

BRIEF REPORT

Mefloquine prescriptions in the presence of contraindications: prevalence among US military personnel deployed to Afghanistan, 2007^{†‡}

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SUMMARY

Purpose Contraindications to mefloquine use include a history of certain prevalent neuropsychiatric disorders, which are thought to increase the risk of severe adverse events including anxiety, paranoia, depression, hallucinations, psychosis, and possibly suicide. Within the US military, the continued availability and use of mefloquine is subject to administrative policies dating to 2002 that require clinicians to exercise added caution during prescribing. This analysis was performed to quantify the effectiveness of these policies in ensuring health care provider compliance with package insert prescribing guidance.

Methods A previously identified cohort consisting of 11 725 active duty US military personnel, among whom 1127 (9.6%) had contraindications to mefloquine use identified through medical surveillance and pharmaceutical databases, was examined to identify individuals receiving prescriptions for mefloquine in the 45 days prior to a combat deployment in 2007.

Results Among the 11 725 cohort members, 4505 (38.4% of the cohort) received a prescription for mefloquine. Among the 1127 cohort members with contraindications, 155 (1.3% of the cohort) were prescribed mefloquine, comprising 13.8% of those with contraindications.

Conclusions Despite the longstanding administrative policies meant to reduce such events, approximately one in seven individuals with neuropsychiatric contraindications received a prescription for mefloquine prior to a recent combat deployment, significantly increasing the risk of subsequent adverse events. Given the prevalence of neuropsychiatric disorders among US military personnel and the continued availability of mefloquine, additional study is recommended to describe and quantify the nature and extent of mefloquine-associated adverse events experienced among this group. Published in 2009 by John Wiley & Sons, Ltd.

KEY WORDS — mefloquine; contraindications; adverse events

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PURPOSE

Mefloquine (previously marketed in the US as Lariam[®]), a 4-quinoline methanol derivative, is a popular and highly effective agent for malaria prophylaxis. Although mefloquine has traditionally not been considered a psychoactive medication, according to the Lariam[®] US package insert (Hoffman-LaRoche Inc., Nutley, NJ),¹ post-marketing surveillance suggests neuropsychiatric adverse events, including anxiety, depression, hallucinations, and

psychotic or paranoid reactions are not uncommonly reported. Mounting experimental evidence in animal models, and observational studies among those prescribed mefloquine for prophylaxis, suggest numerous plausible mechanisms of neurotoxicity may underlie at least some of these events.^{2,3} Despite the absence of proof of a relationship,¹ popular media coverage continues to link the drug to spectacular adverse events, including suicide.⁴

To protect against the risk posed by malaria, prophylaxis is mandatory for US military personnel deploying to certain geographic regions, including Africa and Afghanistan. Mefloquine remains available as an option for malaria prophylaxis,⁵ although its use is carefully controlled by administrative policy. Since 2002, when such administrative policy was issued,⁶ the US military has advised health care providers that

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careful prescribing of mefloquine is “critically important” to minimize the potential for severe neuropsychiatric adverse events, which may include acute psychoses, anxiety, depression, paranoia, myoclonus, and seizure.⁷ The US package insert¹ cautions that mefloquine “should not be taken for prophylaxis in patients with active depression or with a recent history of depression, generalized anxiety disorder, psychosis, or schizophrenia or other major psychiatric disorders.”

A high prevalence of mental health disorders has been reported among cohorts of previously deployed US service members.^{8,9} The possible role of mefloquine, including that of its inappropriate prescribing to those with contraindications, in contributing to this prevalence remains unclear. This analysis was performed to quantify the effectiveness of US military administrative policy in assuring compliance with mefloquine package insert prescribing guidance, and to suggest directions for future study.

METHODS

A retrospective period prevalence study was performed using data from a previously identified cohort.¹⁰ Briefly, all active duty US military personnel deployed to Afghanistan within 6 months of a reference date in early 2007 were identified. For each member of the cohort, the Defense Medical Surveillance System,¹¹ a US military medical surveillance database, was queried for International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9CM) medical diagnosis codes assigned during one or more inpatient or outpatient visits occurring within the 365 days prior to the date of deployment, consistent with diagnosis of a psychiatric or neurological contraindication to mefloquine use. Similarly, an extract from the US military Pharmacy Data Transaction Service (PDTs) database¹² was examined for prescription drugs dispensed at military, retail and mail-order pharmacies within the 180 days prior to deployment, any prescription of which regardless of quantity or duration of therapy would be consistent with treatment of psychiatric and neurological contraindications to mefloquine use. A full list of diagnoses and corresponding ICD-9CM codes, and prescription drugs used to define a medical contraindication are provided as Figure 1.

