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July 31, 2018

Foreign Affairs, Defence and Trade Committee
Department of the Senate
PO Box 6100
Parliament House
Canberra, Australian Capital Territory 2600

Sent electronically

Re: Use of the Quinoline Anti-Malarial Drugs Mefloquine and Tafenoquine in the Australian Defence Force

Dear Committee Members,

The Quinism Foundation is pleased to submit the enclosed report for consideration by the Foreign Affairs, Defence and Trade References Committee in their inquiry on the use of the quinoline anti-malarial drugs mefloquine and tafenoquine in the Australian Defence Force (ADF).

This report focuses on the following three terms of reference:

- a comparison of international evidence/literature available on the impact of quinoline anti-malarials;
- the current and past policies and practices for prescribing quinoline anti-malarial drugs to ADF personnel, and identifying and reporting adverse drug reactions from quinoline anti-malarial drugs among ADF personnel; and
- how other governments [the United States] have responded to claims regarding quinoline anti-malarials

Our foundation, on careful consideration, believes that a Royal Commission is needed to fully investigate several issues related to these terms of reference, particularly past policies and practices for prescribing quinoline anti-malarial drugs to ADF personnel.

We thank you in advance for your careful attention to the issues in this report, the text of which, in part, has been modified from several of my publications submitted for publication elsewhere. I would be pleased to address any questions the committee may have in a further written report, and, on suitable arrangement, to appear as a witness at a future public hearing, as the committee may deem appropriate.

Sincerely,

Remington Nevin, MD, MPH, DrPH
Executive Director, The Quinism Foundation

Enclosure: as described

Report of The Quinism Foundation Submitted to the Australian Senate Foreign Affairs, Defence and Trade References Committee's Inquiry into the Use of the Quinoline Anti-Malarial Drugs Mefloquine and Tafenoquine in the Australian Defence Force (ADF)

1. The Quinism Foundation

The Quinism Foundation is a U.S. nonprofit charitable organization established January 1, 2018 in White River Junction, Vermont. The Quinism Foundation promotes and supports education and research on the family of medical disorders caused by poisoning by quinoline drugs.

2. Qualifications of the Author

Dr. Remington Nevin earned a BSc (Honors) in Theoretical Physiology from the University of Toronto, Canada; an MD from the Uniformed Services University of the Health Sciences, Bethesda, Maryland, where he was awarded the Captain Richard R. Hooper Award in Preventive Medicine; and an MPH, DrPH, and certificate in Pharmacoepidemiology and Drug Safety from the Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, where he was elected an Alumni Inductee of the Delta Omega Honor Society, Alpha Chapter, and was later recognized with an Outstanding Recent Graduate award. Dr. Nevin attended residency training in Preventive Medicine at the Walter Reed Army Institute of Research where he was awarded the George Miller Sternberg Award in Preventive Medicine. Dr. Nevin also attended additional postdoctoral fellowship training in Occupational and Environmental Medicine at the Johns Hopkins Bloomberg School of Public Health.

Dr. Nevin is licensed to practice medicine in the U.S. states of New York, Maryland, and Vermont, and is board certified in Occupational Medicine and Public Health and General Preventive Medicine by the American Board of Preventive Medicine. He is also Certified in Public Health by the U.S. National Board of Public Health Examiners. Dr. Nevin served a 14-year career as a Preventive Medicine Officer in the U.S. military that included overseas service in malaria-endemic areas in Afghanistan and Africa. He has authored over 80 scientific and medical publications, including over 30 on various topics on drug safety related to mefloquine and related quinoline drugs. He is presently a consulting physician epidemiologist in private practice in White River Junction, Vermont, where he serves as executive director of The Quinism Foundation.

3. International Evidence/Literature Available on the Impact of Quinoline Anti-Malarials

Both mefloquine and tafenoquine are members of a neurotoxic drug class known as quinolines. Tafenoquine is a recently-developed 8-aminoquinoline, whereas mefloquine is a 4-methanolquinoline. Evidence increasingly points to central nervous system (CNS) neurotoxicity as a class effect common to all members of the quinoline class¹. This section of our report will discuss evidence of the CNS neurotoxicity of tafenoquine and mefloquine and will provide evidence of the causal association of this property with acute and chronic adverse effects and with risk of permanent disability. This submission will then discuss the likely epidemiology of these effects, and their association with other deployment-related conditions, including post-traumatic stress disorder (PTSD) and traumatic brain injury (TBI).

3.1. Evidence of Tafenoquine CNS Neurotoxicity

During a large-scale U.S. World War II-era anti-malarial drug development program², 8-aminoquinolines were the subject of significant neurohistopathological testing in animal models, particularly in rhesus monkey, during which time the drugs were found to be uniformly neurotoxic. A leading researcher involved in this testing noted "all of nearly one hundred and forty 8-aminoquinolines examined in this laboratory... produce rather remarkable and highly specific lesions in the central nervous system"³.

