LETTER TO THE EDITOR

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Dear Editor:

Mefloquine Exposure May Confound Associations and Limit Inference in Military Studies of Posttraumatic Stress Disorder

I read with interest the recent article by Steele and colleagues **(Mil Med 2017; 182(5/6): e1632)**, which examined associations between combat experiences and symptoms of posttraumatic stress disorder (PTSD), as measured among U.S. Navy personnel deployed to Afghanistan between December 2009 and June 2010. The authors modeled associations using logistic regression, and employed statistical methods to identify mediators and moderators in these associations. Based on their findings, the authors speculated that nightmares may partially mediate the relationship between combat experiences and PTSD symptoms.

I am concerned that the authors' findings may be invalid due to their failure to control for a potentially critical confounder in their model, and that this speculated mediation may in fact reflect an unmeasured association.

During the period of the authors' study, certain U.S. Navy personnel deployed to Afghanistan were exposed to mefloquine, an antimalarial drug whose lasting neuropsychiatric effects, including vivid nightmares—described as often of "technicolor clarity"—can readily mimic certain symptoms of PTSD.

U.S. military authors writing for the Centers for Disease Control and Prevention (CDC) have cautioned that mefloquine use may "confound the diagnosis" of PTSD, while others at the Walter Reed Army Institute of Research (WRAIR) where mefloquine was developed, have noted that "the significant overlap in symptoms associated with mefloquine toxicity and PTSD obscures the distinction between these diagnoses". A recent epidemiological study found that non-combat-deployed U.S. military personnel prescribed mefloquine had a significant—and nearly doubled—risk of subsequent diagnosis of PTSD than those prescribed an alternative antimalarial drug atovaquone/proguanil.

Exposure to mefloquine among U.S. Navy personnel may be correlated with certain combat experiences assessed by the Combat Exposures Scale (CES). This exposure creates a separate causal pathway which could directly predict nightmares and certain other PTSD symptoms assessed by the PTSD checklist (PCL). Unmeasured mefloquine exposure may therefore serve as a strong and potentially critical confounder in association studies between combat experiences and PTSD symptoms, and limit inference on mediating and moderating variables.

As few studies of PTSD have assessed current or prior mefloquine exposure, this confounding threatens to become a significant concern in the interpretation of much recent military PTSD literature. Because of the very significant threats to validity that can arise from this confounding, researchers conducting studies of PTSD among those deployed to combat areas should attempt as best as possible to report current and prior mefloquine exposure status among their study subjects, and control for this exposure in analysis.

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