Case in Point

FDA Black Box, VA Red Ink?
A Successful Service-Connected Disability Claim for Chronic Neuropsychiatric Adverse Effects From Mefloquine

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More veterans are likely to present to the VA with service-connected claims for adverse effects related to exposure to a prophylactic antimalarial drug commonly used by the military for more than 2 decades.

Mefloquine is a synthetic antimalarial drug structurally related to quinine. The drug was developed by the Walter Reed Army Institute of Research during a decades-long program that started during the Vietnam War in response to concerns of rising resistance to chloroquine.1

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The prelicensing clinical testing of mefloquine, originally known as WR 142,490, was conducted in part among U.S. military service members.2,3 Soon after receiving FDA approval in 1989, under the brand name Lariam, it was recommended for use within the U.S. military.4 Over the following 2 decades, mefloquine was a common exposure during military deployments to malaria endemic areas.

Although the original U.S. mefloquine drug label noted that neuropsychiatric reactions could occur with use, changes to the drug label mandated by the FDA in July 2013, including a black box warning, described a potential for these to persist long after the drug has been discontinued.5,6 These changes have served to reinforce earlier U.S. military policy changes beginning in 2009 that de-prioritized use of the drug in favor of safer and better-tolerated antimalarials. Consequently, more than a quarter century after its introduction, mefloquine now is only rarely prescribed to members of the U.S. military.7

In addition to limiting current use of the drug, the recent boxed warning may have important implications for service-connected disability claims adjudication by the VA for veterans previously exposed to the drug. This report presents a case of a nondeployed veteran exposed to mefloquine during an early military postmarketing study who developed chronic neuropsychiatric symptoms linked to the drug that were recently deemed service-connected. This report concludes with some comments on the likely implications of this case for future similar disability claims.

CASE PRESENTATION

In 2014, a 56-year-old nondeployed U.S. Marine Corps veteran submitted a claim to the VA for disabling conditions. The veteran alleged these conditions were due to his exposure to mefloquine while in military service more than 2 decades
earlier. The veteran enlisted in 1975 and experienced a motor vehicle accident with prolonged loss of consciousness in 1978 but had no other significant medical history.

Thirteen years later, stationed in Hawaii in 1991, he was encouraged to volunteer for a double-blinded postmarketing study, evaluating the adverse effects (AEs) of chloroquine and mefloquine.8 As documentation following the trial revealed, he was randomly assigned to the mefloquine arm and received a loading dose of 250 mg daily for 3 days, followed by 250 mg per week for 11 weeks.

During the study he experienced insomnia, abnormal dreams, and nightmares. He also developed symptoms of anxiety, depression, cognitive dysfunction, and changes in personality—including anger and irritability—that were severe enough to be noted by his family members. The patient had not been advised of the significance of these symptoms and therefore did not report them during the clinical trial, nor did he report their intermittent presence after the study’s conclusion through his retirement in 1996, fearing adverse career consequences. Subsequent exacerbations of these chronic symptoms later contributed to the patient’s loss of civilian employment in 2010.

After becoming aware of the 2013 boxed warning that these chronic symptoms could be due to his earlier exposure to mefloquine, the veteran sought evaluation by a VA clinician. On evaluation, the clinician noted no history of deployment, and no history of posttraumatic stress disorder (PTSD) criteria A stressors, and posited that the veteran’s chronic neuropsychiatric symptoms were most likely a consequence of his earlier use of mefloquine. The VA subsequently awarded the veteran 50% disability for an anxiety disorder characterized by chronic sleep impairment and frequent panic attacks, attributing these to his service-connected use of the drug.

**DISCUSSION**

Although the original 1989 FDA-approved mefloquine label had warned to discontinue the drug if specific prodromal symptoms of “anxiety, depression, restlessness or confusion” were noted, as illustrated by this case, this guidance was not always consistently communicated to service members.5 Indeed, few service members in the 1991 military postmarketing study discontinued the medication even after reporting such symptoms.8 Vivid dreams, often described as “terrifying nightmares with technicolor clarity” were reported by 7% of study participants. Similarly, concentration problems were reported in 5%; irritability in 4%; anger and moodiness each in 1%; and insomnia in 25%. Two study participants, after failing to discontinue mefloquine at the onset of severe insomnia, were later hospitalized for severe depression and suicidal thoughts, later deemed due to preexisting conditions. Despite these seemingly unfavorable results, mefloquine was nonetheless deemed well tolerated.8