Of the World War II-era 8-aminoquinolines for which published data are available, all have been determined to cause injury to microscopic focal areas of the brain and brainstem, the localization of which generally reflects the signs and symptoms observed clinically with use of the drugs.

In contrast to the extensive published evidence of neurohistopathological testing conducted during the World War II-era drug development program on 8-aminoquinolines then under development, no publicly-available data are available to suggest that tafenoquine, developed over the last 30 years by the U.S. military's Walter Reed Army Institute of Research (WRAIR), has ever been suitably tested preclinically for neurotoxicity in rhesus monkey or in a comparable primate model. In contrast, available published data on the neurotoxicity of tafenoquine *in vivo* is limited to that collected in a rat model — a model which has been well-described in the literature as being inadequate to identify evidence of clinically-significant CNS neurotoxicity in other members of the class⁴.

For example, although tafenoquine has been administered at various doses to rhesus monkey during preclinical testing for effectiveness⁵⁻⁷, no neurohistopathological data are publicly available from these studies. The Australian Defence Force Malaria and Infectious Disease Institute, previously the Australian Army Malaria Institute (AAMI), has noted in response to a Freedom of Information Act request seeking information “related to tafenoquine neurotoxicity testing on monkeys by AAMI or affiliated organizations”, that “no neurotoxicity testing has been performed on primates” at AAMI⁸.

Similarly, a Freedom of Information Act request for information “produced or reviewed by the U.S. Army Medical Research and Materiel Command and subordinate activities, to include WRAIR, related to research on the neurotoxicity of the experimental antimalarial drug tafenoquine” reveals no documents related to neurohistopathological testing of tafenoquine on rhesus monkeys. Instead, this request resulted in only a single research poster, co-authored by staff at WRAIR, describing the results of *in vitro* neurotoxicity testing of tafenoquine in cultured rat neurons, which concluded “[t]afenoquine (IC 50 =12.1 µM) is the only antimalarial more toxic than [m]efloquine (IC 50 =20 .1 µM) as indicated by the relative IC 50 values⁹. These results were presented at a national research meeting in 2009¹⁰, but were subsequently not published, and were not cited in a recent paper¹¹ — featuring preclinical data which was strangely collected in a rat model only after extensive clinical testing of tafenoquine had already been performed — in which tafenoquine was concluded, without published photographic neurohistopathological evidence, to not be neurotoxic in a rat model. Of note, this paper made reference to results of neurohistopathological examination only of the rat gracile nucleus, an area previously shown to be particularly susceptible to neurotoxicity from the related 4-methanolquinoline mefloquine¹², but did not specifically comment on whether careful examination was made of the mesencephalic V nucleus — the area shown in the uncited World War II-era literature to be most susceptible in the rat model to neurotoxicity from the structurally-related 8-aminoquinoline plasmocid⁴.

3.2. Evidence of Mefloquine CNS Neurotoxicity

Mefloquine is believed by international drug regulators and by the U.S. military to be neurotoxic. For example, in a 2014 cooperative research and development agreement between the U.S. military and 60 Degrees Pharmaceuticals, a sponsor of tafenoquine's commercial development, it was acknowledged that mefloquine “is no longer recommended for use due to neurotoxicity”⁹. Similarly, drug regulators in Europe, on reviewing accumulated pharmacovigilance data, have 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”¹³.

The neurotoxicity of mefloquine was first reported in papers published more than three decades after the drug's reported synthesis¹⁴, following experiments in cultured rat neuroblastoma and embryonic rat neuron cell lines¹⁵ over a range of neurophysiologically plausible concentrations¹⁶. In subsequent years, confirmatory evidence of the drug's neurotoxicity was also obtained^{17–19}.

In direct histopathological testing in a rat model, high dose mefloquine induced neuronal degeneration in the nucleus gracilis, nucleus cuneatus, and solitary tract¹², and was accompanied by "anxiousness/hyperactivity" and functional changes in motor activity. Study authors noted that the brainstem injury induced by mefloquine was "permanent in nature"¹². Independent authors subsequently demonstrated mefloquine neurotoxicity in rat cortical neurons^{20,21} and in human neuronal cell lines^{22,23}.

3.3. Clinical Features of Quinoline Neurotoxicity

The Quinism Foundation has proposed the term chronic quinoline encephalopathy, otherwise known as neuropsychiatric quinism, to define the clinical disorder caused by quinoline CNS neurotoxicity. The clinical features of neuropsychiatric quinism reflect the localization of observed neurotoxic injury across the broader quinoline class¹, with chronic dysfunction in affected areas of the brain and brainstem providing the most parsimonious explanation for the pattern of observed signs and symptoms from the disorder¹.

