Written evidence submitted by The Quinism Foundation

1. Executive Summary

a. Mefloquine is a neurotoxic antimalarial drug that has been widely issued to deployed U.K. military personnel for the past quarter century. Although recently deprioritized for use in the U.K. military, mefloquine was previously the “drug of choice” for the U.K. military on deployments to several areas including training missions in Africa.

b. Mefloquine is acknowledged by drug regulators to cause lasting adverse psychiatric effects. Chronic adverse effects that contribute to psychiatric disability are likely to affect significantly more than 1% of those prescribed the drug.

c. Chronic psychiatric symptoms caused by mefloquine poisoning can frequently mimic those of other psychiatric conditions affecting veterans, including posttraumatic stress disorder (PTSD), resulting in a risk of misdiagnosis and confounding.

d. Current mental health statistics, including for PTSD, among U.K. military personnel exposed to mefloquine are likely to overestimate the true incidence and prevalence of these conditions, as a result of misdiagnosis and confounding resulting from adverse psychiatric effects of mefloquine being misattributed to these conditions.

e. The accuracy of mental health statistics among U.K. military personnel has been limited by a failure to accurately document mefloquine exposure among U.K. military personnel; by a failure to accurately document symptoms that occur during such exposure; and by a failure to assess U.K. military personnel for a history of symptomatic exposure to mefloquine during subsequent psychiatric evaluations.

f. The accuracy and validity of mental health research conducted among U.K. military personnel has been similarly affected by a failure to account for the confounding effects of symptomatic mefloquine exposure.

2. The Author

a. Remington Nevin, MD, MPH, DrPH, is executive director of The Quinism Foundation. Dr. Nevin is a consultant physician epidemiologist board certified in Occupational Medicine and Public Health and General Preventive Medicine by the American Board of Preventive Medicine. Dr. Nevin has also earned a graduate certificate in Pharmacoepidemiology and Drug Safety from the Johns Hopkins Bloomberg School of Public Health.

b. The Quinism Foundation promotes and supports education and research on quinism, the family of medical disorders caused by poisoning by quinoline drugs, including the antimalarial drug mefloquine (marketed in the U.K. as Lariam).
c. Dr. Nevin has previously provided evidence to the Defence Committee inquiry, “An Acceptable Risk? The Use of Lariam by Military Personnel”.

d. Dr. Nevin has also provided evidence to the U.S. Senate and the Canadian Parliament on matters related to the mental health effects of mefloquine poisoning among veterans.

e. Dr. Nevin serves as consultant and expert witness in legal cases involving claims of adverse effects from antimalarial drugs, including in legal cases pending in the U.K. related to the use of mefloquine among members of the U.K. armed forces. No specific matters subject to pending litigation are discussed in this evidence.

3. Introduction and Background

a. Mefloquine is a neurotoxic antimalarial drug. Mefloquine was developed by the U.S. military’s Walter Reed Army Institute of Research (WRAIR). The U.S. military has acknowledged that mefloquine is neurotoxic and that this neurotoxicity now limits the drug’s utility as an antimalarial.

b. Mefloquine poisoning can cause a serious and potentially life-threatening medical condition known as neuropsychiatric quinism, or chronic quinoline encephalopathy. This condition has been previously referred to by various terms including mefloquine intoxication syndrome.

c. Psychiatric symptoms of neuropsychiatric quinism can include anxiety, panic, depression, paranoia, delusions, personality change, cognitive dysfunction, and sleep disturbances including abnormal dreams and nightmares. Mefloquine poisoning is associated with a risk of suicidal ideation and completed suicide, as well as violence towards others.

d. Psychiatric symptoms of neuropsychiatric quinism can frequently mimic those of other psychiatric disorders. Military authors writing for the U.S. Centers for Disease Control and Prevention have noted that mefloquine use may “confound the diagnosis and management” of PTSD. Researchers at WRAIR, where mefloquine was developed, have

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warned that “the significant overlap in symptoms associated with mefloquine toxicity and PTSD obscures the distinction between these diagnoses”\(^4\).

