MEFLOQUINE PROPHYLAXIS AS A CAUSE OF SUICIDE AND CHRONIC NEUROPSYCHIATRIC ILLNESS: MISMANAGEMENT AND NEGLECT IN THE AUSTRALIAN DEFENCE FORCE

Supplementary Submission to the Senate Foreign Affairs, Defence and Trade References Committee Inquiry into the Mental Health of Australian Defence Force Serving Personnel

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*"The clinical utility of mefloquine or a mefloquine-like drug would be enhanced if measures could be employed to negate the **toxicity** of the drug. This could be achieved through the use of an intrinsically less neurotoxic analog or by lowering the required dose of a similarly **neurotoxic** analog."*

Geoffrey S. Dow et al. (Walter Reed Army Institute of Research),
The Antimalarial Potential of 4-Quinolinecarbinolamines May Be Limited due to Neurotoxicity,
4 March 2004

*"OBJECTIVE: To define the biological mechanisms of **mefloquine neurotoxicity**, identify genetic and other predispositions to **mefloquine neurotoxicity**, and identify whether **mefloquine neurotoxicity** may extend to other anti-malarials as a class effect. … Unfortunately, as many as 25% of individuals taking mefloquine at prophylactic doses (250 mg per week) … experience neurological or psychiatric adverse effects. … [Previous studies into the] effects in humans, form a growing body of evidence of a biological basis of **mefloquine neurotoxicity**."*

U.S. Army Research Office,
A06-T034 - Neurotoxicity Associated with Mefloquine, an Anti-Malarial Drug, 2006

Executive Summary

This is a supplementary submission to the Senate Foreign Affairs, Defence and Trade References Committee *Inquiry into the Mental Health of Australian Defence Force Serving Personnel*. The main body of this submission is a forthcoming paper that provides a detailed review of the use of mefloquine in the Australian Defence Force (ADF), in the context of contemporaneous health, mental health and risk management policies. The main finding of the paper is that despite the risk of mefloquine neurotoxicity being both evident and foreseeable, that risk was apparently excluded from ADF health risk-benefit risk analyses, with those whose health has been adversely affected by the drug being systematically mismanaged as a result.

Mefloquine is a quinoline anti-malarial drug that was first synthesised in 1971 and developed by the U.S. Army Walter Reed Army Institute of Research (WRAIR) through the 1970s. Initial drug trials were conducted on prisoners, soldiers and subjects in developing countries. The results of those trials were given as a free good to the manufacturer, Roche, which we now know from a separate inquiry pays effectively no tax in Australia. Mefloquine was then approved for the market by drug regulators in the late 1980s and early 1990s, including by the Therapeutic Goods Administration, in the absence of the necessary phase III clinical trials. The ADF has been directly involved in research and development of synthetic quinolines since the 1940s, many of which are known neurotoxicants, and has been specifically involved in research and development of mefloquine since at least the 1980s in close cooperation with WRAIR and the manufacturer.

Early case reports of mefloquine side effects in the late 1980s included not only acute psychiatric disorders such as psychoses, but chronic psychiatric and neurological disorders including depression, neuropathies, ataxia, vestibular disorders and hearing loss. In response to these reports, and in the absence of the necessary phase III clinical trials, WHO and the manufacturer conducted a 1989 study that included a "crudely calculated" estimate of the frequency of serious side effects that is widely cited to this day – 1:10,000, or "rare". As the drug has been more widely exposed since, the manufacturer now warns that many of those neuropsychiatric side effects are in fact "common", including anxiety, depression, dizziness, and vertigo. Less common neuropsychiatric side effects reported by the manufacturer include agitation, restlessness, mood swings, panic attacks, confusional state, hallucinations, aggression, bipolar disorder, psychotic disorder including delusional disorder, depersonalisation and mania, paranoia, suicidal ideation, balance disorder, somnolence, syncope, convulsions, memory impairment, neuropathies, encephalopathy and vestibular disorders (long term) including tinnitus and hearing impairment. Many of these disorders have been determined by the Repatriation Medical Authority (RMA) to be causally linked to the use of quinolines, or mefloquine specifically. Under the relevant law, the RMA may only make determinations for chronic diseases; acute or transient conditions are excluded.

WRAIR researchers publicly raised concerns about mefloquine neurotoxicity in 2004 (Attachment 1). In the same year, the U.S. Department of Veterans' Affairs raised concerns about the long-term health impacts of mefloquine (Attachment 2), including a recognition that mefloquine could cause "symptoms similar to post-traumatic stress disorder (PTSD)." Many of the conditions identified at that time have since been recognised by the RMA as both chronic and causally linked to mefloquine use.

Mefloquine was found to be neurotoxic in 2006, causing lesions that are "permanent in nature" in parts of the brain linked to the above symptoms. That same year, the U.S. Army

Research Office solicited private industry proposals “to define the biological mechanisms of mefloquine neurotoxicity, identify genetic and other predispositions to mefloquine neurotoxicity, and identify whether mefloquine neurotoxicity may extend to other anti-malarials as a class effect” (Attachment 3). More recently, in 2013-2014 the human pathophysiology of mefloquine’s ability to cause lasting or permanent brain injury and chronic neuropsychiatric illness was published in the medical-scientific literature. The author of the 2014 paper describes the long term effects of mefloquine neurotoxicity as “chronic sequelae of a well characterised but idiosyncratic central nervous system toxicity syndrome … associated with a risk of permanent neuronal degeneration within specific central nervous system regions including the brainstem.”

Mefloquine is a known cause of suicide. In a small number of users this can be as a direct result of an acute psychiatric reaction while they are taking the drug. More insidiously, it can be as an indirect result of chronic psychiatric disorders that the manufacturer now identifies as “common”. The Dunt suicide study of 2009 identified “risk factors for suicide that can be of use when planning prevention strategies”, citing research that provides “a detailed assessment of the strength of evidence for risk factors associated with suicide in the general population”, including “Level A evidence [that] is strong evidence with conclusive results”. Four of those 11 “Level A” risk factors are directly linked to mefloquine use, including a variety of symptoms that the manufacturer identifies as “common” (Attachment 4).

Debilitating mefloquine side effects are not rare. Recent information from the U.K. Ministry of Defence indicates that of the 17,000 British soldiers who have used mefloquine since 2008, 6-8.4% subsequently required psychiatric treatment; a figure three to four times higher than the overall incidence of mental health disorders during the same period. The well-known stigma that prevents soldiers from reporting mental health problems suggests the true figure is much higher. Chronic neurological symptoms such as cognitive (memory and concentration) impairment, migraines, vertigo, tinnitus and hearing loss are probably more common again.

The ADF has specific policies in place for the care and management of patients with post-traumatic stress disorder (PTSD) and traumatic brain injury (TBI). Senior U.S. military health officials including the U.S. Army Surgeon General have recognised that mefloquine use can confound the diagnosis of both of those conditions (Attachment 5). In Australia, the ADF was aware of mefloquine neurotoxicity a decade ago. No studies have been undertaken into the health impacts of mefloquine use on ADF personnel and veterans. Side effects of prescription drugs have been excluded from every recent health study relating to ADF personnel and veterans. No clinical guidelines for diagnosis and management have been developed. Many of those affected by mefloquine neurotoxicity have likely been misdiagnosed, mistreated, undiagnosed, accused of malingering and/or simply left to fend for themselves.

The 2000-2002 Army Malaria Institute (AMI) clinical drug trials involving 1,300 soldiers administered with mefloquine while on operations in Timor Leste were not only unethical but *unlawful*. The relevant clinical practice guidelines for the conduct of pharmaceutical trials, which have their genesis in the Nuremburg trials, are mandated under the *National Health and Medical Research Council Act*. Those guidelines describe “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.” The guidelines state that “foreseeable risks and inconveniences should be weighed against the anticipated benefit for the individual trial subject and society,” and

"the rights, safety, and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society." At the time of the trials, mefloquine was only used as a second line anti-malarial in the ADF, in recognition of its neuropsychiatric side effects. The outcome of the trials was simply that mefloquine continue be used as a second line drug; there was no appreciable, beneficial outcome of the trials. The guidelines state that "during *and following* a subject's participation in a trial, the investigator/institution should ensure that adequate medical care is provided to a subject for *any adverse events*, including those related to the trial." Yet no proper follow-up or care has been provided to the participants since the drug was found a decade ago to be neurotoxic, able to cause lasting or permanent brain injury. The guidelines state that trial subjects must be given properly informed consent, yet they were *not* informed of the foreseeable risk that mefloquine can cause lasting or permanent brain injury.

In my initial submission to the Committee I recommended that the Commonwealth conduct "a full, independent inquiry into mefloquine use in the ADF and its impact on veterans and their families, including the conduct of clinical trials by the AMI, the involvement of the manufacturer, decisions by senior ADF leadership and the involvement of foreign governments and organisations." The publicly available evidence included in this submission clearly indicates gross, systemic neglect and mismanagement on the part of the ADF. The recommended inquiry needs to have judicial powers. Such an inquiry would almost certainly find multiple breaches of the *National Health and Medical Research Council Act*, the *Work Health and Safety Act*, the *Therapeutic Goods Administration Act*, the *Defence Force Discipline Act*; cases of senior ADF officials misleading Commonwealth ministers; and possibly evidence of criminal neglect or criminal corruption.

More importantly, the Commonwealth must now urgently initiate a dedicated outreach program for those affected by mefloquine neurotoxicity. This needs to include awareness for patients and clinicians, a neurotoxicology study, and the development of clinical guidelines for diagnosis and management. The Commonwealth owes ADF personnel and veterans affected by mefloquine neurotoxicity a duty of care that has been neglected for a decade.

Attachments:

1. Geoffrey S. Dow et al., "The Antimalarial Potential of 4-Quinolinecarbinolamines May Be Limited due to Neurotoxicity and Cross-Resistance in Mefloquine-Resistant Plasmodium falciparum Strains", *Antimicrobial Agents and Chemotherapy*, vol. 48, no. 7, pp. 2624-2632, 2004.

2. Arthur S. Hamerschlag, *Under Secretary for Health's Letter: Possible Long-Term Health Effects from the Malarial Prophylaxis Mefloquine (Lariam)*, IL 10-2004-007, U.S. Department of Veterans' Affairs, Washington D.C., 23 June 2004.

3. U.S. Army Research Office, *Neurotoxicity Associated with Mefloquine, an Anti-Malarial Drug: Small Business Technology Transfer (STTR): Solicitation Topic Number A06-T034 (Army)*, 2006.

4. "Level A" Suicide Risk Factors (Dunt, 2009) and Mefloquine Side Effects (Roche, 2014).

5. Remington L. Nevin, "Chapter 19: Mefloquine and post-traumatic stress disorder", in Elspeth C. Ritchie (Ed.), *Forensic and Ethical Issues in Military Behavioural Health*, Borden Institute, Surgeon General U.S. Army, Falls Church, 2014.

Malaria Prevention, Mefloquine Neurotoxicity, Neuropsychiatric Illness and Risk-Benefit Analysis in the Australian Defence Force

Stuart McCarthy, August 2015

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Abstract

The Australian Defence Force (ADF) has used mefloquine for malaria chemoprophylaxis since 1990. Mefloquine has been found to be a plausible cause of a chronic central nervous system toxicity syndrome and a confounding factor in the diagnosis of existing neuropsychiatric illnesses prevalent in the ADF such as post-traumatic stress disorder and traumatic brain injury. Individual health risks appear to have been mitigated by restricting the drug's use, however additional individual and organisational risks were realised when significant numbers of ADF personnel were subjected to clinical trials involving the drug. The full extent of the exposure, health impacts for affected individuals and consequences for ADF health management including mental health are not yet known but mefloquine may have caused or aggravated neuropsychiatric illness in large numbers of patients who have subsequently been misdiagnosed, mistreated or otherwise failed to receive proper care. Findings in relation to chronic mefloquine neurotoxicity were foreseeable but this eventuality appears not to have been considered during risk-benefit analyses. Thorough analysis by the ADF would have identified this long term risk as well as other qualitative risk factors, including barriers to recognition and reporting of adverse drug effects, duration and repetition of exposures, and the conduct of clinical trials in a military setting. Historical exposure of ADF personnel to mefloquine neurotoxicity now also necessitates ongoing risk monitoring and management in the overall context of broader health policies.