Auditory disturbances associated with neuropsychiatric quinism, including hyperacusis and tinnitus^{24,25}, are consistent with dysfunction of the cochlear, superior olivary, and facial nuclei, and of the inferior colliculus. Visual disturbances including photophobia, binocular dysfunction, and difficulties in focusing, convergence, and accommodation^{26–29}, are similarly consistent with dysfunction in the oculogyric and Edinger-Westphal nuclei. Similarly, symptoms of nystagmus, dizziness and vertigo^{30–32} are consistent with dysfunction in the vestibular nuclei. Related complaints of disequilibrium and unsteady gait^{33,34} can reflect these effects possibly worsened by loss of distal proprioception, consistent with dysfunction in the dorsal columns and gracile and cuneate nuclei. Paresthesias and dysesthesias, frequently attributed to peripheral causes, are similarly consistent with dysfunction in these areas and in other sensory nuclei. Movement disorders, such as ataxia and extrapyramidal syndrome^{35–37}, are also consistent with such dysfunction, and with related dysfunction in the globus pallidus, inferior olivary, red, and lateral reticular nuclei. Similarly, a propensity towards seizures in neuropsychiatric quinism^{38–41} is consistent with a broader dysfunction and the creation of seizure foci. Headaches and migraine, a common finding in various neurotoxicity syndromes, are also reported. Dysautonomia has also been reported in neuropsychiatric quinism, marked by lasting orthostatic hypotension, and sexual dysfunction including erectile and ejaculatory dysfunction⁴². These and other complaints, such as altered thermal regulation, are broadly consistent with dysfunction in various areas of the brainstem, including the paraventricular, supraoptic, and anterior hypothalamic nuclei, while related complaints of neuroendocrine abnormalities are consistent with dysfunction in adjacent areas.

An interesting manifestation of neuropsychiatric quinism is its effects on the gastrointestinal system. In human cases, lasting gastrointestinal complaints, including often severe abdominal pain and tenderness^{29,43,44}, often manifest only several days after dosing⁴² and remain persistent, consistent with dysfunction of the dorsal motor horn of the vagus. Common related complaints, including nausea, emesis, and diarrhea, are consistent with such dysfunction, and to dysfunction in related brainstem chemoreceptor trigger areas. Neuropsychiatric quinism is also associated with the interesting manifestation of both central and obstructive sleep apnea, the latter of which is consistent with impaired innervation of the genioglossal muscle from dysfunction of the hypoglossal nucleus^{45–47}. Similarly, complaints of impaired swallowing²⁶ are consistent with such dysfunction, and with impaired innervation of the esophagus, resulting from dysfunction in the nucleus ambiguus and the dorsal motor horn of the vagus.

While less understood, the diverse psychiatric effects seen in neuropsychiatric quinism plausibly reflect dysfunction in the hippocampus, and in diverse other regions of the brain known to be affected by quinoline neurotoxicity, including the substantia nigra, habenular and pulvinar nuclei, and the medial dorsal nucleus. As with the association of neuropsychiatric quinism with seizure, these effects may also affect to some degree the onset of an acquired temporal lobe epilepsy consistent with the creation of seizure foci⁴¹.

Case reports of poisoning by quinoline drugs are consistent with encephalopathy of the limbic system, with symptoms of anxiety, depression, mania, irritability, paranoia, personality change, psychosis, and cognitive dysfunction⁴⁸. Neuropsychiatric quinism is also associated with a risk of violent behavior^{49–51}, and consistent with its association with psychosis and other symptoms of mental illness, with an a risk of self-injurious behavior, suicidal ideation, and completed suicide^{51–53}.

Symptoms of anxiety seen in cases of neuropsychiatric quinism can include a sense of apprehension, unease, or a sense of impending doom or death, panic, and fear and various phobias, including agoraphobia. Symptoms of depression can include tearfulness, sadness, fatigue, malaise and lethargy, and a sense of helplessness, pessimism, or hopelessness. Symptoms of mania can include emotional lability, euphoria, expansiveness, flight of ideas, inattention, disinhibition, inappropriate behavior, and hypersexuality and occasional paraphilia^{48,54,55}.

Neuropsychiatric quinism can also include symptoms of irritability, and in some cases can include symptoms of aggression, anger, and often extreme rage. Those suffering from neuropsychiatric quinism may also suffer from paranoia. Personality change, often with paranoid features, is a common feature of the disorder, with persecutory delusions, magical thinking, and hyper-religious thoughts not uncommonly reported. Other symptoms of psychosis can include auditory, olfactory, and visual hallucinations, often featuring zoopsia, and often with some degree of preserved insight. In certain cases, neuropsychiatric quinism may include delusional misidentification and dissociative symptoms, including derealization and depersonalization^{48,54,55}.

Symptoms of cognitive dysfunction in neuropsychiatric quinism are diverse and include temporo-spatial disorientation, disturbances in attention and concentration, including impairment of short-term and working memory, problems with word-finding, and impairment of explicit memory, including anterograde and retrograde amnesia. In acute cases, dysfunction can progress to delirium or can mimic delirium with consciousness preserved^{48,54,55}.