e. Neuropsychiatric quinism is frequently predicted by the onset of prodromal symptoms including insomnia, abnormal dreams and nightmares, anxiety and depression, that typically develop during early use of mefloquine\(^5\).

f. The current U.K. Summary of Product Characteristics (SPC) for mefloquine includes a boxed warning that cautions (in boldface, for emphasis)\(^6\):

“Mefloquine may induce psychiatric symptoms such as anxiety disorders, paranoia, depression, hallucinations and psychosis. Psychiatric symptoms such as insomnia, abnormal dreams/nightmares, acute anxiety, depression, restlessness or confusion have to be regarded as prodromal for a more serious event… Cases of suicide, suicidal thoughts and self-endangering behaviour such as attempted suicide… have been reported”.

“Patients on malaria chemoprophylaxis with mefloquine should be informed that if these reactions or changes to their mental state occur during mefloquine use, to stop taking mefloquine and seek medical advice immediately so that mefloquine can be replaced by alternative malaria prevention medication”.

g. A sizeable minority of those prescribed mefloquine for prophylaxis will experience prodromal symptoms of neuropsychiatric quinism that require the drug’s immediate discontinuation in accordance with the manufacturer’s guidance. A recent high-quality meta-analysis finds that symptoms of insomnia occur in 13% of those using mefloquine for proprophylaxis, abnormal dreams and nightmares occur in 14%, anxiety occurs in 6%, and depression occurs in 6%\(^7\).

h. In 2014, the European Medicines Agency (EMA) concluded there was evidence “supporting a causal relationship between mefloquine and the occurrence of long-lasting and even persistent neuropsychiatric effects” and speculated that these were due to “permanent brain damage”. The EMA could not identify risk factors for these effects and

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concluded that “only the advice – to stop taking mefloquine if neuropsychiatric reactions or changes to their mental state occur – can be given as a precautionary measure”.

i. Psychiatric symptoms from use of mefloquine can persist chronically in a significant minority of users for months to years after use of the drug has been discontinued. For example, among those reporting nightmares with use of mefloquine, 21% report these continuing over three years after discontinuing use. As abnormal dreams and nightmares are reported in at least 14% taking mefloquine, it is likely that 21% of these, or over 2% of those taking mefloquine, continue to experience nightmares chronically after use. It is also likely that a significant proportion of those who experience these effects — described in one study as “terrifying nightmares with technicolor clarity, which were vividly remembered days later” — will experience some degree of disability as a result.

j. There is other evidence of a much higher rate of serious and disabling chronic psychiatric adverse effects from mefloquine than has been previously recognized. In one early study of 203 U.S. Marines administered mefloquine, two were hospitalized for serious psychiatric symptoms, and one was later awarded disability benefits by the U.S. Department of Veterans Affairs (VA) for chronic psychiatric symptoms including abnormal dreams and nightmares, anxiety, depression, cognitive dysfunction, and changes in personality, which the VA concluded were caused by use of the drug, and which have persisted for over 20 years.

k. Such available evidence suggests that significantly greater than 1% of those using mefloquine for prevention of malaria will experience a serious psychiatric adverse reaction such as lasting psychiatric disability — a rate at least 100 times higher than the rate of 1 in 10,000 for serious adverse effects long cited by the U.K. MoD.

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11 Ibid.
13 See, for example: U.K. Headquarters Personnel and Training Command. Surgeon General’s Policy Letter 6/97, 1997. This publication states, with respect to mefloquine: “The incidence of serious neuropsychiatric reactions has been assessed at approximately 1 in 10,000 with prophylactic doses. Probably between 0.1% and 1% suffer very unpleasant and temporarily disabling effects.”
l. Although recently deprioritized for use in the U.K. military, mefloquine was previously the “drug of choice” for the U.K. military on deployments to several areas including troop training missions in Africa\textsuperscript{14}, and has been widely used since the early 1990s. Although U.K. MoD statistics suggest that fewer than 20,000 U.K. military personnel have been prescribed mefloquine between 2007 and 2015\textsuperscript{15}, this figure reflects only prescriptions properly documented electronically in the Defence Medical Information Capability Programme (DMICP) system. Recent reports suggest that the DMICP system has been subject to significant problems that have limited its use by prescribing clinicians\textsuperscript{16}, threatening the validity of mefloquine usage statistics produced by the MoD, and suggesting that these statistics may be significant underestimates of true usage.