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1. Introduction

Two of the most significant threats to the health of Australian Defence Force (ADF) personnel are vector-borne diseases such as malaria[1-3] and environmental or operational stress, which can cause a variety of psychiatric disorders.[4-6] The ADF commits extensive resources to address these risks including research, training, prevention, diagnosis and treatment.[1,3,4-7] In the case of malaria, preventative medications such as doxycycline, atovaquone-proguanil, primaquine and mefloquine play an important role in overall preventive health strategies.[3] However recent insights into mefloquine's neurotoxic properties, chronic neuropsychiatric adverse effects and factoring in neuropsychiatric illness[8-10] make it timely to re-assess the benefits of using the drug for malaria prophylaxis against the risks of causing or aggravating neuropsychiatric illness, or otherwise exacerbating the management of mental health, in the ADF population.

Mefloquine hydrochloride (trade name *Lariam*) is a 4-quinolinemethanol synthetic quinoline that has been used to treat chloroquine resistant *P. falciparum* malaria,[11] although since its introduction into the market in the late 1980s and early 1990s has mainly been used for malaria prophylaxis.[12-16] The drug is prescription-only and the manufacturer states that when used "in chemoprophylaxis the safety profile of mefloquine is characterised by a

predominance of neuropsychiatric adverse reactions."[12] Concerns over the frequency and severity of these neuropsychiatric reactions have been a subject of controversy since its introduction.[14,16-18] Although there are other adverse effects, the neuropsychiatric effects remain the focus of this article.

Mefloquine was found to be neurotoxic in 2006,[19] although uncertainties remain as to dosages, idiosyncratic effects and the precise biochemical mechanisms of action.[8,9,19-24] More recently, it was found that mefloquine prophylaxis can cause a chronic central nervous system (CNS) toxicity syndrome evident in a number of other quinolines historically used as anti-malarials and anti-parasitics.[9] This finding synthesised a body of clinical observations, pharmacoepidemiological findings and experimental neuropharmacological evidence to describe a syndrome of symptoms linked to neuronal injury particularly in the vestibular system and brainstem, establishing mefloquine CNS toxicity as a plausible cause of acute and chronic neuropsychiatric symptoms[8,9] previously attributed to other causes.[17,24] Medical authorities have also found that mefloquine prophylaxis can confound the diagnosis of neuropsychiatric illnesses prevalent in the ADF including post-traumatic stress disorder (PTSD) and traumatic brain injury (TBI).[9,25]

The prevalence of mental health disorders among ADF serving personnel and veterans has been extensively studied in recent years, including risks associated with operational stress, environmental stress and the use of non-prescription drugs.[26,27] Mental health management has undergone significant policy reform, including the implementation of a number of risk management measures.[5,6,28] Policies have been introduced to manage a variety of specific neuropsychiatric illnesses including PTSD and TBI.[29,30] Pharmaceutical risk-benefit analysis (RBA) in this context extends beyond individual decisions by clinicians and patients to include more challenging organisational and policy level analysis and interdisciplinary decision-making. ADF preventative health doctrine includes guidance on risk assessment[1] and more broadly the ADF adopted the organisation-wide, systematic Australian Defence Risk Management Framework in 2003.[31,32]

This article critically reviews the use and management of mefloquine by the ADF in light of the drug's ability to cause or aggravate neuropsychiatric illness, with reference to the literature on RBA, neurotoxicology and other relevant disciplines. The inclusive term *neuropsychiatric* is used advisedly in this article, in relation to causal factors, drug effects, symptoms, disorders and sequelae,[33] noting the mental health focus of this edition. *Mental health* is commonly used exclusively in relation to psychiatric disorders resulting from environmental stressors. However the article also considers disorders with neurobiological causes such as neurotoxicity or physical forces causing neuronal damage, due to their overlapping symptomology, comorbidity and prevalence in the ADF population. Many of the relevant drug effects and symptoms are also commonly described as *neuropsychiatric* in the existing literature, hence the use of this term inclusive of *mental health* disorders.

2. Materials and Methods

The review originated with the premise that the recent description in the medical-scientific literature of a previously unrecognised chronic CNS toxicity syndrome,[8,9] which can be caused by a drug in the ADF pharmaceutical inventory,[3,12] necessitates a reappraisal of the risks associated with the drug's use. Conducting an actual RBA is beyond the scope of this paper in the absence of the necessary medical records and other data, however it was determined that a comprehensive literature review would provide a useful summary of the evidentiary basis from which to initiate a reappraisal of risk by policy makers. The review

required both a prospective and retrospective approach to risk analysis and evidence. Prospective in the sense of identifying risks associated with continued use of the drug, and new or established approaches for addressing risks arising from the exposure of significant numbers of personnel to a neurotoxic agent. Retrospective in the sense of reappraising existing assumptions, policies or practices relating to historical use of the drug that may now be invalidated by the evidence of mefloquine neurotoxicity.

Within the methodological framework described below, the general approach to identifying relevant material was to search PubMed, Scopus and Google Scholar using search terms such as drug names, chemical names, symptoms, disorders and author names. Previously published meta-analyses and literature reviews provided a baseline to initiate the literature search. Several experts in epidemiology, tropical medicine, pharmacology and neurotoxicology were also consulted to assist in identifying relevant material. This was an invaluable aspect of the review given its broad, interdisciplinary scope.

The first subject of the literature search was pharmaceutical RBA, focusing on the organisational or policy level in comparison to individual clinical settings.[34] There is extensive literature on this subject, including the use and interpretation of qualitative versus quantitative evidence[35-38] in relation to study design,[39-41] including for drugs with idiosyncratic adverse effects.[41] Given that neuropsychiatric effects were evident in mefloquine's safety profile early in its history,[14,16] and concerns over veterans' exposure to neurotoxicants including medicines became prominent in the 1990s,[42-44] the literature search then included the discipline of neurotoxicology. This literature describes the manifestation, symptomology and evidentiary basis of toxic encephalopathies,[45-48] neurotoxicity syndromes [49,50] methods for neurotoxicity testing[51-54] and risk assessment.[55-57] This section of the review provided a general frame of reference within which to refine the search and analysis of literature relating specifically to mefloquine toxicity.

The two papers cited in the introduction that describe the chronic mefloquine CNS toxicity syndrome[8,9] were then closely examined, including the material cited in those papers, to determine the analytical approach used by the authors to find that mefloquine prophylaxis is able to cause lasting toxic injury to the CNS with chronic sequelae. This established that the findings were a synthesis of historical medical-scientific evidence relating to the toxicity of quinolines, with more recent evidence drawn from three related disciplines, namely clinical observation, pharmacoepidemiology and experimental neuropharmacology. The search and analysis of literature for the next section of the review was therefore structured in accordance with those four lines of investigation.

Literature identified in each of those four areas was then critically analysed, beyond the literature cited in the two papers, initially by examining published clinical case reports and related investigations[58-62] systematic reviews,[16,17,24] meta-analyses[63-64] and experimental neuropharmacological studies[19-23] relating to the safety and tolerability of mefloquine prophylaxis, either conducted by or cited by public or military health authorities. A further search was then conducted to identify published pharmacoepidemiological studies relating to the safety and tolerability of mefloquine prophylaxis in healthy adult travellers and military personnel from developed countries,[65-81] including all studies conducted by the ADF[75-78] as well as longitudinal or follow-up studies relating to the original study populations[79] or more generally.[80] Most of the studies include reporting of acute and subacute effects during or immediately following prophylaxis.[65-79,81] However one study of chronic psychiatric effects was identified and this was limited to individuals who had submitted adverse event reports to a national drug regulator.[80] Two studies that include both treatment and prophylaxis are

relevant because they provided a basis for widely cited estimates for the incidence of neuropsychiatric adverse events, including prophylaxis.[16,148] Studies relating exclusively to treatment doses or use in specific groups such as children or pregnant women were not considered in detail. Another study was selected because it examined user acceptability, with a high proportion of mefloquine respondents citing convenient weekly dosing as the main reason for their choice.[65] Although the review initially set out to include civilian studies of long term prophylaxis that included clinical observation of the subjects, a paucity of these in the literature lead to the selection of these civilian studies merely to illustrate a variety of study methodologies. This section of the review analysed the evidentiary basis of mefloquine's adverse toxic properties as it evolved through the history of the drug's development and use, in contemporaneous literature available to policy makers involved in RBA.

One key area of dispute that became apparent by this stage of the review was systemic under-reporting of adverse effects in pharmacoepidemiological studies.[16,58-60] A retrospective statistical analysis of these studies was considered unwarranted as it would bring little value to the literature. However it was determined that a qualitative assessment of the various study methodologies could provide valuable insight, not only in relation to the history of the drug's safety but more importantly by informing any future longitudinal, epidemiological or toxicological studies into populations affected by mefloquine neurotoxicity. A number of the studies incorporated aspects of observational study[66-68,73,80] and reported results that could inform future study design, although in all but one case[80] these were limited to assessing acute or subacute neuropsychiatric effects during or shortly after prophylaxis. Summarising the strengths and limitations of these study methodologies became a key focus of the review.

A complete search of all Australian Repatriation Medical Authority (RMA) determinations was then conducted to identify those that list mefloquine or quinolines as causal factors in service related diseases. The RMA is an independent, statutory medical authority whose determinations are legal instruments used to assess eligibility for veterans' entitlements. The relevant legislation recognises a disease only where it is chronic or recurrent and explicitly excludes "a temporary departure from the normal physiological state", i.e. transient, acute conditions.[82,83] The standard of evidence used by the RMA is medical or scientific publication subjected to a peer review process, and standard epidemiological criteria are used in their assessment of causation.[82] Although the RMA is yet to publish a determination on the mefloquine CNS toxicity syndrome, its recognition of mefloquine or quinoline causation in other neurological and psychiatric conditions provides a useful indication of the availability of published evidence to policy makers.

The review then examined all available ADF health policies, doctrine and major research studies relevant to malaria prevention, risk management and mental health. There is extensive literature on the prevalence of psychiatric or mental health disorders in ADF personnel[26,27] and veterans,[27,84] and substantial policy reforms have been made in this area,[5,6,28,29] although the literature search indicates that the use of prescription medications as a possible causal factor has to date been excluded from consideration. No studies on the prevalence of neurological disorders in the ADF could be identified since a study of 1991 Gulf War veterans in relation to medical and chemical exposures, which showed increased reporting of neurological symptoms, however the study does not indicate which malaria prophylaxis regimens were used.[42] The comprehensive review of ADF health policies and doctrine included those relating to preventative health,[1] malaria,[3] mental health and psychiatric illness. [4-6,27,28] This included examining specific policies on the management of PTSD[29] and

TBI,[30] given recent findings that mefloquine prophylaxis can confound the diagnosis of those prevalent conditions.[10,25]

Finally, a critical analysis of this body of literature then deduced a number of qualitative risk factors that could reasonably have been included in RBA relating to mefloquine prophylaxis in the ADF, both in general use and specifically in drug trials, with reference to contemporaneous medical-scientific literature. In the case of drug trials, further reference was made to the applicable international standard for good clinical practice, mandated under the relevant Australian legislation.[85] One limitation of this review is that actual RBA relating to mefloquine use in the ADF are not publicly available, however ADF malaria policy[3] and published papers on the drug's historical use in the organisation [2,3,15,67,68,75-78] provide sufficient insight to inform this analysis in that the risk of neuropsychiatric adverse effects is cited as a reason for limiting the drug's use.