These diverse neuropsychiatric effects may be preceded by prodromal symptoms such as abnormal dreaming or restlessness and often severe insomnia, which herald an idiosyncratic susceptibility to quinoline toxicity at the lower doses used in prophylaxis of parasitic disease, such as the weekly use of mefloquine for prevention of malaria⁴⁸. The vivid dreams associated with the prodrome of neuropsychiatric quinism are occasionally associated with parasomnias, such as sleep paralysis, and hypnopompic and hypnagogic hallucinations^{48,56}, and have been described as “awakening dreams which at times were of a frightening and nightmare quality”⁵⁷, and “terrifying nightmares with often technicolor clarity — often remembered days later”⁵⁸.

3.4. Epidemiology of Neuropsychiatric Quinism

Those suffering from neuropsychiatric quinism may appear to be suffering from various neurologic disorders, as well as from a wide range of psychiatric disorders listed in the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5). These span the diagnostic nosology, particularly as various anxiety disorders, depressive disorders, manic and bipolar disorders, personality disorders, and conversion and factitious disorders.

As a newly described disorder, previously mistaken for other conditions, the epidemiology of neuropsychiatric quinism remains poorly defined. For example, although efforts have been made to ascertain the burden of various psychiatric and neurologic disorders to which symptoms of quinoline exposure have been attributed^{59,60}, such effects have failed to define the epidemiology of neuropsychiatric quinism as a distinct disorder, and have themselves been hampered by methodological limitations including inadequate power, misclassification, and bias⁶¹.

Based on limited studies, certain chronic effects consistent with those of neuropsychiatric quinism are likely to affect considerably greater than 1% of those exposed to mefloquine. For example, among those reporting nightmares with use of mefloquine, 21% report these continuing over three years after discontinuing use⁵⁶. As abnormal dreams and nightmares are reported in at least 14% taking mefloquine⁶², it is likely that 21% of these, or over 2% of those taking mefloquine, continue to experience nightmares chronically after use.

As the quinolines have been ubiquitous exposures among certain populations, including among military personnel, neuropsychiatric quinism is likely to be the cause of a significant burden of disease in these groups.

3.5. Neuropsychiatric Quinism, TBI, and PTSD

One factor previously limiting recognition of neuropsychiatric quinism as a distinct disorder is that, particularly in recent military settings where confounding exposures such as traumatic stressors and blast are common, the symptoms of neuropsychiatric quinism are likely to have been misattributed to TBI and to PTSD⁶³.

As a chronic encephalopathy, and therefore, an acquired form of brain injury, many of the neurological symptoms of neuropsychiatric quinism may seem indistinguishable from those of TBI, particularly tinnitus, dizziness, vertigo, visual disturbance, and headache. Similarly, psychiatric symptoms such as cognitive dysfunction, irritability, personality change, and insomnia, are common to both TBI and to neuropsychiatric quinism. More specific combinations of psychiatric symptoms of neuropsychiatric quinism, including nightmares, insomnia, anxiety, depression, irritability, aggression, panic, and dissociation, may similarly readily mimic those of PTSD.

Although a strict application of DSM-5 PTSD diagnostic criterion H — which requires the condition not be due to the physiological effects of a substance or medication — will formally exclude the diagnosis of PTSD in cases of neuropsychiatric quinism, this diagnostic exclusion did not apply to diagnostic criteria under earlier versions of the DSM⁶³. U.S. military authors have cautioned that mefloquine use may “confound the diagnosis” of PTSD⁶⁴, and that “the significant overlap in symptoms associated with mefloquine toxicity and PTSD obscures the distinction between these diagnoses”³⁴. There is evidence that this has resulted in PTSD being diagnosed disproportionately in those exposed to mefloquine. For example, in one military study of non-combat-deployed personnel, exposure to mefloquine resulted in a near-doubling of the rate of PTSD diagnosis as compared to those who lacked such exposure⁵⁹. Similarly, the high number of cases of PTSD observed among members of the ADF exposed to tafenoquine suggests a similar possibility of misdiagnosis the effects of exposure to this drug.

4. Current and Past Policies and Practices for Prescribing Quinoline Anti-Malarial Drugs to ADF Personnel, and Identifying and Reporting Adverse Drug Reactions from Quinoline Anti-Malarial Drugs Among ADF Personnel

Most use of mefloquine and tafenoquine within the ADF has been within the context of clinical trials overseen by the AAMI, during peacekeeping operations in Timor-Leste (formerly known as East Timor) during the period 2000–2002^{65,66}. This section of our report will argue that when assessed

against the applicable contemporary ethical standards for clinical trials, the AAMI's 2000–2002 trials in Timor-Leste that used ADF personnel as subjects were unethical. Evidence suggests that subjects were coerced into participating and were provided with misleading or inaccurate information on the risks associated with participation. Foreseeable risks were excessive in comparison to the likely benefit of the studies, and the rights, safety and well-being of the subjects were compromised through their conduct. The ADF has thus far failed to meet its obligation to identify and provide proper medical care for subjects who may be experiencing chronic adverse effects from the drugs administered during the trials.

