WHITE PAPER: Establishing Chronic Quinoline Encephalopathy as an approved research topic area within the Peer-Reviewed Medical Research Program (PRMRP) (DoD-CDMRP)

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BACKGROUND: The use of a particular class of drugs used to combat malaria, antimalarial quinolines (e.g., mefloquine, marketed as Lariam), has been widely recognized in the medical and scientific literature as resulting in both acute and chronic adverse health effects. Concerns by veterans, veterans service organizations (VSOs), advocacy organizations, the media, and Congress led the U.S. Department of Veterans Affairs (VA) to contract with the National Academies of Sciences, Engineering, and Medicine (NASEM) for a limited-scope, ad hoc committee, "*to assess the long-term health effects that might result from the use of antimalarial drugs by adults, in particular mefloquine, for the prophylaxis of malaria*."[1(p.21)] The committee was charged with looking at "long-term health effects" with "special attention" "to possible long-term neurologic effects, long-term psychiatric effects and the potential development of posttraumatic stress disorder (PTSD)."[p.21] The committee was also directed to "consider approaches for identifying short-term, long-term, and persistent adverse health effects of antimalarials."[p.21] While it was directed to "develop findings and conclusions based on its review of the evidence,"[p.21] it was prohibited from reviewing patient reports[p.ix] or making recommendations. [p.21]

On February 25, 2020, the committee publicly released its final report. It observed a "disconnect between the level of concern raised–millions of people have used the drugs, and there are many known concurrent events and case reports of adverse events–and the systematic research that has been conducted, *particularly in areas such as the use of mefloquine and persistent neurological or psychiatric outcomes."*[p.14] The committee found "there is a sharp contrast between the *abundant* amount of literature pertaining to concurrent adverse events that are experienced while a drug is being used or shortly following its cessation and the *dearth* of information, especially high-quality information, pertaining to adverse experiences after the use of that drug has ended."[p.356] *[emphases added].*

While there is a substantial volume of research published in the medical literature showing the long-term health effects of these drugs, the lack of research meeting the committee's consideration criteria was made abundantly clear: While "[t]he committee did not collect original data or perform any secondary data analyses," it, "considered more than 12,000 abstracts and examined more than 3,000 full-text articles and book chapters" but found only 21 epidemiological studies that met the Committee's criteria for consideration – including just 11 on mefloquine.[p.3] The report identified no long-term health outcomes with "sufficient evidence of a causal relationship," only one with "sufficient evidence of an association," none with "limited or suggestive evidence of an association," but thirty (30) with "inadequate or insufficient evidence of an association" needing more research.[pp.8-9] In his *Preface*, the Committee's chair, Professor David Safitz, noted, "the lack of evidence of adverse effects is not evidence of a lack of adverse effects."[p.x]

The committee also noted that "there is a very limited body of research that directly addresses the pathways by which these drugs might result in persistent changes that produce adverse events that may or may not be reversible. In general, while the animal and in vitro studies support different biologic actions of the antimalarials, the published experimental research has not rigorously tested biologic plausibility in its fullest sense with regard to the impact of prolonged treatment (as would occur in prophylaxis) of relevant doses on well-defined behavioral and neurologic endpoint… The pathways by which drug use for a defined period

[1] National Academies of Sciences, Engineering, and Medicine 2020. *Assessment of Long-Term Health Effects of Antimalarial Drugs When Used for Prophylaxis*. Washington, DC: The National Academies Press. https://doi.org/10.17226/25688.

leads to irreversible biological changes that manifest as clinically recognizable symptoms or diagnoses have simply not been pursued."[p358]

Thus, there is a great unmet need not only for epidemiological studies that would meet the committee's consideration criteria, but also for laboratory studies exploring the neurotoxicity and adverse neurophysiological effects of quinoline antimalarials, particularly mefloquine, and for studies aimed at aiding the countless afflicted military servicemembers, veterans, civilians, and those who care for them.

SYMPTOMS of chronic quinoline encephalopathy, or neuropsychiatric quinism – including tinnitus, dizziness, vertigo, paresthesias, visual disturbances, gastroesophageal and intestinal problems, nightmares, insomnia, sleep apnea, anxiety, agoraphobia, paranoia, cognitive dysfunction, depression, personality change, and suicidal thoughts – have been shown in the medical literature to frequently mimic those of particular psychiatric or neurological disorders affecting veterans, including traumatic brain injury (TBI) and post-traumatic stress disorder (PTSD)[2].