3. Pharmaceutical Risk-Benefit Analysis and Neurotoxicology

3.1 Interdisciplinary Risk-Benefit Analysis at the Policy or Organisational Level

The practice of RBA, which is defined as "examination of the potential positive and negative results of undertaking a specific therapeutic course of action,"[86] is a cornerstone of medical practice including preventative medicine. In a civilian context this is typically the domain of individual judgement by a patient and/or prescriber, balancing therapeutic efficacy with safety risks to prevent or treat a single illness, relying principally on information from the manufacturer and drug regulators.[34,36,38] While there is often only a single benefit, there may be multiple risks even for an individual. Perceptions of risks versus benefits are also greatly influenced by context and may therefore differ from actual risks and benefits.[35]

In military organisations such as the ADF, RBA is more complex because it requires a broader analysis of context and organisational factors, drawing upon the considerable resources of its health system including a capacity to conduct internal research and/or commission independent research. This necessitates an interdisciplinary approach in which expertise is drawn from all relevant disciplines, broadening the assessment in response to new evidence as necessary.[31,32] The process is not static but requires ongoing re-evaluation of the risk-benefit balance as greater knowledge of a drug's efficacy and adverse effects is obtained throughout its life cycle.[35,36] This is emphasised in ADF preventative health doctrine, which states that "evaluation is an ongoing process [which] provides medical staff with feedback on the accuracy of hazard identification and the consecutive risk assessment."[1]

The literature on mefloquine indicates that the present policies relating to the drug's safety have been based principally on pharmacoepidemiological studies.[3,7,8,12-14,16-18,24,60, 58-59,75-91] From an interdisciplinary perspective however, early reports of neuropsychiatric reactions in 1989,[16] subsequent direct evidence of neurotoxicity in 2006,[19] and the more recent description of a chronic CNS toxicity syndrome in 2013-2014,[7-8] would each have warranted a broadening of this approach to include the discipline of neurotoxicology.[49-57] In retrospect, incorporating the methodologies of that discipline into subsequent studies would likely have resulted in a better understanding of the drug's properties, health impacts and risks than is currently the case.

3.2 Qualitative versus Quantitative Evidence and Study Design

Viewed narrowly within the discipline of pharmacoepidemiology, there is a wealth of literature on the interpretation of quantitative versus qualitative evidence in RBA by researchers, clinicians, regulators and policy makers.[35-41] Quantitative aspects of RCTs are prominent in RBA throughout the life cycle of a drug, however there are key limitations. Statistical evidence can be used to demonstrate efficacy of a drug over a placebo or comparator. Although safety data can be gathered, overall safety cannot be fully determined within RCTs because a drug's safety profile involves multiple safety issues.[37,39,40] In the case of individual RCTs, design of the trial can limit its internal validity in that specific adverse effects can only be assessed once they have been observed,[39] then they can be ignored or disregarded if assumed to be idiosyncratic.[41] The external validity of the trial can then be further limited by the homogeneity of the trial subjects.[37,39,40] For these reasons, an interdisciplinary approach to pharmacoepidemiological study using both RCTs and observational studies is important in understanding a given drug's safety profile early in its use.[40]

Regardless of any interdisciplinary considerations, regulators typically assess quantitative data from RCTs and post market reporting, as well as qualitative evidence from clinical case studies and pharmacovigilance activities such as adverse event reports as a drug is used more widely.[34,37] The more extensive use of the drug over time is also important as the drug is exposed to a larger population, of broader heterogeneity compared to earlier trials, with a longer duration of exposure.[37,39,40] Long term exposure is critical in understanding a drug's safety profile, particularly so with adverse effects such as chronic organ toxicity.[37] Individual health practitioners and patients can of course make their own qualitative RBA based on their individual context,[35,36,38] however policy makers in military organisations can direct the use of a given drug based on questionable rationale that are not necessarily transparent to individual personnel.

3.3 Manifestation of Toxic Encephalopathies and Neurotoxicity Syndromes

The term toxic encephalopathy refers to brain dysfunction caused by toxic exposure. This includes a spectrum of symptomology ranging from subclinical deficits to overt clinical disorders. The clinical manifestations of toxic encephalopathy are related to the affected brain regions and cell types. Neurotoxic chemicals capable of damaging the CNS are quite prevalent, including heavy metals, organic solvents and other industrial chemicals. Many of these have been found to cause relatively specific neurological syndromes including diffuse acute or chronic toxic encephalopathy, chronic solvent encephalopathy, cerebellar syndrome, parkinsonism, and vascular encephalopathy.[45,46] There are a number of well-known iatrogenic (pharmaceutical) causes of toxic encephalopathy, for example some cancer chemotherapeutics[87,88] and psychotherapeutics.[47] In some cases, the neuropsychiatric symptoms of the iatrogenic encephalopathy are difficult to distinguish from those of the disease being treated, including higher treatment doses of mefloquine and other quinolines.[89,90]

The discipline of neurotoxicology recognises a number of fundamental principles that are relevant to this consideration of mefloquine. Firstly, compared to toxic diseases of other organs, the nervous system's limited regenerative capacity means that more sequelae persist after the removal of a neurotoxic agent. Secondly, multiple neurological syndromes may occur in response to a single neurotoxic agent, depending on the level and duration of the exposure. Thirdly, few neurotoxic agents result in pathognomonic neurological syndromes.

CNS clinical disorders instead have varying presentations involving a host of non-specific symptoms, with the symptoms of neurotoxic exposure often mimicked by various other neuropsychiatric diseases.[45] These provide a useful frame of reference for the literature relating specifically to mefloquine.

3.4. Neurotoxicology and Risk Assessment

The discipline of neurotoxicology became prominent in the latter part of the 20th century, as advances were made in the neurosciences, and widespread health impacts of common environmental and industrial neurotoxic agents such as heavy metals, solvents and pesticides became apparent. By the 1990s, insights into the development and application of neurobehavioral toxicology methods saw the adoption of standardised neurobehavioral test batteries, neuroimaging techniques, biochemical markers, questionnaire studies, and epidemiological studies of neurotoxic disorders.[51-53] Similarly, standardised neurotoxicity risk assessment practices have been in place since the mid-1990s.[54-57]

Neurologists have a key role in hazard identification and risk assessment. The nature of CNS and peripheral nervous system disorders is such that the patient is commonly unaware of the relationship between his symptoms and possible causes, and may not recognise changes in his behaiviour until they are brought to his attention by family or co-workers. Nonspecific effects of neurotoxicants include headache, nausea and dizziness. When patients among a group are exposed to neurotoxicants, the effects may vary from one to another because of differences in susceptibility and other risk factors.[54] This suggests that even pharmacoepidemiological studies that include neurobehavioural observations would not necessarily be able to make accurate causal attribution in the absence of clinical investigation of individual patients using the appropriate methods, particularly when the pathophysiology of the toxic agent in question has yet to be described in the literature, and where its symptoms mimic those of other prevalent conditions. Further, this would warrant inclusion of qualified neurotoxicologists in RBA processes as soon as there are indications that a pharmaceutical product may be linked to CNS injury.

4. Development, Use and Safety of Mefloquine

Mefloquine was discovered and developed by the U.S. military's Walter Reed Army Institute of Research (WRAIR) during the 1970s, mainly in response to the onset of chloroquine resistant *Plasmodium falciparum* malaria in Southeast Asia,[8,9,14] with its ongoing use and development closely linked to military requirements and operations since that time.[9,14] First synthesised in 1971[91] the drug was initially trialled on prisoners, soldiers and subjects in developing countries.[8,14] After licensing and introduction into the civilian market in the late 1980s and early 1990s it became widely used for chemoprophylaxis, favoured over other efficacious drugs for the convenience of its once weekly dosage,[13,16,17] with more than 20 million people having taken the drug worldwide.[3] Notably, initial licensing occurred in the absence of phase III clinical safety and tolerability trials in a normal study population of healthy civilian volunteers,[14] although various trials have been subsequently undertaken.[8,14,63,64,66,67] During the mid to late 1990s concerns were raised over the frequency and severity of mefloquine's acute adverse neuropsychiatric effects, including reports of hallucinations, psychosis and suicidal behaviour, with the drug's safety attracting controversy since that time.[8,14,17,18] Nonetheless the drug remained first line malaria prophylaxis in numerous military forces for many years, including the U.S. until 2009,[92] and to date in Canada[93] and the U.K.[94]

Mefloquine was introduced into the ADF anti-malarial inventory in 1990.[95] The drug has been used principally for suppressive chemoprophylaxis in personnel contraindicated for the ADF's first line prophylactic doxycycline, initially as a second line agent[75,76,96,97] and currently as third line.[3] Approximately 5-10% of ADF personnel do not tolerate doxycycline.[3] Another quinoline drug, primaquine, is used for terminal prophylaxis to eradicate any residual liver stages of vivax malaria.[3] Current ADF malaria policy notes that mefloquine is contraindicated for personnel with pre-existing psychiatric illness and prohibits specialist personnel including aircrew and divers from using the drug, citing the acute adverse neurological effects. The policy attributes concern over the drug's safety to "public perception."[3] Documented uses of mefloquine by the ADF have occurred since 1988, including clinical trials conducted by the Army Malaria Institute (AMI) during training exercises in malarious countries[75] and deployments to United Nations peacekeeping missions in Somalia and Cambodia.[76] The largest documented populations of ADF recipients were administered the drug during AMI clinical trials in East Timor from 2000 to 2002, totalling more than 1,300 personnel.[77,78] Although overall historical figures are not publicly available, these published figures combined with the numbers of ADF personnel deployed to malaria endemic areas since 1990, as well as the proportion of personnel who do not tolerate doxycycline, place the overall total in the thousands.

The manufacturer currently cites a randomised control trial (RCT) in which treatment-related neuropsychiatric adverse events occurred in 139/483 (28.8%) of patients receiving mefloquine and 69/493 (14%) patients receiving the comparator, atovaquone-proguanil. Neuropsychiatric adverse events among the mefloquine recipients included: strange or vivid dreams – 66 (13.7%); insomnia – 65 (13.5%); dizziness or vertigo – 43 (8.9%); visual difficulties – 16 (3.3%); anxiety – 18 (3.7%); and depression – 17 (3.5%).[12]

Post-marketing data is also cited by the manufacturer to report the incidence of neuropsychiatric adverse effects. Psychiatric disorders include: very common (>1/10) – abnormal dreams and insomnia; common (≥ 1/100 to < 1/10) – anxiety and depression; uncommon (≥ 1/1,000 to < 1/100) – agitation, restlessness, mood swings, panic attacks, confusional state, hallucinations, aggression, bipolar disorder, psychotic disorder including delusional disorder, depersonalisation and mania, paranoia and suicidal ideation. Neurological disorders include: common (≥ 1/100 to < 1/10) – dizziness, headache and vertigo; uncommon (≥ 1/1,000 to < 1/100) – balance disorder, somnolence, syncope, convulsions, memory impairment, peripheral sensory neuropathy and peripheral motor neuropathy (including paraesthesia, tremor and ataxia), encephalopathy and vestibular disorders (long term) including tinnitus and hearing impaired.[12]

Despite evidence of quinoline CNS toxicity dating back to the 1940s[9] and numerous early reports linking mefloquine use to a variety of acute psychotic events,[8,9,58-60] even reports of toxic encephalopathy,[58] direct evidence of mefloquine neurotoxicity was not established until a series of experimental studies conducted well over a decade after the drug's introduction.[19-23] Developers appear to have assumed for considerable time that neurological effects from the 4-quinolinemethanol class were only transient.[98,99] Direct evidence eventually published in 2006 found that mefloquine is neurotoxic, causing brain stem lesions that are "permanent in nature" in animal models at dosages equivalent to those used in malaria treatment.[19] Further studies have shown mefloquine neurotoxicity in animal neurons[20,21] and human neuronal cell lines.[22,110] Clinical observations following prophylaxis have also shown behavioural effects consistent with lasting cognitive impairment symptomatic of neurotoxic brainstem lesions.[8,9,61] A recently published review synthesised the above findings with studies of

historically used quinolines to describe mefloquine neurotoxicity as "chronic sequelae of a well characterised but idiosyncratic central nervous system toxicity syndrome … associated with a risk of permanent neuronal degeneration within specific central nervous system regions including the brainstem."[9] The same author has elsewhere described mefloquine neurotoxicity as a cause of neurotoxic vestibulopathy.[111]

There is no explicit acknowledgement from the manufacturer that mefloquine can cause the neuropsychiatric disorders listed above, however product information warns that during prophylactic use "signs of unexplained acute anxiety, depression, restlessness or confusion … may be considered prodromal to a more serious event," in which case "the drug must be discontinued."[12] No definition of "a more serious event" is offered, however this statement has significant safety implications. Acknowledging barriers to recognition and reporting of such symptoms that are examined in section 7.3. below, it is considered reasonably likely that a significant proportion of military users, among others, would continue taking the drug and experience such unspecified "serious events". Further, such a statement may constitute tacit rather than explicit acknowledgement by the manufacturer of the drug's neurotoxicity and potential causality in chronic neuropsychiatric disorders, exemplifying what some authors describe as "miscoding" of data including serious adverse effects by pharmaceutical companies,[35,36] i.e. the statement may be "code" for "neurotoxic".