As previously described,¹⁰ this study cohort comprised 11 725 subjects, of whom 558 subjects (4.8%) had a medical contraindication, 837 (7.1%) had a pharmacologic contraindication, and 1127 (9.6%) had either or both. The study cohort comprised mainly

young adults; 93.8% were under the age of 40, and 90.5% were male. Among the cohort, 39.3% had at least one prior deployment.

For this analysis, among members of this cohort, PDTs records were reexamined for evidence of any prescription of mefloquine within 45 days of the date of deployment, and descriptive statistics, including associated 95% binomial confidence intervals (CIs) were produced for the prevalence of mefloquine prescription in the presence of contraindications. Risk of prescription across major strata of contraindication were compared by risk ratio (RR).

Data were requested under military command approval, with analysis performed consistent with Department of Defense Directives (DoDD) 6590.2 and DoDD 6490.02E and as non-research exempt from Institutional Review Board (IRB) requirements in accordance with United States Code of Federal Regulations (CFR) section 38 CFR 16 (“The Common Rule”). Identified health data were securely transmitted, processed, and retained on data systems compliant with DoD information assurance policies.

RESULTS

Among the 11 725 cohort members, 4505 (38.4% of the cohort) received a prescription for mefloquine. Among the 10 598 cohort members without contraindications, 4350 (41.0%) were prescribed mefloquine. Among the remaining 1127 cohort members with contraindications, 155 (13.8%) were prescribed mefloquine, comprising 1.3% of the total deployed cohort. Among the 290 with only medical contraindications, 92 (31.7%) were prescribed mefloquine; as compared to those without any contraindications the RR of prescription was 0.703 (95% CI 0.590–0.836). Among the 569 with only pharmacologic contraindications, 46 (8.1%) were prescribed mefloquine; as compared to those without any contraindications the RR of prescription was 0.197 (95% CI 0.149–0.260). Among the 268 with both medical and pharmacologic contraindications, 17 (6.3%) were prescribed mefloquine; as compared to those without any contraindications the RR of prescription was 0.155 (95% CI 0.098–0.245). Other percentages by specific strata of contraindication, not necessarily mutually exclusive, are listed in Table 1.

DISCUSSION

This is the first study to formally assess the prevalence of mefloquine prescription in the presence of contraindications to its use. This study found that 13.8%, or

MEFLOQUINE PRESCRIPTIONS IN THE PRESENCE OF CONTRAINDICATIONS

<u>Diagnosis</u>	<u>ICD-9CM Codes</u>
Major depressive disorder	296.2--296.3
Adjustment disorder with depressed mood	309.0, 309.28
Prolonged depressive reaction	309.1
Dysthymic disorder	300.4
Depression	311
Cyclothymic disorder	301.13
Generalized anxiety disorder	300.02
Psychoses (non-organic)	298
Schizophrenia	295
Bipolar and manic disorders	296.0, 296.1, 296.3--296.8
Obsessive-compulsive disorder	300.3
Panic disorder (with and without agoraphobia)	300.01, 300.21
Attention-deficit disorders (with or without hyperactivity)	314.0
Dissociative, conversion and factitious disorders	300.1
Delusional disorders	297
Post-traumatic stress disorder	309.81
Parkinsonism	332
Extrapyramidal diseases and movement disorders	333
Epilepsy	345

ADHD Treatments

Amphetamines, atomoxetine, methyphenidate, modafinil

Anticonvulsants

Carbamazepine, clonazepam, divalproex sodium, gabapentin, lamotrigine, levetiracetam, oxcarbazepim, phenytoin, pregabalin, topiramate

Antidepressants

Citalopram, duloxetine, escitalopram, fluoxetine, flurazepam, mirtazapine, nefazodone, nortriptyline, paroxetine, sertraline, venlafexine

Antiparkinsonians

Bromocriptine, ropinirole

Antipsychotics

Aripiprazole, haloperidol, olanzapine, olanzapine/fluoxetine, quetiapine, risperidone

Sedatives – anxiolytics

Alprazolam, buspirone, chlordiazepoxide, diazepam, lorazepam, oxazepam, temazepam, trazodone, triazolam

Figure 1. Medical diagnoses and corresponding ICD-9CM codes, and prescription drugs, consistent with a contraindication to mefloquine use. *Note:* figure adapted from Reference [10].

approximately one in seven, deployed US military service members with neuropsychiatric contraindications were prescribed mefloquine in the 45 days prior to deployment.

This analysis found a significant difference in the prevalence of prescription between individuals with and without pharmacologic contraindications. Among those with a history of medical diagnosis but no recent pharmaceutical records suggestive of such diagnosis, the risk of mefloquine prescription was 70.3% that of those without any contraindications. Conversely, those with pharmacologic contraindications, with or without records of medical contraindications, were at significantly reduced risk as compared to those without pharmacologic contraindications, at 15.5 and 19.7% respectively. These results may be best explained by the widespread use within the US military at the time of this analysis of electronic systems which display active and recently expired prescriptions, but not necessarily past medical history, at the time of new prescription entry. Such systems might have been expected to alert health care providers to the presence of a pharmacologic contraindication, independent of the service member volunteering a history of neuropsychiatric diagnosis at the time of prescription.