**Military Use of Mefloquine**

Beginning in 1992, use of mefloquine for prophylaxis of malaria was then widely directed within the U.S. military during operations in Somalia. There, a majority of personnel received mefloquine under conditions of command-directed and directly observed administration of the drug.9,10 Again, drug label guidance describing the prodromal psychiatric symptoms that should have prompted discontinuation of mefloquine were either not consistently adhered to or not communicated. In one Somalia-era study, only 1 in 344 service members, or 0.3%, discontinued the drug.11

Throughout the remainder of the 1990s, mefloquine remained the antimalarial drug of choice for most U.S. military operations, and when combat began in Afghanistan in 2001, widespread use was also directed there.12,13 The following year, after national attention was directed to concerns of severe behavioral toxicity from the drug among personnel returning from Afghanistan, the manufacturer issued subtle changes to the mefloquine label warnings.5,14

These label changes adjusted the previously exclusive list of prodromal symptoms to an illustrative list, emphasizing that “if psychiatric symptoms such as [emphasis added] acute anxiety, depression, restlessness or confusion occur, these may be considered prodromal to a more serious event. In these cases, the drug must be discontinued and an alternative medication should be substituted.”5

In 2001 a randomized double-blinded trial demonstrated that symptoms of anxiety and depression occurred in at least 4% of mefloquine users, insomnia in 13%, and abnormal dreams in 14%. Nevertheless, an Army memorandum issued soon after the labeling change significantly understated the known risks of developing such psychiatric symptoms, erroneously claiming that these occurred from mefloquine only “at a rate of one per 2,000 to 13,000 persons.”15,16

**Updated FDA Guidelines**

In 2003, with widespread use of the drug being again directed during operations in Iraq, the FDA
required that all mefloquine prescriptions be accompanied by a patient medication guide with warnings echoing those of the drug label that users seek medical attention should “possible signs of more serious mental problems” develop.5,17 However, surveys suggested that few U.S. service members received these warnings or even verbal instructions to that effect.17-19 During later congressional testimony, a service member who had experienced 3 weeks of nightmares prior to self-discontinuing the drug testified “every soldier I know has problems with it.”20 In response, a senior military medical leader—failing to recognize that the nightmares the soldier reported were in fact psychiatric symptoms and possible signs of more serious mental problems that required the drug’s discontinuation—may have undermined the FDA-directed warnings by dismissing the soldier’s testimony as “perception,” maintaining instead “that perceptions can become realities” should it become “held that this medication is widely problematic.”20

Given that certain preexisting conditions, including anxiety and depression, were known to confound recognition of incident psychiatric symptoms that required discontinuation of the drug, the original 1989 mefloquine label had noted that the drug should be used with caution in such patients. In subsequent years, this language was strengthened, and such patients were formally contraindicated the drug.21

Citing formal policy, senior military medical leaders provided assurance during congressional testimony that service members with these conditions would not be prescribed mefloquine.16,18,20 However, later analysis of a large group of deployed service members revealed that 1 in 7 with contraindications to mefloquine had been prescribed the drug contrary to drug label guidance.21

**Black Box Warning**

With growing recognition of the challenges in using mefloquine as directed by the drug label, a 2009 Army policy memorandum prioritized the use of safer and better-tolerated daily medications, such as doxycycline and atovaquone-proguanil, and stated that “[m]efloquine should only be used for personnel with contraindications to doxycycline.”22 This policy was extended throughout the other military services later that year.23 After concerns were raised that service members were still being prescribed the drug contrary to policy, further restrictions were formalized in early 2013 prior to the boxed warning, with mefloquine reserved for those only “with intolerance or contraindications” to the first-line drugs.24,25

In a later memorandum announcing the July 2013 boxed warning, the military revealed that the number of active-duty personnel prescribed mefloquine had steadily decreased in prior years from 17,361 in 2008 to only 2,040 in 2012.7 Although the military has not released precise figures on the number of U.S. military personnel exposed to mefloquine since the drug’s introduction, based on a variety of sources, the total is likely to far exceed 100,000.7,26

The major changes to the mefloquine label in 2013, including the boxed warning, clarified that neurologic and psychiatric effects from mefloquine could “persist after mefloquine has been discontinued.” The accompanying FDA Drug Safety Communication noted neurologic AEs from the drug, which include but are not limited to “dizziness, loss of balance, or ringing in the ears,” could “occur at any time during drug use, and can last for months to years after the drug is stopped or can be permanent.”76 Other neurologic symptoms listed in the drug label include vertigo, hearing impairment, headache, visual disturbances, sensory and motor neuropathies, including paresthesia, tremor, ataxia, convulsions, and encephalopathy.6