The research community, drug regulators and policy makers appear to be gradually accepting the finding that mefloquine is neurotoxic. As early as 2006 for example, researchers associated with WRAIR stated that the institute "is currently investigating mefloquine analogues, seeking one with similar efficacy but reduced neuropsychiatric toxicity".[102] In the same year, the U.S. Army Research Office solicited private industry proposals "to define the biological mechanisms of mefloquine neurotoxicity, identify genetic and other predispositions to mefloquine neurotoxicity, and identify whether mefloquine neurotoxicity may extend to other anti-malarials as a class effect".[103] More recently, in 2013 the U.S. Food and Drug Administration (FDA) updated its public information for mefloquine, mandating its most serious "black box" warning, to advise in part that "neurologic side effects can occur at any time during drug use, and can last for months to years after the drug is stopped or can be permanent."[104] There now appears to be little doubt that the drug is able to cause lasting or irreversible injury to the CNS, rather than merely transient neuropsychiatric effects while it remains active, as was previously accepted.[3,9,13,16-18]

5. Emerging Evidence of Mefloquine Central Nervous System Toxicity

5.1. Historical Quinoline Central Nervous System Toxicity

The Australian military became directly involved in development, use and research of synthetic quinolines, in conjunction with the U.S. military, during the Second World War. Disruption of quinine supplies,[105] coupled with a high rate of malaria casualties in the South West Pacific in 1942-43, led to the establishment of an Army medical research unit which was the forerunner of the AMI.[106,107] This unit conducted clinical experiments and trials with alternative quinolines in Northern Australia and was responsible for the first identification of human malaria drug resistance.[108,109]

The recent description of a mefloquine-induced chronic CNS toxicity syndrome[9] draws upon evidence of CNS toxicity in three quinolines historically used as anti-malarials or anti-parasitics, namely pamaquine, plasmocid, and clioquinol.[9] Pamaquine is an 8-aminoquinoline that was the first drug to be synthesized with a marked activity against human malaria

parasites.[110] In 1945 this drug was trialled by the Australian military as prophylaxis against New Guinea strains of *P. vivax*, finding that it did not prevent primary attacks but did prevent relapses.[108,l11] A number of pamaquine clinical trials were undertaken by the U.S. Army Medical Department, which reported the incidence of severe toxic reactions at 1-10%, including "symptoms referable to the central nervous system, principally headache, dizziness, 'nervousness,' psychosis, and coma."[112] A 1949 post mortem examination of one case involving fatal overdose found significant neuronal degeneration within specific brain structures including the brainstem.[9,113] Neurological reactions to pamaquine similar to those observed in clinical trials were also observed in animal testing involving low doses, including histopathology that revealed swelling and subtle degeneration in neurons throughout various brainstem nuclei.[9,114]

At the time of Australian military research into pamaquine, another quinoline - atebrin (aka atebrine, quinacrine, mepacrine) - had become the main malaria prophylaxis drug, protecting against *P. vivax* and *P. falciparum*[96-99] although an outbreak of the latter in one area of Northern New Guinea led to the discovery of atebrin resistance.[108] Atebrin was used at various dosages for both treatment and prophylaxis, with dosages altered in response to overseas findings of adverse neuropsychiatric reactions.[109] A series of case reports and studies since the mid-1930s had documented toxic psychiatric reactions including psychosis, mania, schizophrenia, depression, lassitude and insomnia.[115-118] Some of the same studies also observed broader symptoms possibly causally related to CNS toxicity rather than peripheral causes, consistent with the pathophysiology and symptomology of the quinoline CNS syndrome described above, including anorexia and tachycardia.[118] Australian military personnel involved in medical treatment of atebrin users also observed numerous neuropsychiatric symptoms including neuropathies and psychosis.[119]

Australian military malaria research ceased soon after the war, but resumed in the mid-1960s as chloriquine resistance became apparent in South East Asia. Chloroquine had become the main drug for prophylaxis and treatment but as a result of this research drugs from other classes such as doxycycline and atovaquone-proguanil were introduced for suppressive prophylaxis, with primaquine for terminal prophylaxis by the 1980s [120]. The AMI was established in 1973 and has been directly involved in numerous research initiatives related to the toxicity of quinolines including chloroquine, primaquine, mefloquine and tafenoquine, in close association with WRAIR, other research institutions, and the pharmaceutical industry.[15,75-78,97,120,121] Notwithstanding any remaining disputes or uncertainties regarding mefloquine toxicity, use of synthetic quinolines has been independently determined by the RMA to be a causal factor in a variety of psychiatric,[122-125] neurological,[126-140] vestibular[131] and cardiac diseases.[142] These are strikingly similar to a list of conditions that the U.S. Department of Veterans' Affairs had identified from case reports in a document advising of possible long term health effects of mefloquine as early as 2004.[133]

5.2. Clinical Investigations

Numerous case reports linking mefloquine prophylaxis to a variety of neuropsychiatric conditions have been published since the drug was introduced into the market. These have been summarised elsewhere, particularly those relating to acute psychotic reactions.[8,9] The present review set out to compare the body of case studies and related research linking mefloquine prophylaxis to recognised psychiatric, neurological and other disorders, in order to assess the whether the recently described mefloquine induced chronic CNS toxicity syndrome[9] may represent a distinguishable neurotoxicity syndrome consistent with the principles summarised in section 3.3., in particular that a single toxic agent may cause

multiple neurological syndromes of varying presentations, involving a variety of non-specific symptoms, often mimicked by other neuropsychiatric diseases.[45] This was aided by a complete search of statutory determinations previously made by the RMA, which uses epidemiological criteria in their assessment of causation and peer reviewed publication in the medical-scientific literature as their standard of evidence.[82] Additionally, the manufacturer lists a number of these same disorders as adverse effects associated with mefloquine prophylaxis, as a reflection of adverse event and clinical case reporting.[12,34]

One of the early case reports relating to mefloquine use involved toxic encephalopathy.[60] A more recent report described a case of limbic encephalopathy and central vestibulopathy, citing much of the literature reviewed here.[161] The RMA is yet to publish a determination relating to mefloquine as a cause of toxic encephalopathy, although it is interesting to note that they have previously recognised chronic solvent encephalopathy as a diagnosable disease.[141] This may provide a useful guide on any future determinations regarding mefloquine CNS toxicity. Reporting of psychiatric disorders linked to mefloquine use includes cases of depression,[132,135,136] anxiety,[133,137] bipolar disorder,[124,138] and suicide or suicidal ideation.[135,149] Reporting of neurological disorders linked to mefloquine use includes cases of neuropathies,[126,127,140,141] vertigo,[128,142] myasthenia gravis[129,143] tachycardia[130,144] and hearing loss or tinnitus.[131,132,144] One interesting observation about this list of disorders is that, although mefloquine is a known ototoxicant,[145,146] there is as yet no direct evidence that it can injure the peripheral nervous system, therefore a number of the recognised peripheral disorders may be more plausibly attributed to the CNS toxicity syndrome previously described.[8,9]

One specific case worthy of mention here is the report of a 1993 post mortem examination of brain tissue specimens from several U.S. military personnel who deceased as a result of combat while serving in Somalia, where mefloquine was used for chemoprophylaxis. The examiners found mefloquine quantities of 14 mg/kg, 8.7 mg/kg and 11 mg/kg in the tissue samples provided;[147] findings that are important to the discussion in section 5.4. regarding the assumed dose-dependence of mefloquine neuropsychiatric adverse effects.

5.3. Pharmacoepidemiological Studies

The understanding of any drug's properties typically improves over time as it is administered to a wider population of users and subjected to more extensive research and reporting.[34,35,37,39] Many authors express concern regarding over-emphasis by policy makers on quantitative data in preference to qualitative evidence epitomised by the clinical observations and experimental studies cited elsewhere throughout this review; emphasising a need for caution in RBA[36-38] particularly in cases where drug reactions are idiosyncratic or alternative efficacious therapies are available.[37,41] Proper study design and implementation early in a drug's use is a critical aspect of gaining that understanding while remaining cognisant of safety, and there are good avenues for incorporating observational methods into the process.[39-40] This warrants a critical analysis of quantitative estimates on the frequency of neuropsychiatric adverse effects associated with mefloquine prophylaxis, including early estimates of the incidence of adverse events and the methodologies of subsequent pharmacoepidemiological studies.

Responding to a series of early neuropsychiatric adverse event reports in 1989, the World Health Organisation (WHO) and F. Hoffmann-La Roche conducted a collaborative study to identify the characteristics of reported cases, measure the frequency of adverse events and generate hypotheses on risk factors relating to mefloquine safety. Interim guidelines were

issued including "a warning statement that persons operating machinery and those requiring fine coordination (e.g. airline pilots) should not take mefloquine prophylaxis."[16] The 1991 report estimated a "frequency of central nervous system disorders from mefloquine [that was] crudely calculated." Prophylaxis use figures were estimated based on sales data and a series of assumptions relating to the proportion drugs sold for treatment versus prophylaxis, the proportion of drugs sold versus actual usage, estimates of malaria treatment based on actual reported cases modified by a factor of two, and an assumption about duration of travel. The estimate of adverse events was made using a total of 140 actual reports related to mefloquine prophylaxis, modified by a factor of two in order to account for under-reporting which in the jurisdictions under consideration varied from 50% to 90%. A ratio of serious versus non-serious adverse events related to prophylaxis was then estimated by reference to the actual adverse event reports and assumptions about dose-dependence, even though "50 (41%) had taken a single 250 mg dose prior to the onset of symptoms" and "there was no statistical difference between the doses taken by patients with serious and non-serious adverse events." Thus it was calculated that 1:10,000 prophylaxis users would experience serious neurophychiatric adverse events.[16] An independent study published in the same year arrived at a similar figure of 1:13,000 but noted "our denominator is too high, and the real incidence of side effects may be greater than that revealed in our study."[148]

The history of mefloquine's development and widespread use by the military is critical in that quantitative data from military phase III drug trials informed early estimates of adverse events in the absence of more appropriate civilian trials, and has continued to influence regulatory and policy decisions.[3,16,63,64] A major 1997 study conducted a meta-analysis of RCTs comparing mefloquine with other standard malaria prophylaxis drugs, which was subsequently revised, updated,[63] and then incorporated into a broader analysis of common anti-malarials in 2009.[64] Ten trials were selected, involving a total of 2,750 adult participants. Five of those were field trials involving mainly male military personnel in a peacetime training setting. Withdrawals were consistently higher in four placebo controlled trials, and in five trials there was no difference in tolerability between mefloquine and the comparator drugs.[63] 516 published case reports of mefloquine adverse effects were identified, including four fatalities, mainly in tourists and business travellers. Significantly, the report makes a number of observations suggesting the limited generalisability of the trial results, noting the predominance of fit, young, male soldiers among the total number of subjects.

The report found that mefloquine is effective in preventing malaria but given evidence from non-randomised studies of its potentially harmful neuropsychiatric effects in civilian travellers, "has adverse effects that limit its acceptability".[63] The study was not able to determine whether mefloquine is well or poorly tolerated. In response to the earlier, widely cited WHO/F. Hoffmann-La Roche estimate of 1:10,000 users experiencing severe neuropsychiatric reactions, the report states that figure "undoubtedly underestimates the true incidence" of less severe adverse effects. Significantly, the report recommended that an international panel of experts be convened to research and resolve the question of mefloquine safety.[63] The subsequent 2009 report stated that "soldiers are a healthy and disciplined study population who, compared to non-soldiers, are likely to under-report adverse events," resulting in "systemic under-estimation of the true frequencies" of adverse effects.[64] This observation is further informed by particular military barriers to reporting neuropsychiatric adverse drug effects including symptom recognition, stigma, and cognitive function, which are identified in Section 7.4. with reference to Australian military literature.