This analysis has a number of limitations. Surveillance data from administrative databases were used to identify contraindications, rather than medical records review. Few studies have quantified the misclassification between such databases and formal diagnostic criteria.¹³ The listed contraindications to mefloquine

use also leave significant room for interpretation.¹⁰ A small number of those prescribed mefloquine may have had their histories interpreted as relative contraindications in the presence of competing contraindications to doxycycline or other available antimarials; prior policy was silent on appropriate prescribing under such circumstances.⁶ Also of note in this analysis, among the nearly 40% with prior deployment, the identified prevalence of mental health conditions¹⁰ was much lower than findings from major studies of the previously deployed,^{8,9} suggesting the prevalence of psychiatric contraindication in this group may be higher than reported.

Mefloquine has been used extensively by the US military, including during operations in Somalia in 1992¹⁴; during the initial invasion of Iraq beginning in 2003¹⁵; and in Afghanistan¹⁰ at least since 2002. The sizeable proportion of US service members having ever receiving this drug is concerning in the context of the high prevalence of mental health conditions noted among previously deployed service members^{8,9}; particularly given that neuropsychiatric symptoms resulting from mefloquine, according to the manufacturer, "on occasions... have been reported to continue long after mefloquine has been stopped."¹ The possibility that mefloquine, administered inappropriately to those with contraindications, might in some measure be contributory to the current burden of mental health disorders among previously deployed US military personnel, seems apparent from this analysis.

Table 1. Cohort members with and without contraindications to mefloquine use, with numbers prescribed mefloquine

	Cohort members		Prescribed mefloquine			RR***
	N	N	%	(95% CI*)		
Total	11725	4505	38.4	(37.5–39.3)		
Without any contraindications	10598	4350	41.0	(40.1–42.0)	Referent	
With any contraindication	1127	155	13.8	(11.8–15.9)	0.335	
Any Medical	558	109	19.5	(16.3–23.1)		
Neurological	27	7	25.9	(11.1–46.3)		
Psychiatric	531	102	19.2	(15.9–22.8)		
Any Pharmacologic	837	63	7.5	(5.8–9.5)		
ADHD Treatments	75	10	13.3	(6.6–23.2)		
Anticonvulsants	83	7	8.4	(3.5–16.6)		
Antidepressants	305	20	6.6	(4.1–9.9)		
Antiparkinsonians	2	0	0.0	(0.0–84.2)**		
Antipsychotics	20	2	10.0	(1.2–31.7)		
Sedatives—antiolytics	441	26	5.9	(3.9–8.5)		
Medical without pharmacologic	290	92	31.7	(26.4–37.4)	0.703	
Pharmacologic without medical	569	46	8.1	(6.0–10.6)	0.197	
Medical and pharmacologic	268	17	6.3	(3.7–10.0)	0.155	

*Binomial exact 95% confidence interval.

**One-sided, 97.5% confidence interval.

***Relative risk.

KEY POINTS

- Among US military personnel deployed to Afghanistan in 2007 with evidence of neuropsychiatric contraindications to mefloquine use, mefloquine was prescribed to approximately one in seven.
- Additional studies describing the nature and extent of mefloquine-associated adverse events among this group are recommended.

CONCLUSIONS

This analysis confirms that longstanding US military administrative policies have been insufficient to ensure mefloquine is prescribed consistently with package insert guidance. Perhaps in recognition of the potential hazards associated with its use, recent US Army policy now reserves mefloquine exclusively for those with contraindications to doxycycline.⁵ However, the drug remains available for use among personnel from other US military services and subject to few additional restrictions beyond those in place at the time of this analysis.

If the prevalence of mefloquine contraindications and mefloquine prescription identified in this analysis can be generalized, approximately 13 of every 1000 US military personnel deployed to areas where mefloquine is utilized will have received mefloquine in the presence of a contraindication, and thus be at increased risk of neuropsychiatric adverse events. Given the already high prevalence of neuropsychiatric conditions among members of the US military, and the potential for adverse events due to inappropriate mefloquine prescription demonstrated in this analysis, additional studies, expanding on previous methods⁷ by including relevant outpatient encounters and patterns of pharmaceutical usage, are recommended to characterize the nature and complete extent of mefloquine-associated adverse events experienced among this group.

DISCLAIMER

The opinions expressed in this paper are those of the author alone and do not reflect those of the Department of the Army, Combined Joint Task Force Horn of Africa, United States Africa Command, or the Department of Defense.

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