Suppl 3):* S48–S56.
21. Costedoat-Chalumeau N, Dunogué B, Leroux G, Morel N, Jallouli M, Le Guern V, Piette JC, Brézin AP, Melles RB, Marmor MF, 2015. A critical review of the effects of hydroxychloroquine and chloroquine on the eye. *Clin Rev Allergy Immunol 49:* 317–326.
22. Braga CB et al., 2015. Side effects of chloroquine and primaquine and symptom reduction in malaria endemic area (Mâncio Lima, Acre, Brazil). *Interdiscip Perspect Infect Dis 2015:* 1–7.
23. Ashley EA, Recht J, White NJ, 2014. Primaquine: the risks and the benefits. *Malar J 13:* 418.
24. Hill DR, Baird JK, Parise ME, Lewis LS, Ryan ET, Magill AJ, 2006. Primaquine: report from CDC expert meeting on malaria chemoprophylaxis I. *Am J Trop Med Hyg 75:* 402–415.
25. Weinke T, Trautmann M, Held T, Weber G, Eichenlaub D, Fleischer K, Kern W, Pohle HD, 1991. Neuropsychiatric side effects after the use of mefloquine. *Am J Trop Med Hyg 45:* 86–91.
26. Stürchler D, Handschin J, Kaiser D, Kerr L, Mittelholzer ML, Reber R, Fernex M, 1990. Neuropsychiatric side effects of mefloquine. *N Engl J Med 322:* 1752–1753.
27. Schlagenhauf P et al., 2003. Tolerability of malaria chemoprophylaxis in non-immune travellers to sub-Saharan Africa: multicentre, randomised, double blind, four arm study. *BMJ 327:* 1078.
28. Toovey S, 2009. Mefloquine toxicity: a literature review. *Travel Med Infect Dis 7:* 2–6.
29. Eick-Cost AA, Hu Z, Rohrbeck P, Clark LL, 2017. Neuropsychiatric outcomes after mefloquine exposure among US military service members. *Am J Trop Med Hyg 96:* 159–166.
30. Ringqvist A, Bech P, Glenthøj B, Petersen E, 2015. Acute and long-term psychiatric side effects of mefloquine: a follow-up on Danish adverse event reports. *Travel Med Infect Dis 13:* 80–88.
31. Van Riemsdijk MM, Ditters JM, Sturkenboom MC, Tulen JH, Ligthelm RJ, Overbosch D, Stricker BH, 2002. Neuropsychiatric events during prophylactic use of mefloquine before travelling. *Eur J Clin Pharmacol 58:* 441–445.
32. Van Riemsdijk MM, Sturkenboom MC, Ditters JM, Ligthelm RJ, Overbosch D, Stricker BH, 2002. Atovaquone plus chloroguanide versus mefloquine for malaria prophylaxis: a focus on neuropsychiatric adverse events. *Clin Pharmacol Ther 72:* 294–301.
33. Van Riemsdijk MM, Sturkenboom MC, Pepplinkhuizen L, Stricker BH, 2005. Mefloquine increases the risk of serious psychiatric events during travel abroad: a nationwide case-control study in the Netherlands. *J Clin Psychiatry 66:* 199–204.
34. Tan KR, Henderson SJ, Williamson J, Ferguson RW, Wilkinson TM, Jung P, Arguin PM, 2017. Long term health outcomes among returned Peace Corps volunteers after malaria prophylaxis, 1995–2014. *Travel Med Infect Dis 17:* 50–55.
35. Food and Drug Administration, 2013. *FDA Drug Safety Communication: FDA Approves Label Changes for Antimalarial Drug Mefloquine Hydrochloride Due to Risk of Serious Psychiatric and Nerve Side Effects*. Available at: http://www.fda.gov/Drugs/DrugSafety/ucm362227.htm. Accessed April 14, 2015.
36. McArdle JJ, Sellin LC, Coakley KM, Potian JG, Quinones-Lopez MC, Rosenfeld CA, Sultatos LG, Hognason K, 2005. Mefloquine inhibits cholinesterases at the mouse neuromuscular junction. *Neuropharmacology 49:* 1132–1139.