This section of the review addresses the question of systemic under-estimation by examining the reporting and attribution methodologies of a number of pharmacoepidemiological studies, with further reference to the above literature on neurotoxicology and neurobehavioural science. Fourteen studies were examined, involving a total population of 10,664 mefloquine prophylaxis subjects during the period 1988 to 2006. These include three RCTs,[66-68] five non-randomised field trials,[69,70,75,77,78] and five longitudinal or retrospective studies of varying designs.[65,62,64,70,71] Severe adverse events were generally defined as those requiring medical intervention, with reporting of non-severe adverse events based on subject completion of questionnaires or answering a non-leading question by an investigator, with four exceptions[67,68,70,71] one of which involved data-mining of medical records with no direct involvement of the subjects.[71] Four of the studies used methodologies that incorporated aspects of observational study design or neurobehavioural testing.[67,68,73,80] The studies are summarised in the attached table. Differences in study design preclude a direct statistical comparison, therefore the adverse event figures are provided merely to illustrate the variation in results.

All ten of the reviewed military studies concluded that mefloquine was safe and well tolerated. One small study designed to compare the efficacy of four different drug regimens found that “mefloquine was well tolerated and no dizziness or neurotoxicity was observed”, while providing no indication in the report as to the methodology underlying that assessment including adverse event reporting.[75] Only one military study[68] used a methodology for adverse event reporting that included neurobehavioural and psychiatric testing. This was a 1993 double-blind RCT involving 359 U.S Marines that compared two groups taking weekly mefloquine prophylaxis, one of which was given an initial loading dose, to a third chloroquine group. Symptom assessment was conducted using physician interview, Environmental Symptoms Questionnaire (ESQ) and the Profile of Mood States (POMS), completed weekly. Sleep and wake cycles were also monitored using actigraph recorders worn by some of the subjects 24 hours a day. The trial was conducted over 12 weeks, with results shown for week 1, week 9-12 and overall. Insomnia was a prominent symptom, particularly in the mefloquine loading dose group. There were 10 withdrawals in the mefloquine groups, 6 of which were attributed to insomnia or vivid dreams. Two mefloquine subjects were withdrawn for depression and suicidal thoughts, neither of which were attributed to the drug [68]. In the non-loading mefloquine group, 43% experienced non-severe neuropsychiatric adverse events, including insomnia (25%), vivid dreams (7%), dizziness (6%), headache (22%), irritability (4%), poor concentration (5%), anger (1%) and moodiness (1%).

The largest of the military studies[70] is worth specific mention as it exemplifies methodologies for reporting and attribution of adverse effects common to many of the reviewed military studies, and contrasts the results of the original study with a follow-up study involving a majority of the original trial subjects.[79] This field study involved 2,289 Dutch military personnel who used mefloquine for weekly chemoprophylaxis while deployed to a United Nations peacekeeping mission in Cambodia in 1992-1993. Adverse events were determined by spontaneous self-reporting, with medical interventions defined as severe adverse events. Possible mefloquine related adverse events were reported by 30.2% of subjects. 22.8% reported neuropsychiatric adverse effects including concentration disorders (7.8%), dizziness (5.6%), visual complaints (2.8%) and insomnia (1.0%). Of the 2,289 subjects, 7 (0.3%) experienced severe symptoms that they attributed to mefloquine, 5 of which were neuropsychiatric. These included 2 seizures, 1 case of serious myoclonus and 2 cases of severe dizziness. Not one of these was subsequently attributed to mefloquine by the

investigators. One seizure patient had a personal history of epilepsy but the other did not, and no further events occurred after that subject changed to doxycycline. The myoclonus patient was free of complaints after being changed to doxycycline. Symptoms also ceased in both dizziness patients when their prophylaxis ceased or was modified.[70] A follow-up study asked 1,733 (68%) of the subjects about the symptoms they experienced during their deployment using a mailed questionnaire. Of those 1,733 respondents, 1,638 (95.6%) reported that they had used mefloquine. 49.6% of the mefloquine respondents reported experiencing adverse effects, compared to 12.5% of doxycycline users. In the group that linked their complaints to their deployment, symptoms included vertigo/dizziness (21.3%), visual complaints (14.5%), memory loss (12.7%), fatigue (12.2%), headache (11.8%) and concentration problems (5.4%). Possible explanations offered in the report for the "very high frequency of side effects" include "a widespread mistrust in mefloquine", suspicion arising from denials on the part of authorities, and recall bias. No clinical observations were made during the study. The report makes no reference to historical evidence of quinoline CNS toxicity,[9] previously published case reports linking mefloquine prophylaxis to a variety of the reported symptoms, or evidence of mefloquine accumulation in human brain tissue following prophylaxis.[145] Similar limitations were found in the other military studies, including the ADF trials discussed in section 7.5. below.

Several of the civilian studies are worth contrasting with the Dutch military study. The first of these is a 1999 double-blind RCT involving 1013 subjects who enrolled at 15 travel clinics across five countries.[66] Each subject travelled to a malarious area for up to 28 days, then was evaluated at 7, 28, and 60 days after return to obtain information about a targeted list of adverse events and potential malaria episodes. Each investigator assessed whether there was a reasonable possibility that each adverse event was caused by the study drug, without knowledge of which drug the subject had been assigned. An adverse event was treatment emergent if it started while the subject was taking the study drug. Accounting for withdrawals due to changed travel plans and other factors, 966 completed the trial. The two groups were well balanced regarding demographics and other factors. Appropriate controls were implemented to account for varying regimens between the mefloquine group and the comparator group, including placebos. Severe adverse events were defined as those requiring medical advice. Of the 2,120 treatment-emergent adverse events across the entire study population, 1,310 (62%) were considered by the investigator to be unrelated to the study drug. Adverse events attributed to the drug occurred in a significantly higher proportion of subjects who received mefloquine (42% vs. 30%) and "the difference was especially pronounced for neuropsychiatric events." Among subjects who discontinued taking the study drug as a result of an adverse event, the event was attributed to the drug in 37 subjects. Treatment-limiting neuropsychiatric events began in 19 subjects while they were receiving mefloquine, in 5 subjects while they were receiving mefloquine placebo, and in 3 subjects while they were receiving the comparator. No severe adverse events were attributed to either drug, however each is listed in the report and they are clearly not attributable to the drug. In the mefloquine group (n = 483) there were 19 non-severe neuropsychiatric adverse events, including insomnia (12), anxiety (9), strange/vivid dreams (7), dizziness/vertigo (7), depression (3), visual difficulties (3), concentration impairment (3) and other (4). The report compares the results with two other studies to find they were consistent.[76]

A Danish retrospective study of adverse event reports[80] is of interest not only for its methodology but because it provides an indication of chronic psychiatric effects associated with mefloquine prophylaxis. This study evaluated both acute and long term psychiatric symptoms in 66 (89%) of 85 individuals who had submitted adverse event reports to the

Danish National Drug Authority from 1996 to 2000. Forty of the subjects had complained of more than one symptom in their original adverse event report, with the group experiencing a range of physical/neurological and psychiatric symptoms including anxiety, sleep disturbances/nightmares, depression, possible psychoses (delusions/hallucinations) and cognitive impairment. Acute psychiatric effects were retrospectively assessed using the standard Symptom Checklist-90-Revised (SCL-90-R) psychometric [159] and Present State Examination (PSE) psychiatric[150] tests, with clinically significant scores for anxiety, phobic anxiety and depression found in 55%, 51%, and 44% respectively of the mefloquine subjects. Substantial acute phase psychotic symptoms were found in 15% and were time-limited. Cases of hypomania/mania in the acute phase were found in 5.5% of the mefloquine subjects. Significant long-term mental health effects were demonstrated in the SF-36 Health Survey[171] subscales of mental health (MH), role emotional (RE), and vitality (VT) in the mefloquine group compared to control groups matched by age and gender.[80]

Methodological limitations identified in many of these pharmacoepidemiological studies tend to reinforce previous findings of a systemic under-reporting of adverse events.[58-59] Regardless, the reported incidence of adverse neuropsychiatric effects has continued to increase over time. For example several studies published in the early 2000s reported an incidence of symptoms such as nightmares, anxiety, and psychosis that were at least 100 times higher[64,66,67] than was reported in the early 1990s.[8,10,64] More recently, the Australian manufacturer's 2014 product information shows an incidence of anxiety, depression, suicidal ideation and encephalopathy[12] ten times higher than the 2013 edition of the same document.[152] As the literature on pharmaceutical RBA would suggest,[34,35,37,39] these more recent figures provide a better understanding of the incidence of mefloquine's neuropsychiatric adverse effects than initial "crudely calculated"[16] estimates made soon after the drug's introduction, which included an explicit caveat that "the real incidence of side effects may be greater than that revealed in our study",[148] in the absence of more appropriate phase III clinical trials.[14] What some of the studies examined above[67,68,73,80] do illustrate however is the utility of observational study design including neurobehavioural testing where this can be appropriately incorporated into drug trials.

5.4. Experimental Neuropharmacology

Early in mefloquine's development the drug was found to have a long elimination half-life relative to other quinolines and classes of anti-malarials,[154] of approximately two to four weeks.[155] This property gave it an advantage over other drugs in the search for alternatives to defeat chloroquine-resistant *Plasmodium* in that a prophylaxis regimen of less frequent doses might also offer improved compliance[156,157] or cost effectiveness[13] relative to those requiring a daily dose. WHO initially recommended a dose of 250 mg once per week, however concerns that toxic accumulation may occur during weekly administration for long-term chemoprophylaxis led the U.S. Centres for Disease Control (CDC) to initially recommend one 250 mg dose every second week. Failure rates in some groups and subsequent pharmacokinetic investigation[62] saw 250 mg per week become the standard in the U.S.[17] The pharmacokinetic study cited by the CDC in recommending this change monitored plasma levels in 15 adult subjects for 13 weeks to find that "toxic accumulation does not occur" at peak levels under a weekly regimen. The report mentions that each subject was given a diary for recording doses and adverse effects, then interviewed by the investigator at the conclusion of the study, but makes no mention of any adverse effect reporting results.[153]

The year following publication of the above pharmacokinetic study, evidence of mefloquine accumulation in post mortem human brain tissue linked to prophylaxis was published,[147] and

in 1997 the drug was demonstrated to cross the blood-brain barrier in animal models.[158] Researchers associated with WRAIR recognised in 2004 that mefloquine's clinical potential may be compromised by neurotoxicity.[159] As a small, lipophilic molecule,[160,161] the drug is easily able to cross the blood-brain barrier,[16,158,160] accumulate in the CNS and interact with neuronal targets[19,160] including the limbic system and brainstem.[8,9,19] The drug's precise biochemical mechanism of action in causing lasting CNS neuronal injury is yet to be determined.[160] The drug is known to interfere with normal gap junction functioning;[22,23,164,164] and the series of studies that first demonstrated its neurotoxicity[19] continued to investigate mefloquine's ability disrupt calcium homeostasis and perturb the endoplasmic reticulum,[20,21] which is a known causal mode of neuronal cell apoptosis.[165,166]

One remaining area of debate is the dose-dependent incidence of neuropsychiatric effects. Health authorities and the manufacturer have maintained throughout the drug's history that a weekly 250 mg prophylactic dose is unable to cause lasting CNS toxicity. While there is caution regarding a higher risk of toxicity with treatment doses,[12] and the U.S. FDA has warned of a risk of lasting or permanent CNS effects at prophylactic doses,[114] the prevailing view has been that any acute effects will cease once the dosing is discontinued and the drug is eliminated.[12] In an apparent contradiction, the WHO/F. Hoffmann-La Roche report of 1991 which addressed this issue of dose-dependence stated that although adverse events "seem to be more frequent when higher doses are used", based on the evidence then available, that "there [was] no compelling evidence that CNS reactions associated with mefloquine are dose-dependent".[16] Almost a quarter of a century after that report was published, a significant body of evidence now exists to suggest that doses associated with mefloquine prophylaxis, not just those used for treatment of malaria, can cause lasting CNS injury with chronic sequelae.[8,9] The seminal 2006 study that found mefloquine to be neurotoxic, equated doses that were used during that study to elicit toxicity-induced behaviours "that are similar to those observed in humans after the treatment [vice prophylaxis] dose."[19] However mefloquine levels measured in the brain of individuals who were taking the drug acutely (750 mg, 37 to 70 hours before death) were found to be 51.5 nmol/g,[167] which equates to plasma levels of approximately 137 nM[168] The prophylaxis-related brain tissue concentrations of 8.7 to 14 mg/kg found in patients examined in the post mortem study cited above[147] also translate to serum levels of 100 to 135 nM,[149] with humans undertaking a long-term prophylaxis suggested to have even higher tissue levels.[168] Together, these studies suggest that treatment with mefloquine at prophylatic levels can give rise to drug concentrations in the brain sufficient to cause CNS toxicity, previously presumed to equate only to higher treatment doses.[19]

One of mefloquine's important characteristics, related to the question of dose-dependence, is the idiosyncratic nature of its neuropsychiatric reactions.[9] Well known idiosyncrasies with other anti-malarial quinolines have been fundamental to drug safety in global malaria eradication programs, for example haemolytic anaemia in primaquine patients with glucose-6-phosphate dehydrogenase (G6PD) enzyme deficiency.[169] Although at least one author has hypothesised as to how some mefloquine users may be genetically predisposed to some of the drug's adverse effects,[170] and it is known that the U.S. Army Research Office approached private industry in part to "identify genetic and other predispositions to mefloquine neurotoxicity" almost a decade ago,[102] the present review was unable to identify a research program dedicated to investigating this aspect of the drug's properties. Absent such research, an assumption that adverse reactions to mefloquine are necessarily dose-dependent or attributable to a pre-existence of latent psychiatric illness[3,12] appears no longer sound.