The updated drug label also made clear that psychiatric AEs from mefloquine, such as anxiety, paranoia, and depression to hallucinations and psychotic behavior, “have been reported to continue for months or years after mefloquine has been stopped.” Other psychiatric symptoms listed in the drug label include memory impairment, confusion, somnolence, insomnia, abnormal dreams, aggression, agitation, restlessness, mood swings, panic attacks, psychosis, and suicidal ideation.6

The 2013 boxed warning also served to reemphasize guidance first articulated in 2002 that any psychiatric symptom—presumably including abnormal dreams and insomnia—occurring during mefloquine use should be considered prodromal, prompting the drug’s immediate discontinuation.5 Specifically, the boxed warning explicitly cautioned that given the risk for serious psychiatric disturbances or
neurologic AEs when used for malaria prophylaxis, “if psychiatric or neurologic symptoms occur, the drug should be discontinued and an alternative medication should be substituted.”

Drug of Last Resort
By late 2013, partially on the basis of the boxed warning, the U.S. military declared mefloquine a “drug of last resort.” The U.S. Army Special Operations Command (USASOC) took the further step of prohibiting use of mefloquine altogether and, according to news reports, directed that medical and command staff assess whether certain personnel experiencing AEs from the drug may mistakenly have been thought to be malingering, have PTSD, or have other psychological problems.

As the boxed warning and the USASOC order suggest, veterans exposed to mefloquine may have incurred a broad range of neurologic or psychiatric disorders or had others aggravated during military service as a result of their use of the drug. The effects of mefloquine may have confounded the diagnosis of neurologic or psychiatric disorders related to military service. As these AEs may be a direct result of mefloquine prescribed during military service, those with disabling diagnoses consistent with these effects may be entitled to claim disability compensation through the VA.

Of potential significant relevance to this adjudication process is a memorandum written in early 2012, in which the military conceded:

Some deploying Service members have been provided mefloquine for malaria prophylaxis without appropriate documentation in their medical records and without proper screening for contraindications. In addition, not all individuals have been provided the required mefloquine medication guide and wallet information card, as required by the Food and Drug Administration.

Veterans claiming a service-connected disability as a result of their use of mefloquine should therefore not always be expected to have documentation of prescribing in their military medical records. Although the VA could consider denying such claims for absence of proof of a nexus to military service, in light of this memorandum, the VA may need to consider other evidence of plausible exposure, including veteran testimony and deployment history.

It is also conceivable that the VA could consider denying such claims by arguing that the veteran directly contributed to the disability through willful misconduct by not adhering to mefloquine label guidance. However, as this memorandum establishes that mefloquine use was frequently directed without communication of the drug label precautions and warnings, the VA should consider that veterans claiming a service-connected disability frequently will not have known or otherwise been unable to discontinue the medication at the onset of prodromal symptoms.

It is also possible that the VA might deny claims on the basis that the claimed disabilities reflect pre-existing conditions. However, as the memorandum establishes, use of mefloquine also was occasionally inappropriately directed to those with documented contraindications to the medication, who would have increased risk of AEs. As a result, veterans with preexisting neurologic or psychiatric conditions or disorders who nonetheless were prescribed mefloquine may reasonably claim these were aggravated during military service.

CONCLUSION
As this case suggests, in the coming years, as awareness of the chronic AEs of mefloquine increases among the veteran population, claims related to prior use of the drug are likely to increase and become of significant interest to the VA. Veterans with plausible exposure to mefloquine with neuropsychiatric disabilities who have yet to file a claim may be able to do so, and those veterans whose claims for service-connection were unfavorably adjudicated may be able to reopen their claims on the basis of the new material evidence in the 2012 military memorandum and the 2013 boxed warning.

This case report also suggests that service-connected disability claims arising from chronic neuropsychiatric AEs from mefloquine may prove to be of significant financial consequence. Further research to better define both the extent of prior mefloquine use among U.S. military personnel and the nature and prevalence of those chronic neurologic and psychiatric disorders caused by the drug would be helpful in informing improvements in the efficient and fair adjudication of such service-connected disability claims.

Author disclosures
Dr. Nevin has been retained as consultant and expert witness in legal cases involving claims of antimalarial toxicity. Dr. Ritchie reports no actual or potential conflicts of interest with regard to this article.

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REFERENCES