RECOMMENDATION: To address the critical research needs identified by NASEM, **Congress should establish chronic quinoline encephalopathy (neuropsychiatric quinism) as a perennial research topic under the Peer-Reviewed Medical Research Program (PRMRP)** within the Department of Defense (DoD) Congressionally Directed Medical Research Program (CDMRP). Furthermore, in response to the needs for further research identified in the NASEM report, the proposed chronic quinoline encephalopathy (neuropsychiatric quinism) PRMRP research topic area **should include the following focus areas:**

1) <u>Defining persistent or latent central nervous system effects</u> of antimalarial quinoline neurotoxicity, particularly mefloquine. In its report, the NASEM Committee noted that *in vitro* studies "provide evidence for potential actions of mefloquine on neurons," and that mefloquine causes "mild neurodegeneration, as reflected in silver staining in rat gracile, cuneate, and solitary tract [i.e. brainstem] nuclei. Behavioral and histologic abnormalities increased as doses exceeded the pharmacologic range". [p.141] However, the NASEM also noted that "[f]rom the perspective of biologic plausibility, the mechanistic links between antimalarial drugs and persistent or latent adverse outcomes have yet to be systematically and definitively explored through experimental studies, and the current literature in that area is not strong." [p.141] ***This focus area should aim to define potential mechanistic links to persistent or latent neurological and psychiatric effects from mefloquine*** (e.g., permanent dizziness and vertigo from mefloquine-induced neuronal dysfunction in the brainstem vestibular nuclei). It should support high-quality *in vivo* and *in vitro* experimental studies to explore the extent of antimalarial quinoline and particularly mefloquine-induced histologic abnormalities within the brainstem and limbic system.

2) <u>Defining adverse neurophysiological effects</u> of antimalarial quinolines, particularly mefloquine. The NASEM report noted that "[m]efloquine is an inhibitor of connexin 36 (Cx36) and connexin 50 (Cx50), which are gap junction proteins responsible for rapid, non-synaptic electrical coupling in neurons and other cells (enabling alterations of cellular excitation without actions at the membrane). Of particular relevance, Cx36 is present in the nervous system and has been implicated in numerous neuronal signaling processes, some of which are relevant to psychiatric or neurologic diseases (e.g.,

[2] See, for example: Ritchie EC, Block J, Nevin RL. Psychiatric Side Effects of Mefloquine: Applications to Forensic Psychiatry. *Journal of the American Academy of Psychiatry and the Law*. 2013;41(June):224-235; Nevin RL. Neuropsychiatric Quinism: Chronic Encephalopathy Caused by Poisoning by Mefloquine and Related Quinoline Drugs. In: Ritchie EC, Llorente MD, eds. *Veteran Psychiatry in the US*. Cham: Springer International Publishing; 2019:315-331; and Nevin RL. Mefloquine and Posttraumatic Stress Disorder. In: Ritchie EC, ed. *Textbook of Military Medicine. Forensic and Ethical Issues in Military Behavioral Health.* Washington, DC: Borden Institute; 2015:277-296.

epilepsy, depression)[3]. The inhibition of the gap junction signaling has led to the use of mefloquine as a pharmacologic tool in studies exploring the biologic actions of gap junctions[4]. For example, mefloquine administration in rats can impair the processing of contextual fear, impairing retrieval and enhancing extinction of freezing responses to the fearful context via inhibition of connexins[5] (suggesting a role for connexins (and perhaps mefloquine) in the modulation of emotional memory processing." [p.142] ***This focus area should aim to further define potential mechanistic links to adverse neurological and psychiatric effects from mefloquine*** (e.g., anxiety from mefloquine-induced neuronal or glial gap junction blockade in the limbic system).

3) <u>Disentangling comorbid neuropsychiatric diagnoses</u> confounded by antimalarial quinoline toxicity, particularly mefloquine. The NASEM report concluded, "Current evidence suggests ***further study of such an association*** ["between the use of mefloquine for malaria prophylaxis and persistent or latent psychiatric effects, including PTSD"] ***is warranted***, given the evidence regarding biologic plausibility, adverse events associated with concurrent use, or data from the existing epidemiologic studies."[p.155] In particular, the NASEM committee noted that "[s]ervice-related characteristics may act as confounders when assessing the association between antimalarial use and psychiatric outcomes".[p.79] [*emphasis added*] The NASEM committee further noted the potential for mefloquine exposure to confound diagnosis of PTSD, and emphasized that for a diagnosis of PTSD to be valid, "as required by the DSM diagnostic formulation… subsequent symptom clusters (i.e., intrusion, avoidance, cognitive or emotional disturbance, or hyperarousal) must be experienced in relation to the traumatic event, and an exclusionary criterion is that the symptoms may not be due to medication [e.g. mefloquine]. Because many studies do not link symptoms to an identified traumatic event, it is often difficult, if not impossible, to ascertain whether symptoms that are reported in the evaluated literature are the result of a medication-related experience, some other trauma, both, or neither, which lends uncertainty to the meaning of these outcomes when associations are found in populations of interest."[p.77] ***This focus area should aim to define the extent and timing of the use of antimalarial quinolines, particularly mefloquine, in relation to traumatic events among servicemembers and veterans later diagnosed with PTSD or TBI*** – particularly the occurrence of prodromal psychiatric symptoms such as nightmares, insomnia, anxiety, depression, restlessness, and confusion during use of mefloquine (a condition known as symptomatic exposure)[6].