37. Dursa EK, Reinhard MJ, Barth SK, Schneiderman AI, 2014. Prevalence of a positive screen for PTSD among OEF/OIF and OEF/OIF-Era veterans in a large population-based cohort. *J Trauma Stress 27:* 542–549.
38. Seal KH, Metzler TJ, Gima KS, Bertenthal D, Maguen S, Marmar CR, 2009. Trends and risk factors for mental health diagnoses among Iraq and Afghanistan veterans using Department of Veterans Affairs health care, 2002–2008. *Am J Public Health 99:* 1651–1658.
39. Lee S, Fonseca VP, Wolters CL, Dougherty DD, Peterson MR, Schneiderman AI, Ishii EK, 2015. Health care utilization behavior of veterans who deployed to Afghanistan and Iraq. *Mil Med 180:* 374–379.
40. Nevin RL, 2010. Mefloquine prescriptions in the presence of contraindications: prevalence among US military personnel

deployed to Afghanistan, 2007. *Pharmacoepidemiol Drug Saf 19:* 206–210.
41. Eber S, Barth S, Kang H, Mahan C, Dursa E, Schneiderman A, 2013. The National Health Study for a new generation of United States veterans: methods for a large-scale study on the health of recent veterans. *Mil Med 178:* 966–969.
42. Dillman DA, Smyth JD, Christian LM, 2014. *Internet, Phone, Mail, and Mixed-Mode Surveys: The Tailored Design Method*, 4th edition. Hoboken, NJ: John Wiley & Sons.
43. Peterson AL, Seegmiller RA, Schindler LS, 2011. Severe neuropsychiatric reaction in a deployed military member after prophylactic mefloquine. *Case Rep Psychiatry 2011:* 350417: 1–4.
44. Javorsky DJ, Tremont G, Keitner GI, Parmentier AH, 2001. Cognitive and neuropsychiatric side effects of mefloquine. *J Neuropsychiatry Clin Neurosci 13:* 302.
45. Boudreau E, Schuster B, Sanchez J, Novakowski W, Johnson R, Redmond D, Hanson R, Dausel L, 1993. Tolerability of prophylactic Lariam® regimens. *Trop Med Parasitol 44:* 257–265.
46. Grabias B, Kumar S, 2016. Adverse neuropsychiatric effects of antimalarial drugs. *Expert Opin Drug Saf 15:* 903–910.
47. Department of Defense (DoD), 2003. *Post-Deployment Health Assessment (PDHA) form, 2003*. Available at: http://www.jiatfs.southcom.mil/Portals/4/Documents/J4/J4_dd2796.pdf. Accessed September 8, 2017.
48. Cronbach L, 1951. Coefficient alpha and the internal structure of tests. *Psychometrika 16:* 297–334.
49. Ware JE Jr., Kosinski M, Keller SD, 1996. A 12-item short-form health survey: construction of scales and preliminary tests of reliability and validity. *Med Care 34:* 220–233.
50. Weathers FW, Litz BT, Herman DS, Huska JA, Keane TM, 1993. *The PTSD Checklist (PCL): Reliability, Validity, and Diagnostic Utility*. Paper Presented at the International Society for Traumatic Stress Studies, San Antonio, TX.
51. Keen SM, Kutter CJ, Niles BL, Krinsley KE, 2008. Psychometric properties of PTSD checklist in sample of male veterans. *J Rehabil Res Dev 45:* 465–474.
52. Spitzer RL, Kroenke K, Williams JB; Patient Health Questionnaire Primary Care Study Group, 1999. Validation and utility of a self-report version of PRIME-MD: the PHQ primary care study. *JAMA 282:* 1737–1744.
53. SAS Institute Inc, 2014. *Base SAS® 9.4 Procedures Guide*, 3rd edition. Cary, NC: SAS Institute Inc.
54. Yoon FB, Jang D, Sukasih A, Kress AM, Barth SK, Mahan CM, Coughlin SS, Dursa EK, Schneiderman AI, 2013. *Adjustments for Misclassification of Deployment Status in a Population Based Health Study of Operation Enduring Freedom and Operation Iraqi Freedom Veterans*. JSM Proceedings, Mental Health Statistics Section. Alexandria, VA: American Statistical Association.