4.1. The Timor-Leste Mefloquine Clinical Trials

The AAMI was the successor to an evolving series of Australian military malaria research organizations first established during the second world war⁶⁷. Scientists later affiliated with AAMI participated in early WRAIR-sponsored testing of mefloquine on prisoners in the 1970s⁶⁸. When mefloquine was approved in Australia in 1993 by the Therapeutic Goods Administration (TGA)⁶⁹, the antibiotic drug doxycycline had long been the first-line antimalarial within the ADF — its use for this purpose having been pioneered by the AAMI⁷⁰. After its approval, owing to concerns of neurological effects, mefloquine was deemed a second-line drug for malaria prevention within the ADF, with doxycycline remaining the preferred drug⁶⁷.

Although an earlier AAMI study in Bougainville (Papua New Guinea) had found atovaquone-proguanil to be safe and effective — and although it subsequently replaced mefloquine as the second line antimalarial in 2006 — AAMI staff had initially recommended against this drug's adoption by the ADF on the grounds of cost⁷¹. AAMI researchers would subsequently cite numerous cases of malaria during military operations in the late 1990s that were 'believed to have resulted from poor compliance' with the recommended lower-cost doxycycline regimen as a rationale for trialing alternatives to atovaquone-proguanil⁶⁶. The large-scale peacekeeping deployment to Timor-Leste commencing in 1999 provided an opportunity for AAMI to conduct these trials among ADF military personnel.

Two trials involving mefloquine were conducted by AAMI during this peacekeeping deployment in cooperation with WRAIR. The first was a phase III randomized active comparator double-blinded trial of the safety, tolerability and efficacy of prophylaxis with the experimental quinoline drug tafenoquine in comparison to mefloquine. Although the ADF would later note "[i]t was the issue of drug resistance and the need to explore alternative treatments that lay behind the tafenoquine trial"⁷², the published report on this trial (the 'mefloquine/tafenoquine' trial) did not mention resistance as a motivation, but in contrast noted that "mefloquine, doxycycline, and atovaquone-proguanil are ... highly effective in preventing malaria but have shortcomings that limit their effectiveness [emphasis added], such as adverse effects, expense, and the difficulty of monitoring daily compliance within deployed military populations"⁶⁵.

Conducted from October 2000 to April 2001, the mefloquine/tafenoquine trial involved the administration of tafenoquine to 492 subjects and mefloquine to 162 subjects, where it was used in place of doxycycline as the active comparator, presumably to facilitate blinding owing to the complicated dosing schedule of the study drug. Consequently, rather than being administered on the licensed weekly basis, an initial off-label loading dose of mefloquine was used, in which 250 mg mefloquine was administered on each of the first three days of the trial, followed by 250 mg mefloquine weekly⁶⁵.

The second trial (the 'mefloquine/doxycycline' trial) was an open-label trial to describe the tolerability of mefloquine prophylaxis in comparison to doxycycline, motivated by the rationale that 'there are limited data on the tolerability of mefloquine for long-term prophylaxis in military personnel'⁶⁶. This trial, which was conducted from April 2001 to May 2002, involved the administration of 250 mg

mefloquine weekly to 1,157 subjects. As with the mefloquine/tafenoquine trial, an initial off-label loading dose of mefloquine was used, in which 250 mg mefloquine was administered on every other day for the first three days of the trial. Both trials were approved by the Australian Defence Medical Ethics Committee (ADMEC), the predecessor to the Australian Defence Human Research Ethics Committee (ADHREC)^{65,66}.

Two contemporary documents had established standards for the ethical conduct of such clinical trials. The first was the National Health and Medical Research Council's (NHMRC) National Statement on Ethical Conduct in Research Involving Humans⁷³. The second was the TGA Note for Guidance on Good Clinical Practice (GCP), which was "an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects"⁷⁴. The GCP specifically described "members of the armed forces" as vulnerable subjects "whose willingness to volunteer in a clinical trial may be unduly influenced by the expectation, whether justified or not, of benefits associated with participation, or of a retaliatory response from senior members of a hierarchy in case of refusal to participate"⁷⁴.

These documents provide the basis for the critical analysis of the ethics of the trials. Specific ethical requirements described in the documents include obtaining informed consent; the weighing of foreseeable risks against anticipated benefits; the prioritizing of the rights, safety and well-being of the subjects; and the provision of appropriate medical care to subjects for adverse events during and following the trials^{73,74}.

4.2. Evidence of Coercion and Inadequate Informed Consent

Informed consent "provides assurance that patients and others are neither deceived nor coerced"⁷⁵. The National Statement notes that "the ethical and legal requirements of consent have two aspects: the provision of information and the capacity to make a voluntary choice"⁷³. Although both trial reports in question state that the subjects provided voluntary, informed consent^{65,66}, there is evidence that subjects were coerced to participate in at least one trial, and that in both trials they were provided by study investigators with inadequate information regarding the risks of participation.

