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Contents

Threats to the validity of studies of post-traumatic stress disorder from unmeasured symptomatic exposure to mefloquine

I read with interest the recent study by Stevelink and colleagues[1] that studied the prevalence of various mental health outcomes, including post-traumatic stress disorder (PTSD), among UK military personnel following the conflicts in Iraq and Afghanistan. I am concerned that several of the authors' conclusions may be invalid, owing to a failure to measure and control for an important confounder in their study.

Participants in the authors' study were at risk of exposure to mefloquine, an antimalarial drug widely used by the UK military during the period, particularly during training missions in Africa and during deployments to Afghanistan. Mefloquine is known to cause psychiatric adverse effects, including nightmares, insomnia, depression and anxiety, which can last years after use. Individuals who experience psychiatric adverse effects during continued use of the drug, a condition known as symptomatic exposure, are at risk of these adverse effects becoming chronic. For example, based on a synthesis of recent data, abnormal dreams and nightmares lasting over 3 years after use of mefloquine may affect over 2% of those exposed to the drug.[2]

Various US military authors have cautioned that mefloquine use can 'confound the diagnosis and management of PTSD',[3] and that given 'the overlapping symptoms of post-traumatic stress disorder and mefloquine toxicity, it can be challenging to distinguish between the two diagnoses'.[4] The importance of identifying past mefloquine exposure is further unscored by the addition of criterion H to the PTSD diagnostic criteria in DSM-5, which requires that the disturbance not be the result of the effects of a medication.[5] As the chronic adverse effects of mefloquine may mimic several symptoms of PTSD, including several symptoms assessed using the 17-item National Centre for PTSD Checklist (PCL-C), the authors use of this instrument without distinguishing which symptoms may have been the result of mefloquine risks the adverse effects of the drug having been misattributed to PTSD.

As mefloquine exposure is correlated with deployment, and as symptomatic mefloquine exposure creates a separate causal pathway for the development of several symptoms assessed by the PCL-C, symptomatic mefloquine exposure serves as a classic epidemiological confounder in the authors' study.[2]

In order to avoid potentially fatal threats to validity that result from such confounding, the authors are encouraged to measure symptomatic mefloquine exposure in future studies and to control for these effects during analysis. Our group has introduced the two-question White River Mefloquine Instrument (WRMI-2)[6] for this purpose and encourages the use of this instrument in research and in the clinical evaluation of recent veterans at risk of mefloquine exposure.

Declaration of interest: R.N has been retained as consultant and expert witness in legal cases involving claims of adverse effects from antimalarial drugs, including mefloquine.

References

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6 The Quinism Foundation. The Quinism Foundation Partners with the National Centre for Trauma to Screen U.K. Veterans for Symptomatic Mefloquine Exposure. July 30, 2018. Available at: https://quinism.org/press-releases/the-quinism-foundation-partners-with-the-national-centre-for-trauma-to-screen-u-k-veterans-for-symptomatic-mefloquine-exposure.

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Author's reply

We appreciate the interest Dr Remington Nevin has shown in our article[1] and thank you for giving us the opportunity to respond. Dr Remington Nevin claims that mefloquine exposure is an important confounder that we have failed to control for and that our lack of adjustment for this variable may have invalidated our conclusions. We respectfully disagree.

First, there is no empirical evidence that mefloquine use confounds the association between deployment-related exposures and post-traumatic stress disorder (PTSD), nor that PTSD is a specific side-effect of mefloquine use. Adverse reactions that are reported in the National Institute for Health and Care Excellence guidelines include anxiety, depression, sleep disorders, abnormal dreams, dizziness, headache, vomiting, digestive problems and skin reactions.[2–4] A recent Cochrane review found a low incidence of side-effects among mefloquine users.[3] Further, mefloquine users do not report more frequent serious side-effects than more commonly used antimalarials such as atovaquone-proguanil or doxycycline.[3]

Second, data from the UK's Defence Medical Information Capability Programme indicated that between 1 April 2007 and 31 March 2015, approximately 120 000 UK armed forces personnel were prescribed an antimalarial drug, of which around 17 000 were prescribed mefloquine (14%).[5] When looking specifically at personnel who deployed to Afghanistan between 1 April 2007 and 31 December 2014, only 536 (0.4%) of the 131 000 of personnel who deployed were prescribed mefloquine. A further 12 908 (10%) were prescribed an unknown malarial prophylaxis. The available data relating to both prescription and use, which is determined by service policy,[6] suggest that mefloquine is not the first-choice malarial prophylactic for UK armed forces personnel other than in circumstances where resistance to other medication is a factor. Hence, it is highly unlikely that mefloquine was prescribed to this 10%. Therefore, its infrequent use would mean that it cannot account for any substantial proportion of the PTSD identified in our study.