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## Screening for Symptomatic Mefloquine Exposure Among Veterans With Chronic Psychiatric Symptoms

**M**efloquine is an antimalarial drug that is associated with a significant risk of chronic neuropsychiatric adverse effects (AEs). The drug was licensed by the FDA in 1989 after development by scientists affiliated with Walter Reed Army Institute of Research (WRAIR). By the early 1990s, mefloquine had become the U.S. military's drug of choice both for treatment of uncomplicated malaria and for antimalarial prophylaxis and was administered as a convenient weekly dose. Mefloquine was prescribed widely to U.S. military personnel beginning with operations in Somalia in 1992 and over the next 2 decades during certain deployments to Iraq and Afghanistan and to other malaria-endemic areas.<sup>1</sup>

In 2013, following a decline of U.S. military use, the FDA added a boxed warning to the mefloquine product documentation to caution that neuropsychiatric AEs from the drug could last years after use and even be permanent. The U.S. military subsequently deemed mefloquine to be a prophylactic "drug of last resort."<sup>2</sup>

Recently, researchers at WRAIR have acknowledged that chronic neuropsychiatric AEs attributable to mefloquine, including nightmares, in-

somnia, anxiety, irritability, and cognitive dysfunction, may confound the diagnosis of posttraumatic stress disorder (PTSD).<sup>3</sup> The VA has awarded at least 1 disability claim for service-connected psychiatric conditions that it attributed to mefloquine exposure, and it is likely that in the coming years such claims will increase.<sup>2</sup>

### SUSCEPTIBILITY TO CHRONIC NEUROPSYCHIATRIC AEs

Why mefloquine seems to cause chronic neuropsychiatric AEs in only certain individuals is unclear, although genetic susceptibility to drug-induced toxic encephalopathy and neurotoxicity are suspected.<sup>1</sup> There is no screening test for susceptibility to AEs before mefloquine use, so the current U.S. product documentation cautiously warns that when used for prophylaxis, mefloquine should be discontinued at the onset of any neurologic or psychiatric symptom, many of which are considered prodromal to more serious AEs that may occur with continued dosing.<sup>4</sup>

Although chronic neuropsychiatric AEs have been reported to develop after only a single weekly dose, most clinically significant chronic AEs seem to occur among those who developed at least 1 prodromal neuropsychiatric symptom during early use but who continued weekly use despite these symptoms in a manner contrary to current

product documentation guidance.<sup>4</sup> In contrast, when mefloquine is administered for the treatment of malaria, typically at 5 times the weekly prophylactic dose and commonly in split doses over 8 to 12 hours, dosing is often complete by the time prodromal symptoms develop. Consequently, when mefloquine is used for treatment of malaria, the risks of more serious AEs are significantly higher than when the drug is used as directed in prophylaxis.<sup>5</sup>

### SCREENING FOR SYMPTOMATIC MEFLOQUINE EXPOSURE

As the boxed warning indicates, certain psychiatric symptoms that occur with mefloquine use may become chronic and may confound psychiatric diagnosis. Particularly among veterans, these symptoms risk being misattributed, potentially affecting treatment decisions.<sup>6</sup> Clinicians caring for veterans with persistent psychiatric symptoms should therefore screen for prior symptomatic mefloquine exposure and consider the possible AEs of the drug when formulating a differential diagnosis and treatment plan.

For example, a veteran with a history of symptomatic mefloquine exposure who later is diagnosed with PTSD may experience 1 or more symptoms, such as insomnia or cognitive dysfunction, which may be

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primarily attributable to the chronic AEs of the drug. The origins of the symptoms may be distinct from exposure to trauma and may not respond as effectively to certain conventional therapies for PTSD, requiring consideration of alternate therapies.<sup>3</sup> The confounding role of psychiatric symptoms attributable to mefloquine exposure may explain failed response to medications and psychotherapy. Multidisciplinary evaluation and management may be appropriate for such patients.

If symptomatic mefloquine exposure is suspected, a clinician must establish evidence of exposure to the drug and the veteran's development of neuropsychiatric symptoms associated with such exposure. The following sections provide guidance to aid in screening both for exposure to the drug and for the development of specific neuropsychiatric symptoms during prophylaxis or following the treatment of malaria.

## MEFLOQUINE EXPOSURE

Mefloquine was licensed in the U.S. as a branded medication (Lariam) from 1989 to 2011, and the drug also has been available in a variety of generic equivalents from 2003 to the present. All versions of mefloquine approved in the U.S. have been formulated as a white/slightly-off-white, smaller than dime-sized round tablet, containing 250 mg of mefloquine hydrochloride.