Specifically, media sources have reported that the commanding officer (CO) of the unit involved in mefloquine/tafenoquine trial directed his subordinates to participate under the threat of being excluded from the deployment to Timor-Leste. One soldier, speaking of mefloquine as the study drug, informed the media, "We were in no doubt that if we didn't take the Lariam [mefloquine] we would not be going to East Timor"⁷⁶. More recently, it was reported that a senior participant alleged that the commanding officer informed his subordinates that refusal to take part in the trial "means you will not deploy"⁷². Although the CO of this unit has maintained that he did not order anyone to take part in the trial, nor threaten non-deployment, he conceded that soldiers, when "handed a drug and told to take it, they do just that", and that consequently, "I find it unreasonable for Defence to ask soldiers to volunteer for a malaria drug trial. Soldiers do not volunteer for anything"⁷⁷.

Notwithstanding any potential coercion in the mefloquine/tafenoquine trial, the information provided to subjects in both trials relating to the risk of neuropsychiatric adverse effects from mefloquine was incomplete and misleading. In 2004, over two hundred of the subjects involved in the trials initiated a legal class action against the ADF and the drug manufacturer on the basis that they did not provide informed consent and suffered chronic neuropsychiatric adverse effects as a result of their use of a study drug^{72,76,78}.

In the mefloquine/tafenoquine trial, subjects were advised only that "mefloquine has also rarely (about 1:10,000) been associated with depression and anxiety", and were not informed of the known increased risk of adverse effects from use of an off-label loading dose⁵⁸. Although the source of the "about 1:10,000" figure was not cited, it coincided with a decade-old estimate by the World Health

Organization (WHO) and the manufacturer for “serious events” that was “crudely calculated” from a series of assumptions early in the drug’s use⁷⁹.

In contrast, more recent results that were then available from a randomized blinded trial, conducted previously among U.S. military personnel, had found that 43% of 157 subjects taking mefloquine weekly, and 59% of 46 taking mefloquine weekly following a three-day loading dose, reported one or more neuropsychiatric symptoms — most commonly insomnia, vivid dreams (described as “often terrifying nightmares with technicolor clarity”, and headache⁵⁸. Although anxiety and depression were not individually assessed in the U.S. trial, “moodiness” was reported in two subjects in the mefloquine loading dose group, and it was noted “[t]he number of individuals with mood changes, reports of feeling depressed [emphasis added] or ‘blue’, appeared increased with mefloquine during the first few weeks of drug administration”⁵⁸. These results, obtained among comparable military subjects, and readily accessible in the published literature, clearly described a risk of neuropsychiatric adverse events that was 400 times the “about 1:10,000” reported in information presented to subjects in the mefloquine/tafenoquine trial.

Comparably misleading and incomplete information was provided to subjects in the later mefloquine/doxycycline trial. Prior to enrolment, subjects were described as receiving a briefing “on the use of mefloquine and the nature of the study”⁶⁶. Subsequently “[t]hose choosing to enroll in the study signed an ‘information and consent’ form”⁶⁶, whose information on risks cited data only from trials of mefloquine use in treatment, rather than from prophylactic use of the drug among military subjects at the intended loading dose. The consent form also did not specifically cite results from the recently concluded mefloquine/tafenoquine trial⁶⁵.

As an open-label trial, it has been claimed in published accounts that information on “[c]ommon, uncommon and rare side effects associated with mefloquine use (detailed in the manufacturer’s product insert) were presented”⁶⁶, but it appears that this information was presented only “during enrolment”, and not necessarily prior to subjects “[c]hoosing to enroll” on the basis of information presented during the earlier briefing⁶⁶. Given the possibility of vulnerable military subjects being “unduly influenced” by the expectation “of a retaliatory response” from senior military leaders “in case of refusal to participate”, the failure to provide accurate risk information prior to the subjects’ decision to enroll precludes concluding fully informed consent was given. Additionally, information in the then-current Australian mefloquine Patient Information, which would have presumably been the only manufacturer’s information to be provided to subjects in an open-label trial, did not contain information on the higher risks of use of the off-label loading-dose.

However, despite their earlier approval of the mefloquine/tafenoquine trial, even members of the ADMEC later became concerned at the nature of frequency of mefloquine side effects. Specifically, documents released in response to a Freedom of Information request⁸⁰ revealed that during consideration of the mefloquine/doxycycline trial protocol, there was

“...considerable debate when it became apparent that [m]efloquine had potentially serious side effects of which ADMEC had been previously unaware [emphasis added]. In particular, CNS side effects of depression and psychosis caused considerable concern to [the] Committee, especially were they to occur in deployed troops”.

The concern of the committee at these effects occurring in troops while deployed appears to have been mitigated when a study investigator explained that “by far the majority of side effects manifest within the first four doses of the drug”. In acknowledgement of the planned off-label use of a loading dose, the investigator noted that these first four doses “will be administered within Australia”⁸⁰.