4) <u>Conducting high-quality epidemiological studies</u> related to persistent and latent health effects of antimalarial quinolines, particularly mefloquine. For an epidemiologic study (observational studies and clinical trials) that had been published in the peer-reviewed literature to be considered by the NASEM committee, it had to: 1) have the drugs used in a prophylactic manner (not for treatment of active cases of malaria or for another disease or condition); 2) report on the presence or absence of adverse events or effects or other health outcome; (3) have a comparison group; and (4) use adult populations (aged 16 years and older). Furthermore, there had to be empirical information about the adverse event (or indicate a lack of such an event) that began or persisted at least 28 days after the cessation (final dose)

[3] Cruikshank SJ, Hopperstad M, Younger M, Connors BW, Spray DC, Srinivas M. Potent block of Cx36 and Cx50 gap junction channels by mefloquine. *Proceedings of the National Academy of Sciences of the United States of America*. 2004;101(33):12364-12369.

[4] *Ibid.*

[5] Bissiere S, Zelikowsky M, Ponnusamy R, Jacobs NS, Blair HT, Fanselow MS. Electrical synapses control hippocampal contributions to fear learning and memory. *Science*. 2011;331(6013):87-91.

[6] See, for example: Nevin RL. Symptomatic Mefloquine Exposure as a Common Data Element in Studies of Military-Related Post Traumatic Stress Disorder. *Military medicine*. October 2019:pii: usz34; and Nevin RL. Screening for Symptomatic Mefloquine Exposure Among Veterans with Chronic Psychiatric Symptoms. *Federal Practitioner*. 2017;34(3):12-14. http://www.mdedge.com/sites/default/files/fedprac/0317fp_nevin.pdf.

of the drug of interest. In a chapter titled *Improving the Quality of Research on the Long-Term Health Effects of Antimalarial Drugs,* the committee noted the importance of epidemiological study designs that "allow for the discovery of symptoms of diagnoses that covary. For example, if certain symptoms or diagnoses occur together in the same patients, there may be reason to consider a syndrome of 'neuropsychiatric' symptoms that co-occur, rather than looking individually at separate neurologic or psychiatric experiences."[p.373] The committee also noted that a "challenge when studying adverse events of drugs is that the occurrence of adverse events [e.g. prodromal psychiatric symptoms such as nightmares, insomnia, anxiety, depression, restlessness, and confusion during use of mefloquine (i.e., symptomatic exposure)] may cause an individual to decide to modify the dose, or even stop the drug completely, without consulting a health professional.[p.361] ***This focus area should aim to fund epidemiological studies meeting the NASEM Committee's criteria relative to persistent and latent health effects of antimalarial quinolines, particularly mefloquine*** – to include valid assessment of symptomatic quinoline exposure and particularly symptomatic mefloquine exposure, and subsequent covarying symptoms or diagnoses consistent with the presentation of chronic quinoline encephalopathy[7].

5) <u>Developing effective treatments</u> for chronic quinoline encephalopathy. Had the committee been directed or allowed to review the medical records of affected patients, the unmet clinical needs of these individuals would have likely been readily apparent. ***This focus area should aim to develop treatable targets and treatments for patients with* chronic quinoline encephalopathy *– including those diagnosed with PTSD or TBI – to improve their health and lives*.**

RELEVANT FUNDING HISTORY: "Neurotoxicity of mefloquine" was included as a PRMRP topic area fifteen years ago and for only one year (FY 2006).[8] DoD has provided other limited funding for toxicity-relevant research, including funding by the Military Infectious Disease Research Program (MIDRP) for a project entitled, Evaluation of Multiple Potential Pharmacogenomic Risk Factors for Chronic Mefloquine Neurotoxicity [i.e. chronic quinoline encephalopathy] Through the Establishment of a Drug Safety Registry.[9]

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[7] See, for example: Nevin RL, Leoutsakos J-M. Identification of a Syndrome Class of Neuropsychiatric Adverse Reactions to Mefloquine from Latent Class Modeling of FDA Adverse Event Reporting System Data. *Drugs in R&D*. 2017;17(1):199-210.
[8] Peer Reviewed Medical, *FY06 Topic Areas*: https://cdmrp.army.mil/prmrp/topicareas/topicareas06.
[9] U.S. Army Medical Research and Materiel Command. *Congressionally Directed Medical Research Programs. 2017 Annual Report.* https://cdmrp.army.mil/pubs/annreports/2017annrep/2017annreport.pdf