

## LETTERS TO THE EDITOR

## Measurement of Mefloquine Exposure in Studies of Veterans' Sleep Disorders

Commentary on Creamer et al. Nightmares in United States military personnel with sleep disturbances. *J Clin Sleep Med*. 2018;14(3):419–426.

Remington L. Nevin, MD, MPH, DrPH

The Quinism Foundation, White River Junction, Vermont

Creamer and colleagues recently investigated the prevalence of nightmares in United States military personnel seen at their center for sleep medicine evaluation and described associations of this and related outcomes with deployment history and with various comorbid psychiatric disorders.<sup>1</sup> I am concerned that the authors have failed to measure and control for an important covariate in their analysis, which may have served to confound associations observed in their study.

Mefloquine is a neurotoxic quinoline antimalarial drug that has been widely used for the prevention of malaria during United States military deployments over the past quarter-century.<sup>2</sup> Prior exposure to mefloquine may be a cause of several of the outcome variables observed in their analysis, including nightmares and insomnia. A recent meta-analysis finds that when mefloquine is used for malaria prevention, symptoms of anxiety and depression are each reported by 6%, insomnia is reported by 13%, and symptoms of abnormal dreams and nightmares, described in one study as “often terrifying... with technicolor clarity... vividly remembered days later,”<sup>3</sup> are reported by 14%.<sup>4</sup>

Although previously thought to resolve following discontinuation of the drug, international drug regulators now warn that such symptoms may last years after use.<sup>5</sup> In a recent study, 21% of those reporting nightmares with use of mefloquine reported these continuing for 3 years or longer.<sup>6</sup>

Military authors have noted that that “the significant overlap in symptoms associated with mefloquine toxicity and posttraumatic stress disorder (PTSD) obscures the distinction between these diagnoses,”<sup>7</sup> and that mefloquine use may “confound the diagnosis and management” of PTSD.<sup>8</sup> Consistent with such confounding, a recent study finds that non-combat-deployed personnel with mefloquine exposure had a significant and nearly doubled risk of subsequent PTSD diagnosis, as compared to those who lacked such exposure.<sup>9</sup>

As mefloquine exposure is correlated with deployment, and as mefloquine exposure provides a separate causal pathway for many outcome variables associated with sleep disorders, unmeasured mefloquine exposure may serve as a potentially critical confounder in studies of sleep disorders among deployed military personnel and veterans. Unmeasured mefloquine exposure has been previously identified as a significant concern in the interpretation of recent military studies of PTSD and

emergence delirium.<sup>10–12</sup> Owing to the potential for confounding, researchers conducting studies of sleep disorders among veterans should measure prior symptomatic exposure<sup>13</sup> and control for its effects in future analysis.

## CITATION

Nevin RL. Measurement of mefloquine exposure in studies of veterans' sleep disorders. *J Clin Sleep Med*. 2018;14(7):1273–1274.

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## SUBMISSION & CORRESPONDENCE INFORMATION

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Address correspondence to: Remington L. Nevin, MD, MPH, DrPH, Executive Director, The Quinism Foundation, P.O. Box 145, White River Junction, VT 05001; Email: rnevin@quinism.org

## DISCLOSURE STATEMENT

The author has seen and has approved this manuscript. The author has served as consultant and expert witness in legal cases involving claims of adverse effects from antimalarial drugs.