4.3. Foreseeable Risks Versus Anticipated Benefits

Both the National Statement and GCP emphasize that foreseeable risks of harm to participants should be weighed against the anticipated benefits of the study^{73,74}. During the mefloquine/tafenoquine trial, subjects randomized to the mefloquine arm appear to have been placed at foreseeable risk by not being advised of critical guidance, promulgated in other settings, to immediately discontinue mefloquine at the onset of certain symptoms. Product insert warnings dating to the U.S. introduction of mefloquine in 1989 noted the drug “must be discontinued” at the onset of certain listed symptoms, including “anxiety, depression, restlessness or confusion”, which may be considered prodromal to a “more serious event”⁸¹. Yet similar guidance in the then-current Australian mefloquine Patient Information to stop taking the drug and to “tell your doctor immediately or go to casualty at your nearest hospital” for “change in mood, for example, depression, restlessness, confusion, feeling anxious or nervous” do not appear to have been communicated to subjects in the mefloquine/tafenoquine trial. These specific symptoms also do not appear to have been specifically assessed during the trial in accordance with product insert guidance, such as after administration of each dose⁶⁵. Had they been assessed, this would have conceivably risked requiring the study investigators to break blinding if these were reported, with a consequent loss of subjects in the comparator arm. The foreseeable risks of a “more serious event” from use of mefloquine — which are now understood to include a risk of permanent neurological disorders¹ — thus appear to have been overlooked, intentionally or not, for the anticipated benefits of facilitating the development of the experimental drug tafenoquine. Despite the risks experienced by the study subjects, the promise of tafenoquine remains marred by lingering concerns of similar occult neurotoxicity⁸², and the possibility of chronic neuropsychiatric adverse effects similar to those now associated with mefloquine¹.

Similarly, in the later, open-label mefloquine/doxycycline trial, although subjects assigned to the mefloquine arm were assumed to have been provided with a copy of the Australian mefloquine Patient Information leaflet, there is no evidence that there was any emphasis made of the need to immediately discontinue the drug at the onset of “changes in mood”, and subjects do not appear to have been specifically assessed for the specific symptoms of “anxiety, depression, restlessness and confusion” after every dose⁶⁶. For example, one subject later reported experiencing immediate effects from mefloquine that were not identified by study investigators⁸³:

“I had nightmares that night and I woke up with a feeling of dread and anxiety ... For some time I kept my mouth shut about it because you were not allowed to serve in East Timor without an antimalarial.”

Another participant in the trial is described as having experienced “depression, episodic anxiety, paranoia, short-term memory loss and suicidal ideation” that required his return to Australia⁶⁶. It is not clear from the study report whether this acute presentation was preceded by prodromal symptoms, which, had they been identified and the drug immediately discontinued as the Patient Information directed, might have prevented his development of this “more serious event”.

In contrast to these risks, the anticipated benefits of the mefloquine/doxycycline trial — to add to what was described as “limited data on the tolerability of mefloquine for long-term prophylaxis in military personnel”⁶⁶ — appears of questionable significance and difficult to justify in contrast to these risks. Specifically, studies of long-term mefloquine prophylaxis had by this time already been conducted involving military personnel⁵⁸, including in comparison to doxycycline in comparable operational settings^{84,85}, providing seemingly ample evidence to adequately inform ADF policy on use of the drug. Despite this evidence, at the meeting of the ADMEC at which this protocol was being evaluated, a study investigator, responding to the Committee’s concerns of CNS side effects from mefloquine, “...emphasized that this study was scientifically necessary in order to accurately categorize the side effect profile of the drug”⁸⁰.

4.4. Rights, Safety and Well-Being of the Trial Subjects

The GCP states that “the rights, safety, and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society”⁷⁴. Despite clearly being in the interests of science to have used another weekly dosed drug, mefloquine, as the active comparator for tafenoquine — given longstanding ADF malaria policy designating mefloquine strictly as a second-line drug owing to its neurological effects⁶⁷, its use as the comparator in the mefloquine/tafenoquine trial would have been ethically justified in accordance with this provision of the GCP only on the basis of credible and legitimate doubts as to the suitability of the first-line drug doxycycline in protecting the safety and well-being of the trial subjects.

While the report of the mefloquine/tafenoquine trial noted that “concerns about adverse effects” made the prevention of malaria problematic “in soldiers who travel to malaria endemic areas”, no specific safety benefit of mefloquine over doxycycline was articulated at the time of the study to justify its use⁶⁵. Only in later published accounts of the mefloquine/doxycycline trial was it articulated that cases of malaria “believed to have resulted from poor compliance” with doxycycline “provided the stimulus to look at other chemoprophylactic options for soldiers in East Timor”⁶⁶. It was claimed following the mefloquine/tafenoquine trial “there were requests for wider use of mefloquine from subsequent military units and soldiers being deployed to East Timor”⁶⁶. However, following the conclusion of both trials, doxycycline remained the ADF’s first-line drug⁶⁶ — raising doubts as to the original ethical justification, much of it articulated retrospectively only following the mefloquine/doxycycline trial, for the use of mefloquine as the active comparator during the initial mefloquine/tafenoquine trial. Tellingly, in subsequent years, acknowledging the limitations imposed by prioritizing the rights of study subjects during prophylactic antimalarial drug trials, authors involved in the development of tafenoquine have argued for the selective relaxation of related ethical standards⁸⁶.