5.5. Confounding Diagnosis of Prevalent Neuropsychiatric Illnesses

Two neuropsychiatric conditions relevant to the use of mefloquine in military populations are PTSD and TBI. Due to their prevalence and overlapping symptomology there is extensive literature on comorbidity and differential diagnosis between those conditions.[172-177] As the understanding of mefloquine neurotoxicity and its prevalence has grown in recent years, attention is now being drawn to the relationships between mefloquine and those two conditions, with the U.S. Centers for Disease Control now advising that mefloquine's "neuropsychiatric side effects may confound the diagnosis and management of post-traumatic stress disorder and traumatic brain injury".[10,25]

PTSD is a psychiatric disorder that can result from exposure to trauma, where the exposure comprised an actual or threatened death, serious injury or sexual violence.[178] Until recently diagnostic criteria for PTSD did not exclude symptoms resulting from direct effects of medications. This means that patients experiencing mefloquine neurotoxicity may have appeared to meet PTSD diagnostic criteria regardless whether their symptoms were caused by traumatic stress. Many of mefloquine's reported adverse neuropsychiatric effects are consistent with key PTSD diagnostic criteria including "intrusion or re-experiencing" (Criterion B), "negative alterations in mood or cognitions" (Criterion D), "increased arousal symptoms" (Criterion E) and may be persistent (Criterion F) in cases of long term or permanent neuronal injury.[10,178]

TBI, which involves brain damage caused by external force, has received widespread attention in recent years due to the exposure of military personnel to blast injuries in Iraq and Afghanistan,[172] however it is more commonly caused by falls, sports and motor vehicle accidents.[173] The injury can result in persistent symptoms, or even post-concussive syndrome (PCS), including somatic complaints, depression, anxiety, personality disorders and cognitive impairment.[174] As yet there are no published studies regarding differential diagnosis between mefloquine neurotoxicity and TBI, however the overlapping symptomology does suggest a prospect of misdiagnosis in cases where there has been no obvious physical trauma and/or the symptoms are relatively mild.

TBI is frequently co-morbid with PTSD and there is evidence that even mild TBI (mTBI) can increase risk for PTSD and other psychiatric conditions. There is debate that post-concussive sequelae including psychiatric disorders and cognitive impairment secondary to mTBI may be attributable to either psychological stress or neurobiological injury, with some authors favouring psychological treatments in cases where the cause is not neurobiological.[175,176] Although a variety of neuropsychological and neuroimaging methods are available to assist in differential diagnosis between PTSD and TBI,[177] the microscopic and highly focal nature of neuronal degeneration associated with mefloquine neurotoxicity is likely undetectable by conventional neuroimaging.[9]

5.6. Synthesis

At his point of the review it is possible to synthesise the published evidence summarised above. Given the time limited nature of most of the pharmacoepidemiological studies conducted to date, overall they cannot reflect a prevalence of a *chronic* mefloquine CNS toxicity syndrome. One exception is a recently published study finding long term mental health impacts on individuals who had previously reported acute or subacute adverse effects.[80] The literature on neurotoxic encephalopathies and syndromes indicates that many typical symptoms may be subclinical, not easily recognised by the patient, non-specific and

mimicked by other neuropsychiatric diseases; with longer exposures to neurotoxic agents more likely to result in a diagnosable illness.[45,46,49,50] The various manifestations of mefloquine CNS toxicity[8,9] are consistent with a variety of chronic psychiatric and neurological diseases independently determined to be causally related to mefloquine use, based on medical-scientific evidence in accordance with epidemiological practice,[122-132] although in some cases mefloquine CNS toxicity provides a more plausible mode of action.[9] Despite findings of systemic under-reporting of adverse events,[63-64] the manufacturer now states that some of these overt disorders, or associated symptoms, are common among mefloquine prophylaxis users.[12] In the absence of appropriately scaled, inclusive, longitudinal, neurotoxicology studies demonstrating otherwise, this evidence suggests that a chronic CNS toxicity syndrome associated with mefloquine prophylaxis may in fact also be common.

6. Neuropsychiatric Illness in the Australian Defence Force

6.1. Prevalence and Research

The prevalence of neuropsychiatric illness in ADF serving personnel and veterans, including suicide, has recently been the subject of extensive study. A 2010 study estimates that 54.1% of the population of just over 50,000 ADF personnel experience psychiatric disorders in their lifetime, including 4,757 (20.8%) with affective disorders and 7,420 (27%) with anxiety disorders. Within the preceding 12 months only, the respective figures were 9.5% for affective disorders and 14.8% for anxiety disorders. No significant difference was found in the prevalence of these disorders between personnel who had deployed on operations and those who had never deployed.[26] Non-operational trauma in the ADF, including bullying and sexual abuse, has also been studied extensively.[178]

The 2010 study found that the prevalence of suicide ideation was “significantly higher in the ADF compared to the community”, although the study does note that ADF members are less likely to complete the act of suicide. Significantly, only half the sample with PTSD or depressive episodes reported receiving treatment in the previous 12 months, due to a variety of barriers including stigma. The study analysed factors such as trauma exposure, caffeine and tobacco use, alcohol and illicit drug abuse and use of dietary supplements, however prescription drugs were not considered.[26]

A 2009 independent study[84] was undertaken specifically to examine suicide among Australian veterans. This study did consider prescription drugs, but only the role of anti-depressants in suicide prevention. Abuse of illicit drugs was also considered. One key section of the report identifies “risk factors for suicide that can be of use when planning prevention strategies”, citing research that provides “a detailed assessment of the strength of evidence for risk factors associated with suicide in the general population”, including “Level A evidence [that] is strong evidence with conclusive results”.[84] List A from the report is reproduced at Attachment 3, with the four (of 11) factors linked to mefloquine use shown in bold. In relation to the psychiatric disorders listed in factor 2, the manufacturer currently advises that anxiety and depression are common ($\geq$ 1/100 to < 1/10); while hallucinations, bipolar disorder, psychotic disorder including delusional disorder, depersonalisation and mania are uncommon ($\geq$ 1/1,000 to < 1/100). In relation to factor 3, the manufacturer currently advises that suicidal ideation is uncommon ($\geq$ 1/1,000 to < 1/100). In relation to factor 10, the manufacturer currently advises that agitation, restlessness, mood swings, panic attacks, confusional state, aggression, depersonalisation and mania and paranoia are uncommon ($\geq$ 1/1,000 to < 1/100).[12]

6.2. Policy Responses

The above research findings have resulted in significant reforms to mental health and related policies by the ADF and Department of Veterans Affairs (DVA). A 2009 review of mental health care in the ADF recommended a series of reforms, including improved governance and policy, improved training, enhanced rehabilitation and transition services, and greater involvement of families.[27] The resulting 2011 ADF mental health strategy emphases the ADF's commitment to "evidence-based treatment and recovery programs" and "innovation and research that improves our understanding of mental health and wellbeing", through key objectives such as "identification and response to the mental health risks of military service" and "building an evidence base about military mental health and wellbeing."[5] The 2013 DVA veteran mental health strategy includes similar objectives, such as "strengthening workforce capacity" and "building the evidence base."[179] Prior to these reforms, existing ADF policies already subjected personnel to mandatory periodic, pre and post-deployment mental health screening.[28]

6.3. Post-Traumatic Stress Disorder

The 2010 ADF mental health study cited above estimated that 8.3% of ADF personnel experienced PTSD in the preceding 12 months.[26] ADF health policy states that its personnel are considered to be a high risk group due to their exposure to traumatic events associated with operational deployments and that exposure to further stressors should be limited for those suffering the condition. The same policy states that PTSD is often co-morbid with mTBI and notes that neuropsychological testing should be undertaken when mTBI is suspected. Treatment should be evidence-based, and the policy endorses trauma-focused cognitive therapy and/or pharmacological therapy as required.[29]

6.4. Traumatic Brain Injury/Post-concussive Syndrome

Detailed data on the prevalence of TBI in the ADF is not publicly available. However in the Australian community the prevalence of mTBI has been estimated at 64-131 cases per 100,000 population each year, with moderate and severe TBI at 15-20 per 100,000 and 12-14 per 100,000 respectively. Prevalence is highest in the 15-35 years age group and significantly more common in males than females by a ratio of 3-4:1. Common causes include falls, sport and motor vehicle accidents.[172,173] ADF health policy notes that one of the signature symptoms of TBI is cognitive impairment. This presents considerable risk in that "cognitive tasks such as safe driving, handling firearms, establishing situational awareness and the ability to control aggression may result in adverse outcomes such as friendly fire incidents." Specific measures to manage risks associated with TBI include the use of protective equipment and mandatory neurocognitive baseline testing for all personnel prior to operational deployments.[30]

7. Mefloquine Risk-Benefit Analysis in the Context of ADF Neuropsychiatric Illness

7.1. Organisational Context

The use of mefloquine and other drugs for malaria prophylaxis in healthy people is in itself a risk reduction method, where the benefit to the individual is the prevention of a serious disease and in the case of a military organisation reduces the costs and further risks associated with treating, managing and evacuating patients, and resulting loss of military capability. Beyond the narrow context of malaria prevention however, the broader military

context highlights key additional risks to both individuals and the organisation. Given the ADF's focus on operational stress and mental health since at least the mid-1990s,[4-6] sound RBA relating to mefloquine use would have considered not merely the direct, individual risk of adverse effects but secondary and organisational risks such as complicating the diagnosis and treatment of other prevalent conditions with similar symptomology.

Although ADF RBA relating to mefloquine use are not publicly available, policies of using the drug as an alternative to contraindicated prophylaxis and prohibiting use by specialist personnel, citing the neuropsychiatric adverse effects, are apparent risk reduction measures. Viewed purely within a context of malaria prevention this RBA approach appears adequate. However evidence of the neuropsychiatric adverse effects since the drug's inception and the comorbidity of neuropsychiatric illness in the ADF would warrant a more comprehensive RBA including several other key factors. These include identification of long term risks, barriers to recognition and reporting of adverse drug effects, duration and repetition of exposures, conduct of clinical trials in a military setting and ongoing risk monitoring and management. Each of these factors is examined below, in relation generally to mefloquine use in the ADF and more specifically to its use in clinical trials that comprised a large proportion of the overall risk exposure to ADF personnel.