When used for prophylaxis in military settings, the drug was often dispensed informally without documentation, sometimes including directly observed therapy under command direction.<sup>1,2</sup> Therefore, even in the absence of prescribing documentation, a veteran who endorses a consistent history of malaria prophylaxis with

mefloquine should be considered as having evidence of exposure.<sup>2</sup>

Exposure to mefloquine is unlikely if the veteran reports taking a daily antimalarial medication—more likely it was doxycycline or atovaquone/proguanil (marketed as Malarone). In rare cases, the drug may have been erroneously prescribed or been mistakenly taken daily for prophylaxis or, in more common cases, a prophylactic “loading dose” (typically 1 tablet daily for 3 days prior to weekly dosing) was used.<sup>7,8</sup>

Exposure also was unlikely if the veteran reports taking an antimalarial that was dosed weekly with a tablet that was not of the appropriate color, shape, and size. More likely that drug was chloroquine. Although most prophylactic use of mefloquine among U.S. veterans followed its licensing by the FDA in 1989, the drug is known to have been administered to a small number of U.S. military personnel prior to its licensing during clinical trials, including personnel deployed on certain operations during the 1980s.<sup>1</sup>

For treatment of malaria, mefloquine was used widely until better-tolerated drugs became available, beginning in the early 2000s, although some use of mefloquine in the military continues to this day. In most cases, clinicians should rely on records of hospitalization to identify whether mefloquine was administered. In rare cases where documentation is unavailable, exposure should be assumed if the veteran reports a reliable history of taking about 5 tablets (corresponding to the usual treatment dose of 1,250 mg) of appropriate color, shape, and size in response to confirmed or suspected malaria infection, either in 1 dose, or in split doses over 8 to 12 hours.

## Symptoms During Prophylaxis

If prophylactic exposure to the drug has been established, the clinician should confirm the presence of neuropsychiatric symptoms during the exposure. Particularly among veterans deploying to malaria-endemic combat areas, such symptoms may have occurred during a period of heightened stress coincident with their initial deployment, and the veterans may have misattributed these symptoms to nonmefloquine factors. The clinician should therefore take a careful history to identify specific symptoms listed in the mefloquine product documentation. Many AEs will commonly manifest following the first 3 doses, and the clinician may find that focusing on this period is useful.<sup>9</sup>

When mefloquine is used for prophylaxis, anxiety and depression each affect between 1% and 10% of users. Other AEs that may develop include panic attacks; severe mood swings; behavioral AEs, including agitation, aggression, restlessness, and mania; symptoms of psychosis, including paranoia, delusions, and hallucinations; dissociative symptoms, including depersonalization; suicidal ideation; and cognitive AEs, including confusion.

The common symptoms of insomnia and abnormal dreaming affect > 10% of users. Particularly if multiple symptoms occur or if any of these symptoms occur following or coincident with symptoms of disturbed sleep, these should be considered strong evidence of symptomatic exposure.<sup>4</sup> Veterans who report a history of continued mefloquine use despite the onset of such symptoms may be at particularly increased risk of chronic AEs.

The clinician should consider as evidence of symptomatic exposure information provided by others, including reports of obvious signs of nightmares or psychosis affecting the veteran. Clinicians should be aware that confusion and other psychiatric AEs caused by mefloquine during prophylactic use may limit the validity of self-reported history. Similarly, a history of seizure with mefloquine use or of the development of specific neurologic symptoms, particularly visual disturbances, dizziness, vertigo, disequilibrium, and paresthesias, also should be considered strong evidence of symptomatic exposure and indication of an increased risk of chronic psychiatric AEs.<sup>4</sup>

### Posttreatment Adverse Effects

Although chronic psychiatric AEs following malaria infection have long been attributed to cerebral involvement, recognition that mefloquine may independently cause chronic neuropsychiatric AEs may require that individual cases be reexamined to properly assign causation.<sup>10</sup> Particularly in uncomplicated cases of malaria, neuropsychiatric symptoms that develop only after treatment with mefloquine should be considered plausibly to be due to the drug and as evidence of symptomatic exposure.

As with use of mefloquine in prophylaxis, these neuropsychiatric symptoms may evolve in the weeks to months following exposure. They also may contribute

to lasting and significant changes in personality, mood, cognition, thought, sleep, and behavior.<sup>6</sup>

### CONCLUSION

Chronic AEs from mefloquine may provide a parsimonious explanation for the onset and persistence of a veteran's psychiatric symptoms, particularly in cases where these may have failed to respond to treatment. Clinicians evaluating veterans who are seeking care for lasting psychiatric symptoms should ensure that they screen for prior symptomatic mefloquine exposure. As recognition grows of the drug's chronic AEs, symptomatic mefloquine exposure is likely to emerge as a significant known confounder in the diagnosis of psychiatric disorders, including PTSD, among the current generation of U.S. veterans. ●

### About this column

*This article is part of a regular column focused on mental health care and traumatic brain injury, edited and occasionally authored by COL (Ret) Elspeth Cameron Ritchie, MD, MPH. Proposals for articles are encouraged and can be sent to fedprac@frontlinemedcom.com.*

### Author disclosures

*Dr. Nevin has been retained as consultant and expert witness in legal cases involving claims of antimalarial toxicity.*

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