Mefloquine Neurotoxicity: PTSD, Traumatic Brain Injury, and Mental Illness in DoD

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Mefloquine is an anti-malarial medication developed by the U.S. military in the 1970s after a decade-long drug discovery effort overseen by the Walter Reed Army Institute of Research. The drug has recently fallen out of favor for civilian use both in treatment and prevention of malaria, but it remains widely available within the U.S. military where it has historically been preferred owing to its weekly dosing schedule which facilitates command-supervised administration.

The drug is structurally related to a number of similar compounds called quinolines first synthesized in the U.S. in the 1940s and 1950s in collaboration with military researchers. Since discovery these compounds have been linked to a rare neurotoxicity syndrome and in susceptible individuals are known to induce symptoms of severe anxiety, psychosis, memory loss, dissociation and personality change that may mimic some features of PTSD. The underlying cause is a limbic encephalopathy that is dose-dependent and idiosyncratic and which, in its most severe form, may feature the impulsivity observed in PCP or ketamine toxicity. In the presence of such encephalopathy, the drug may also cause microscopic damage to the brainstem resulting in permanent disability including balance problems, subtle visual disorders, and other symptoms that may later mimic or be mistaken for some forms of traumatic brain injury (TBI).

During the drug’s development and testing, and despite these effects being well known among other members of the quinoline class, mefloquine was initially thought to be safe and free of these side effects. At the time, the Food and Drug Administration (FDA) did not require formal neurotoxicity testing and potential brainstem injury was not formally evaluated with careful animal studies.

Mefloquine was tested as an Investigational New Drug among military personnel during the 1980s and possibly late 1970s. It is not clear whether testing among military personnel, who typically underreport mental health symptoms and concerns, may have biased early studies in favor of concluding the drug’s safety. After FDA licensure in 1989, the drug became widely adopted for first-line use within the U.S. military during operations in the Middle East and Somalia in the 1990s. Its use during this period was anecdotally linked to numerous reports of serious side effects including suicide. These concerns were heightened during the early 2000s when reports surfaced of clusters of violence linked to the drug’s use in Iraq and Afghanistan. Later reports of clusters of long-term vertigo led to calls for further careful research. In response to these concerns, Congress was promised further study by DoD, but of the numerous formal investigations undertaken during this period, only a single study of hospitalization risk has yet been published. Promised publications investigating suicide risk and vertigo remain incomplete.

Use of mefloquine among those with pre-existing mental illness or using psychotropic drugs is associated with a significantly increased risk of harm. Such use may result in symptoms of a developing limbic encephalopathy being erroneously attributed to the pre-existing condition, or being masked by the drug, risking the development of more serious neurotoxicity. With rising rates of mental illness and psychotropic drug use among deployed military personnel, in 2007, researchers confirmed that mefloquine had been widely misprescribed to those with mental health conditions or who had been previously prescribed psychotropic medications, including anti-depressants. In response, in February 2009 the U.S. Army sharply restricted the drug’s use. A similar recommendation by DoD Health Affairs followed in September 2009. Both the U.S. Central Command and the U.S. Africa Command have issued similar policies prohibiting the drug’s use as first-line agent, although these are poorly enforced. Recent case reports suggest DoD continues to issue the medication without proper mental health screening and without issuance of the mandatory medication guide and FDA-mandated wallet card describing under which conditions the drug should be discontinued. Additionally, despite hundreds of veterans noting a consistent syndrome resembling PTSD and TBI linked to their use of the drug, there remains no formal DoD or VA referral center dedicated to evaluate the side effects of the drug, and no dedicated research agenda to study the potential long-term effects of mefloquine neurotoxicity.