7.2. Identification of Long Term Risks

Policies on health and risk management in the ADF emphasise an “evidence-based” approach to management.[1,5] The ADF has been directly involved in research into the quinolines since the 1940s[106-110] and mefloquine specifically since at least 1988[75-78,96,97] with AMI having had a long association with WRAIR and other organisations that have studied the drug’s toxic properties.[15,75-78,96-97,120-121] Mefloquine’s safety profile has been characterised by adverse neuropsychiatric effects since its introduction.[16] Clinical evidence of toxic encephalopathy linked to mefloquine use was published in 1987.[59] Direct evidence of mefloquine accumulation in human brain tissue was published in 1994.[147] A meta-analysis of mefloquine trials that found systemic under-reporting of neuropsychiatric adverse effects “that limit its acceptability” was published in 2000.[63] Direct evidence of neurotoxicity was published in 2006[19] as part of a series of published studies conducted by researchers associated with WRAIR,[20-23] which in the same year solicited private industry proposals “to define the biological mechanisms of mefloquine neurotoxicity.”[103] The RMA has made a series of independent determinations that mefloquine and other quinolines can cause a variety of psychiatric,[122-125] neurological,[126-130] vestibular,[131] and cardiac diseases,[132] similar to a list included in a 2004 U.S. Department of Veterans’ Affairs document raising concerns regarding the long term health impacts of mefloquine use.[133] Therefore it is reasonable to conclude that the recent findings relating to mefloquine neurotoxicity[19-23] as a cause[8,9] or significant confounding factor in prevalent neuropsychiatric illness[9,10,25] were foreseeable.

The ADF did apparently mitigate the risk of more widespread exposure by limiting the general use of mefloquine to a second or third line agent.[12,75,76,96,97] However it is not apparent that the organisation recognised the above evidence by assessing the longer term risks of complicating the health management of personnel who have previously been exposed to mefloquine neurotoxicity. Despite its involvement in a number of longitudinal neurotoxicological studies to assess the exposure of other specific populations to environmental and medical toxic agents,[42,182] no such studies into the health impacts of mefloquine use have been conducted.

7.3. Barriers to Recognition and Reporting of Adverse Drug Effects

Sound RBA involving significant adverse drug effects would include critical analysis of any barriers to recognition and reporting of those effects by patients, trial subjects and health practitioners. In the case of mefloquine use in military settings there are at least several barriers that result from the context of the environment and perceptions of mefloquine users and health practitioners.

Firstly, many of mefloquine's documented neuropsychiatric effects are not reasonably distinguishable from normal psychological or physiological reactions to psychological or environmental stressors prevalent in military settings where the drug is used. Well documented psychological stressors include danger of being killed or maimed, exposure to trauma, loss of sleep, long duration of deployments and separation from family,[4,7] while physiological stressors include exposure to extreme temperatures, loss of sleep, fatigue, disease, poor air and water quality, noise, vibration and toxic materials.[7] Many neuropsychiatric symptoms linked to these prevalent stressors, including depression, anxiety, headache and dizziness[4,7,182-184] are also reported by the manufacturer to be common effects of mefloquine.[12]

This operational context suggests that personnel who experience acute symptoms may be more likely to endure them or attribute them to other prevalent environmental factors than report them as adverse drug effects. In cases where chronic symptoms persist after a deployment in which mefloquine was used, there are additional relevant factors. Typically, cessation of mefloquine chemoprophylaxis would coincide with an individual's departure from the stressful operational environment described above. The manufacturer's advice that any adverse effects would cease once the drug is discontinued would tend to reinforce an individual's tendency to attribute any persistent symptoms to other factors. Further, when ADF personnel depart an operational area they are required to complete a general health questionnaire that prompts them to record their exposure to "hazardous situations", including many of the stressors listed above.[185,186] However prescription medications are not listed on this documentation, so this process in itself would tend to result in a bias towards attributing any symptoms to the "officially acknowledged" exposures.

A second barrier is the well documented stigma of reporting and seeking treatment for neuropsychiatric symptoms among military personnel.[26,187-189] Stigma for reporting neuropsychiatric illness identified in current ADF mental health doctrine including concerns by individuals that they would not be deployable (or, by extension, removed from a current deployment), that they would be treated differently by other people, or that their careers would be adversely affected.[6]

A third barrier is that a common symptom of the neuropsychiatric conditions associated with mefloquine[9,12,101] is cognitive impairment.[26,101] The capacity of an individual to recognise symptoms that are already difficult to distinguish from normal reactions and already attract stigma would clearly be further diminished by cognitive impairment. An expectation that an individual experiencing cognitive impairment would identify and report the symptoms of cognitive impairment would be perverse. These barriers to reporting symptoms, either acute symptoms while taking mefloquine or chronic symptoms after cessation, exacerbate risk by reducing reporting during drug trials or submitting adverse reports to drug regulators, and reducing the likelihood of personnel with chronic conditions from receiving subsequent care.

7.4. Duration and Repetition of Exposures

Mefloquine use has coincided with a period of high operational tempo for the ADF. In 2010 the ADF population had a mean length of service of 11.6 years. An estimated 43% had experienced multiple overseas operational deployments, ranging from four to 12 months.[26] Although figures on mefloquine use are not publicly available, a large proportion of ADF personnel were deployed to malarious areas where they were also exposed to the other stressors identified above. Notably, the risk of developing PTSD, TBI and other neuropsychiatric illnesses is not exclusive to operational deployment and many personnel may not seek treatment, leaving them pre-disposed to additional stressors. While it may be true that adverse mefloquine reactions can be attributed to pre-existing neuropsychiatric illness in some cases, the reverse may also be true in others, that exposure to mefloquine toxicity could predispose individuals to other prevalent neuropsychiatric disorders. Given the duration and repetition of these combined exposures, this warrants identification of mefloquine use in an individual's history to aid in correct diagnosis and subsequent care for neuropsychiatric patients.

7.5. Conduct of Clinical Trials in a Military Setting

The AMI has conducted several trials involving mefloquine use by ADF personnel as trial subjects.[75-78] Two of these involved personnel deployed on peacekeeping operations in East Timor time the drug had been on the market for approximately a decade but concerns regarding its neuropsychiatric effects were prominent,[14,15,17] with doxycycline used as the first line prophylaxis and mefloquine second line.[13,23,24,76-78] The current international standard for good clinical practice in pharmaceutical trials had been mandated by the Australian government's health and medical research statutory body in 2000.[85] Several key aspects of that standard are relevant to the conduct of the trials by AMI in a military setting. Firstly, the standard describes "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." Secondly, "foreseeable risks and inconveniences should be weighed against the anticipated benefit for the individual trial subject and society." Thirdly, the standard 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." Fourthly, "during and following a subject's participation in a trial, the investigator/institution should ensure that adequate medical care is provided to a subject for any adverse events, including those related to the trial." Finally, in obtaining the informed consent of trial subjects, the institution should adhere to "the ethical principles that have their origin in the Declaration of Helsinki."[85]

The first trial[77] was a phase III RCT for the safety and efficacy of tafenoquine prophylaxis, with mefloquine used as the comparator drug, including a prophylaxis phase and a follow-up treatment phase. 492 subjects received tafenoquine and 162 received mefloquine. Adverse event reports were elicited by the investigator asking the non-leading question "do you feel differently in any way since starting the new treatment?" Severity and attribution to mefloquine prophylaxis was then determined by a study physician. No neurobehavioural testing was conducted. In the mefloquine prophylaxis group, 143 (88.3%) of the subjects reported at least one adverse event, 23 (14.2%) of whom reported neuropsychiatric adverse events. 19 (11.7%) mefloquine subjects experienced adverse events with a "suspected/probable" relationship to prophylaxis. Three (1.9%) mefloquine subjects withdrew from the study as a result of adverse events, with those 3 subjects reporting 5

(3.1%) adverse events between them. There are ambiguities in the report regarding the withdrawals. A table in the report shows that 4 (2.5%) mefloquine subjects withdrew from the trial due to adverse events, 4 (2.5%) changed to other anti-malarial drugs and 1 (0.6%) withdrew for a reason unrelated to the trial, leaving 153 (94.4%) to complete the trial. The text of the report states that there were 3 (2%) severe adverse events experienced by mefloquine subjects but none of these were neuropsychiatric. The report does not state whether any of the mefloquine subjects who withdrew from the trial or changed to other drugs experienced non-severe neuropsychiatric adverse effects. A further ambiguity is found in the abstract, which states that "Three subjects on tafenoquine (0.6%) and none on mefloquine discontinued prophylaxis because of possible drug-related adverse events." This suggests that the investigator did not attribute the adverse events experienced by the withdrawn subjects to mefloquine use, although that is not stated in the report. Regardless of these ambiguities, the non-severe adverse neuropsychiatric events experienced by the mefloquine group included vertigo 8 (5%), somnolence 6 (4%), abnormal dreams 2 (1%), dizziness 2 (1%), insomnia 3 (2%), abnormal coordination 1 (<1), and depression 1 (<1). The report found that "mefloquine was well tolerated by the Australian soldiers, which is in accordance with the results of other randomized, double-blind studies of military populations," citing two trials which are summarised in this review.[68,71] Eventually published some nine years after the trial in 2010, by which time WRAIR had established a permanent research laboratory at AMI,[121] the report makes no reference to the fact that mefloquine had been found to be neurotoxic four years earlier.[19]

The second trial[78] was an open-label, prospective study, to describe the tolerability of mefloquine malaria prophylaxis in comparison to doxycycline. 1,157 of the subjects were administered mefloquine, on the rationale that "there are limited data on the tolerability of mefloquine for long-term prophylaxis in military personnel." Participation was claimed to be voluntary, with non-volunteers using doxycycline,[78] however it has since been reported that the commanding officer of approximately half of the subjects directed his subordinates to participate under threat of being excluded from the deployment [190]. 75 (6.5%) of the mefloquine subjects withdrew due to adverse events attributed to the drug, 62 (5.3%) withdrew due to neuropsychiatric adverse events. 57% reported at least one adverse event. There were three severe neuropsychiatric adverse events "possibly relating to mefloquine." One of these three subjects "experienced depression, episodic anxiety, mild paranoia, short-term memory loss and suicidal ideation" and his "mental state continued to deteriorate" despite ceasing mefloquine. Only preliminary figures are reported for non-severe adverse events. In the discussion, the report states, "when monitoring the tolerability of a drug under military operational conditions, there is a need to account for the physiological and psychological stress associated with such activities that may confound the relationship between drug intake and adverse events." The trial report concluded that mefloquine was "well tolerated" by the subjects and simply recommended that it "continue to be used for those intolerant of doxycycline."[78] In 2004, approximately one quarter of the mefloquine subjects initiated legal action against the ADF and the manufacturer, reporting that they were not adequately informed of side effects and complaining of symptoms such as depression, paranoia, and suicide ideation.[191]

Given the clinical standards quoted above,[85] it is difficult to conclude that these trials were ethical or that their resultant findings as to the tolerability of mefloquine are valid. While the trial reports state that the subjects were properly informed volunteers, one quarter of them subsequently initiated legal action on the basis that they were not and there is no mention of this even though the reports were published after the legal action was initiated. There is

further evidence that as many as half of them were unduly influenced to participate in the trials.[190] The safety and well-being of the subjects were placed at risk for no appreciable benefit, as mefloquine was already licensed and was being used only as a second line drug in recognition of its neuropsychiatric safety risk. Although both reports analyse neuropsychiatric adverse events, there is no analysis of the barriers to reporting described above, either during or subsequent to the trials.[77,78] One of the reports does note the limited external validity of the trial, however his only observation relates to gender rather than the military operational setting of the trial.[78] From a RBA perspective, the trials exposed the participants to significant risk with little appreciable benefit.

7.6. Ongoing Risk Monitoring and Management

RBA is not static but comprises part of a continuing, dynamic risk management process that should logically extend not only through a drug's lifecycle but also address any subsequent adverse outcomes. Recognition that historical mefloquine use poses a higher risk than was earlier appreciated therefore warrants an introduction of additional risk management measures, beginning with the identification and screening of previous mefloquine users. The ADF already has standard procedures for reducing risks associated with malaria and neuropsychiatric illness. For example, in order to minimise the risk of haemolytic anaemia caused by ADF's terminal prophylaxis drug, primaquine, all ADF personnel are tested for G6PD deficiency, with the results recorded in their health records.[3] Risk management measures for neuropsychiatric illness include the general health screening, mental health screening and neuropsychological baseline testing cited above.