4.5. Inadequate Medical Care Following the Trials

Although subjects were provided with medical care during the trials, the GCP notes that “the investigator/institution should ensure that adequate medical care is provided to a subject for any adverse events” both “during and following [emphasis added] a subject’s participation in a trial”⁷⁶.

The Australian Department of Defence has acknowledged “that some people do continue to experience on-going issues” after use of mefloquine⁸⁷, however, recent calls for the ADF to implement a program to re-assess the health of the trial participants and provide appropriate medical care to subjects whose adverse effects may have plausibly been overlooked or misdiagnosed have been rejected by senior officials including the Assistant Minister for Defence on the grounds that this would cause ‘unnecessary distress’ to the participants⁷².

4.6. Reporting Adverse Drug Reactions Among ADF Personnel

There is strong and compelling evidence that adverse drug reactions to mefloquine and tafenoquine, particularly neuropsychiatric adverse reactions, were significantly underreported among ADF personnel by the AAMI. For example, on the basis of data in the most recent meta-analysis of published data⁶², it is now recognized that when mefloquine is used for prophylaxis, psychiatric symptoms including abnormal dreams and insomnia are each reported in greater than 10% of users. However, as shown in the enclosed table, rates of reported adverse events for mefloquine during the mefloquine/tafenoquine trial⁶⁵ were significantly lower than those reported in the definitive meta-analysis⁶². The most parsimonious explanation for this significant discrepancy is systematic underreporting, which is likely to have affected tafenoquine comparably to mefloquine.

Table: Comparison of Reported Rates of Adverse Event in the AAMI Mefloquine/Tafenoquine Trial, vs. Published Meta-Analysis

Adverse Event	Mefloquine/Tafenoquine Trial ⁶⁵		Meta-Analysis ⁶²
	Tafenoquine %	Mefloquine %	Mefloquine %
Abnormal dreams	1	1	14 (10-21)
Insomnia	1	2	13 (8-23)
Anxiety	<1	0	6 (2-21)
Depression	<1	<1	6 (2-20)
Dizziness	1	1	8 (4-15)
Abdominal pain	5	8	5 (3-8)

Similarly, in comparison to published studies, which suggest that certain chronic effects consistent with those of neuropsychiatric quinism, including abnormal dreams and nightmares, are likely to affect considerably greater than 1% of those exposed to mefloquine, evidence suggests that the AAMI has similarly underreported rates of chronic adverse events. For example, among those reporting nightmares with use of mefloquine, 21% report these continuing over three years after discontinuing use⁵⁶. As abnormal dreams and nightmares are reported in at least 14% taking mefloquine⁶², it is likely that 21% of these, or over 2% of those taking mefloquine, continue to experience nightmares chronically after use. There is no evidence that the AAMI has reported this rate of adverse events occurring in ADF personnel. The most parsimonious explanation for this significant discrepancy is systematic underreporting.

5. How the United States Government Has Responded to Claims Regarding Quinoline Anti-Malarials

In the United States, claims regarding disability related to military service are administratively adjudicated by the U.S. Department of Veterans Affairs (VA). The author of this report is personally familiar with several successful mefloquine-related military service-connected disability claims, in which the VA has acknowledged a causal relationship between the veterans' military service-connected use of mefloquine, and the development of disabling neuropsychiatric conditions. Certain of these cases have been published in the medical literature^{31,34,63,88}, while several others are pending publication. The VA has not publicly denied such a connection, and notes in public materials that "Veterans may file a claim for disability compensation for health problems they believe are related to mefloquine use during military service. VA decides these claims on a case-by-case basis"⁸⁹.

The Quinism Foundation has recommended that the VA screen all recent veterans for a history of symptomatic mefloquine exposure⁹⁰. Although an empirically-validated screening instrument exists⁹¹, screening for symptomatic exposure during a clinical encounter can be as quick and simple as asking the veteran "Did you take mefloquine", and if so, "While you were taking the drug, did you experience one or more of these symptoms?". If the veteran reports symptomatic exposure, clinicians should retain an index of suspicion that any chronic neurologic or psychiatric symptoms, including those reported, could represent the effects of mefloquine poisoning⁹².

Authors' Note

Portions of this report have been modified from manuscripts submitted by the author for publication elsewhere, including a manuscript co-authored by Stuart McCarthy. The international spelling of certain quoted materials in this report has been modified for consistency.

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