55. Kuha J, Skinner C, 1997. Categorical data analysis and misclassification. Lyberg LE, Biemer PP, Collins M, de Leeuw ED, Dippo C, Schwarz N, Trewin D, eds. *Survey Measurement and Process Quality*. New York, NY: John Wiley & Sons.
56. Barrett PJ, Emmins PD, Clarke PD, Bradley DJ, 1996. Comparison of adverse events associated with use of mefloquine and combination of chloroquine and proguanil as antimalarial prophylaxis: postal and telephone survey of travellers. *BMJ 313:* 525–528.
57. Van Riemsdijk MM, van der Klauw MM, van Heest JA, Reedeker FR, Ligthelm RJ, Herings RM, Stricker BH, 1997. Neuropsychiatric effects of antimalarials. *Eur J Clin Pharmacol 52:* 1–6.
58. Schlagenhauf P et al., 1996. Mefloquine tolerability during chemoprophylaxis: focus on adverse event assessments, stereochemistry and compliance. *Trop Med Int Health 1:* 485–494.
59. Schlagenhauf P, Johnson RJ, Schwartz E, Nothdurft HD, Steffen R, 2009. Evaluation of mood profiles during malaria chemoprophylaxis: a randomized, double-blind, four-arm study. *J Travel Med 16:* 42–45.
60. Ollivier L, Tifratene K, Josse R, Keundjian A, Boutin JP, 2004. The relationship between body weight and tolerance to mefloquine prophylaxis in non-immune adults: results of a questionnaire-based study. *Ann Trop Med Parasitol 98:* 639–641.
61. Jaspers CA, Hopperus Buma AP, van Thiel PP, van Hulst RA, Kager PA, 1996. Tolerance of mefloquine chemoprophylaxis in Dutch military personnel. *Am J Trop Med Hyg 55:* 230–234.
62. Schneider C, Adamcova M, Jick SS, Schlagenhauf P, Miller MK, Rhein HG, Meier CR, 2013. Antimalarial chemoprophylaxis and the risk of neuropsychiatric disorders. *Travel Med Infect Dis 11:* 71–80.
63. Wells TS, Smith TC, Smith B, Wang LZ, Hansen CJ, Reed RJ, Goldfinger WE, Corbeil TE, Spooner CN, Ryan MA, 2006. Mefloquine use and hospitalizations among US service members, 2002–2004. *Am J Trop Med Hyg 74:* 744–749.
64. Lobel HO, Miani M, Eng T, Bernard KW, Hightower AW, Campbell CC, 1993. Long-term malaria prophylaxis with weekly mefloquine. *Lancet 341:* 848–851.
65. Kolifarhood G et al., 2017. Prophylactic efficacy of primaquine for preventing *Plasmodium falciparum* and *Plasmodium vivax* parasitaemia in travelers: a meta-analysis and systematic review. *Travel Med Infect Dis 17:* 5–18.
66. Ebringer A, Heathcote G, Baker J, Waller M, Shanks GD, Edstein MD, 2011. Evaluation of the safety and tolerability of a short higher-dose primaquine regimen for presumptive anti-relapse therapy in healthy subjects. *Trans R Soc Trop Med Hyg 105:* 568–573.
67. Schwartz E, Regev-Yochay G, 1999. Primaquine as prophylaxis for malaria for nonimmune travelers: a comparison with mefloquine and doxycycline. *Clin Infect Dis 29:* 1502–1506.
68. Baird JK et al.; United States Naval Medical Research Unit 2 Clinical Trials Team, 2001. Randomized, parallel placebo-controlled trial of primaquine for malaria prophylaxis in Papua, Indonesia. *Clin Infect Dis 33:* 1990–1997.
69. Nevin RL, Croft AM, 2016. Psychiatric effects of malaria and antimalarial drugs: historical and modern perspectives. *Malar J 15:* 332.