m. Nonetheless, even if only 20,000 U.K. military personnel have been exposed to mefloquine, given available evidence, this would suggest that at least 200 are suffering disabling or other serious adverse effects from the drug. Given the significant underestimates in U.K. military mefloquine usage statistics, the true number of U.K. veterans suffering from adverse psychiatric effects of mefloquine is likely significantly higher than this.

4. Issues

a. Per the scope of the current inquiry, the committee seeks to examine whether current statistics accurately reflect the level of mental health issues in serving armed forces personnel and veterans, including PTSD. It further seeks to identify challenges in accurately assessing the extent of mental health issues in serving armed forces personnel and veterans. The committee also seeks to identify how the government could improve its understanding of these issues.

b. Unrecognized chronic adverse effects from mefloquine are likely critically affecting the accuracy of statistics for mental health conditions among U.K. military personnel and veterans.

c. Although chronic adverse effects from mefloquine have been acknowledged by international drug regulators, neuropsychiatric quinism, the disorder caused by mefloquine poisoning, is not yet widely understood or recognized by U.K. clinicians, and little to no formal diagnosis of this condition yet occurs.


d. As U.K. clinicians typically do not screen for prior symptomatic mefloquine exposure when conducting psychiatric evaluation, chronic adverse effects from the drug are likely being misattributed to PTSD and to other mental disorders, resulting in overestimates of the prevalence and incidence of these disorders.

e. Consistent with the chronic adverse effects of mefloquine being misattributed to PTSD, a recent epidemiological study of non-combat-deployed U.S. military personnel found that those prescribed mefloquine had a significant and nearly doubled risk of subsequent PTSD diagnosis as those prescribed the alternative antimalarial drug atovaquone/proguanil\(^\text{17}\).

f. As symptomatic exposure to mefloquine may be correlated with combat exposure, and as symptomatic exposure to mefloquine also creates a separate causal pathway that can predict symptoms of PTSD, unmeasured symptomatic mefloquine exposure may serve as a potentially critical confounder between combat exposure and PTSD symptoms. This confounding has been previously identified as a significant concern in the interpretation of recent military PTSD literature\(^\text{18}\), including in research conducted among U.K. military personnel\(^\text{19}\).

5. Recommendations

a. Mental health clinicians in the U.K. should screen for a history of symptomatic exposure to mefloquine among populations at high risk of exposure to the drug, including U.K. military veterans with a history of deployment to training areas in Africa, and on certain combat missions, where mefloquine has been widely employed.

b. Screening for a history of symptomatic mefloquine exposure should include a review of the veteran’s available paper and electronic medical records for evidence of a prescription for mefloquine. If no such records exist, veterans can be asked if they were ever exposed to the drug.

c. Among veterans for whom exposure is confirmed or suspected, they should be asked if they experienced any psychiatric or neurological symptoms during their use of the drug. The onset of these symptoms in relation to drug use, and in relation to potential combat stressors should be documented.

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d. This information should be considered by the evaluating psychiatrist in formulating a differential diagnosis. For example, symptoms of nightmares whose onset clearly precedes exposure to subsequent combat stressors should be considered as potentially indicating an adverse reaction to mefloquine, and potentially calling into question a later diagnosis of PTSD. According to current diagnostic criteria for PTSD in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), a diagnosis of PTSD is excluded if the symptoms can be attributed to the effects of a medication such as mefloquine.

e. Researchers conducting studies of PTSD among military personnel deployed to combat areas must similarly attempt to measure symptomatic mefloquine exposure among their study participants, and to control for its effects in future analyses.

f. The published evidence base should be assessed for scientific conclusions that may be invalid due to the confounding effects of unmeasured mefloquine exposure.

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