Given that mefloquine is a prescription drug, now recognised as a factor in neuropsychiatric illness that can confound diagnosis of prevalent neuropsychiatric conditions, and noting the above barriers to recognising symptoms of the drug's chronic effects, similar screening for mefloquine recipients would be a prudent risk reduction measure. Screening for mefloquine neurotoxicity could begin by identifying users from pharmaceutical records and include neurological vestibular function and neuropsychological cognitive function tests for those identified. These would assist investigation, correct diagnosis and differential diagnosis, not only improving the management of other prevalent illnesses but reducing the risk of misdiagnosis and subsequent mistreatment. For example pharmacotherapy presents an array of possible adverse effects.[192] Despite misconceptions to the contrary, trauma-focused psychotherapies can cause adverse effects such as depression, panic attacks, suicide ideation and substance abuse relapse, even when found to be efficacious in correctly diagnosed patients.[193,194] Minimising extraneous exposure to these therapies reinforces the case for proactively identifying and screening mefloquine recipients to aid correct diagnosis, rather than relying on self-reporting of psychiatric symptoms. A further measure would then be to develop guidelines to assist clinical care providers in identifying personnel affected by mefloquine neurotoxicity, conducting differential diagnosis with other prevalent conditions, and providing ongoing care and management.

8. Conclusions

Both positive and negative conclusions can be drawn from the experience of mefloquine use in the ADF in an RBA context. The individual and organisational benefits of chemoprophylaxis as a measure for preventing the serious illness of malaria are well established, including the use of alternatives for personnel contraindicated for first line drugs. Risks arising from general mefloquine use since its introduction in the ADF have evidently been reduced via policies that limited its use as a second or third line malaria prophylactic

and prohibiting its use by specialist personnel, explicitly citing the drug's acute neuropsychiatric adverse effects among other factors.

There are two negative conclusions. Firstly, the particular use of mefloquine in clinical trials, involving large numbers of personnel in a military operational setting, contrary to relevant guidelines, represents an apparent failure to identify the foreseeable risk of causing or aggravating neuropsychiatric illnesses prevalent in the military population from which the trial subjects were drawn. Secondly, the ADF did not appropriately monitor the risks of mefloquine use as insights into the drug's neurotoxicity, the chronic nature and frequency of its neuropsychiatric adverse effects and its ability to confound the diagnosis of other prevalent illnesses were revealed by the manufacturer and independent research. Nor has the ADF subsequently managed those risks by implementing appropriate measures to care for affected personnel. In effect the mental health, medical and social costs have thus far been transferred to patients and other members of society.

The full extent to which mefloquine use in the ADF has exacerbated the already difficult problem of mental health management is not yet known and may never be. At best, it has complicated the diagnosis, treatment and management of neuropsychiatric illnesses prevalent in the target population including PTSD and TBI. At worst, it may have caused or aggravated neuropsychiatric illness in large numbers of patients who have subsequently been misdiagnosed, mistreated or otherwise failed to receive proper care, despite mental health being a major focus of recent ADF research and policy reform. These risks were foreseeable and should have been considered by health officials during RBA, policy decisions and ongoing risk management.

The case of mefloquine use in the ADF also provides a useful insight into the interpretation of quantitative versus qualitative evidence by researchers, policy makers and clinicians in drug safety, particularly prophylactic drugs where alternative drugs and other preventive measures are available. Perceptions of mefloquine as a “safe” drug have emanated from an uncritical bias towards quantitative evidence suggesting that the incidence and severity of the drug’s neuropsychiatric adverse effects were relatively low, attributable to other factors such as pre-existence or predisposal to psychiatric illness, or merely transient until prophylaxis has ceased. More prudent RBA would have better considered the qualitative evidence indicating that mefloquine’s neurotoxic properties can cause lasting injury to the CNS with chronic sequelae, thereby compounding the risks of neuropsychiatric illness already prevalent in the population.

Notwithstanding this specific focus on the ADF, a key finding of this review is that there is now compelling evidence for the previously described chronic CNS toxicity syndrome [8, 9], linked to mefloquine prophylaxis, consistent with the literature on epidemiology and neurotoxicology. There is direct evidence that mefloquine is able to accumulate in the human brain and interact with neuronal targets in the CNS, consistent with both clinical observations and plausible pathophysiological mechanisms. There is direct evidence that mefloquine concentrations equivalent to human prophylaxis are able to cause lasting or permanent injury to neurons in animal models, eliciting behavioural responses consistent with equivalent behaviours observed in human prophylaxis users and published in case reports. Multiple neurological syndromes occur in response to this single neurotoxic agent, including a variety of chronic, clinical disorders which have been determined as causally linked to mefloquine use by competent medical authorities, in accordance with epidemiological principles, against an appropriate standard of medical-scientific evidence. The syndrome has varying presentations involving a host of non-specific symptoms. The symptoms are often mimicked

by other prevalent neuropsychiatric disorders, with competent medical authorities having determined that mefloquine use is able to confound the diagnosis and management of those disorders. This now places an onus on public and military health officials to conduct appropriate longitudinal neurotoxicology studies, further medical research, and develop clinical guidelines necessary for the proper diagnosis, care and management of those affected. This would ensure not only adequate care, but mitigate the continued risk of administering contraindicated treatments. Given that many of those affected by mefloquine neurotoxicity are veterans or serving members of the military, one might reasonably expect such endeavours to be afforded a high priority for funding and a certain degree of urgency.

The interdisciplinary focus of this edition warrants one final conclusion. In a complex organisation such as the ADF, with large numbers of personnel exposed to a wide range of complex health threats, sound risk management necessitates the inclusion of multiple fields of expertise to identify, assess and mitigate risk. Shortcomings in RBA identified in the present review appear to have resulted from a bias towards prevention of a serious but well-known disease, drawing narrowly on expertise resident in one specialist research institution, focusing on the beneficial effects of a drug without critically analysing its significant adverse effects. This continued even as the ADF health system was undergoing major reforms to implement evidence-based mental health strategies. With benefit of hindsight, such bias may have been avoided had ADF senior health officials adopted a more inclusive, comprehensive approach, incorporating the fields of neurology, toxicology, psychiatry, psychology and epidemiology to identify, assess and mitigate risks as they became evident in research from those fields. The necessity of a critical, inclusive, interdisciplinary approach to organisational health management and risk management is a salient lesson for general and specialist health practitioners, researchers and policy makers alike.

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The Antimalarial Potential of 4-Quinolinecarbinolamines May Be Limited due to Neurotoxicity and Cross-Resistance in Mefloquine-Resistant *Plasmodium falciparum* Strains

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The clinical potential of mefloquine has been compromised by reports of adverse neurological effects. A series of 4-quinolinecarbinolamines were compared in terms of neurotoxicity and antimalarial activity in an attempt to identify replacement drugs. Neurotoxicity (MTT [thiazolyl blue reduction] assay) was assessed by exposure of cultured embryonic rat neurons to graded concentrations of the drugs for 20 min. The 50% inhibitory concentration (IC_{50}) of mefloquine was 25 μM, while those of the analogs were 19 to 200 μM. The relative (to mefloquine) therapeutic indices of the analogs were determined after using the tritiated hypoxanthine assay for assessment of the antimalarial activity of the analogs against mefloquine-sensitive (W2) and -resistant (D6 and TM91C235) *Plasmodium falciparum* strains. Five analogs, WR157801, WR073892, WR007930, WR007333, and WR226253, were less neurotoxic than mefloquine and exhibited higher relative therapeutic indices (RTIs) against TM91C235 (2.9 to 12.2). Conventional quinoline antimalarials were generally less neurotoxic (IC_{50}s of 400, 600, and 900 for amodiaquine, chloroquine, and quinine) or had higher RTIs (e.g., 30 for halofantrine against TM91C235). The neurotoxicity data for the 4-quinolinecarbinolamines were used to develop a three-dimensional (3D), function-based pharmacophore. The crucial molecular features correlated with neurotoxicity were a hydrogen bond acceptor (lipid) function, an aliphatic hydrophobic function, and a ring aromatic function specifically distributed in the 3D surface of the molecule. Mapping of the 3D structures of a series of structurally diverse quinolines to the pharmacophore allowed accurate qualitative predictions of neurotoxicity (or not) to be made. Extension of this in silico screening approach may aid in the identification of less-neurotoxic quinoline analogs.

Malaria remains a global public health problem, with approximately 300 million clinical cases and as many as 2.7 million deaths a year (30), most of which occur in sub-Saharan Africa. Malaria also poses a significant risk to travelers and military personnel deployed for long periods of time to countries where malaria is endemic. There are no effective malaria vaccines, and the efficacy of the available antimalarial drugs continues to decline as a consequence of the emergence of drug-resistant parasites (11). The list of available drugs for malaria prophylaxis in the United States includes doxycycline, mefloquine (Lariam), atovaquone-proguanil (Malarone), chloroquine, and hydroxychloroquine sulfate (18). Doxycycline, Lariam, and Malarone are used in countries where malaria is endemic and where chloroquine resistance has been reported (18). Mefloquine remains the drug of choice for U.S. military deployments in such regions, primarily because its longer half-life (compared to those of Malarone or doxycycline [22]) allows weekly administration, thereby making compliance less problematic. However, compliance will inevitably be affected when a drug causes—or is suspected to cause—adverse effects.

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Adverse central nervous system (CNS) events have been associated with mefloquine use. Severe CNS events requiring hospitalization (e.g., seizures and hallucinations) occur in 1:10,000 patients taking mefloquine for chemoprophylaxis (22). However, milder CNS events (e.g., dizziness, headache, insomnia, and vivid dreams) are more frequently observed, occurring in up to 25% of patients (22). The rate of adverse neurological events associated with mefloquine is higher than for Malarone (20), and subjects receiving mefloquine in clinical trials are more likely to withdraw from the trial than those receiving placebo (8). The higher incidence of adverse events observed when the drug is used at the higher doses needed for malaria treatment (22, 23) implies a dose effect. There is no accepted biochemical basis for the neurotoxicity of the drug; however, we recently showed that mefloquine severely disrupts calcium homeostasis in rat neurons in vitro at concentrations in excess of 20 μM, an effect closely related to the acute neurotoxicity of the drug in terms of dose effect and kinetics (10). Peak plasma levels of mefloquine are 3.8 and 2.1 to 23 μM after prophylaxis and treatment, respectively (16, 25). However, the drug crosses the blood-brain barrier and accumulates as much as 30-fold in the central nervous system and mefloquine brain concentrations as high as 50 μM have been reported in human postmortem cases (14, 21). Mefloquine brain concentrations as high as 90 μM have been reported in rats given a therapy-equivalent dose rate, with concentrations in

TABLE 1. Molecular structures, neurotoxicity, and in vitro and in vivo antimalarial activity of 4-quinolinecarbinolamines analogs

Category and analog	Molecular structure of:			In vivo antimalarial activity (MfI)[a]	Neurotoxicity (IC_{50} in μM)	Antimalarial activity [(IC_{50} against *P. falciparum* strain in nM)/(therapeutic index relative to mefloquine)][e]		
	R1	R2	R3			W2	D6	TM91C235
Training set								
WR187044	$-(CH_2)_3-$[b]	Me	Me	NC	200	130 (0.61)	190 (1.4)	750 (0.87)
WR073872	CF_3	Me	Me	NC	110	15 (2.9)	37 (3.9)	59 (6.1)
WR228974	CF_3	Cl	H	0.03	70	14 (2.0)	45 (2.1)	110 (2.1)
WR157801	Ph-3′-CF_3	CF_3	H	1.2	63	<5.4 (4.6)[d]	9.7 (8.6)	17 (12.2)
WR073892	Ph-4′-Cl	Me	H	0.07	58	<6.6 (3.5)[d]	14 (5.5)	27 (7.1)
WR007333	Ph	Ph[c]	H	0.1	35	6.3 (2.2)	16 (2.9)	26 (4.4)
WR007573	Ph-4′-Cl	Ph[c]	H	NC	33	5.7 (2.3)	14 (3.1)	34 (3.2)
WR007552	Ph	Me	H	NC	33	14 (0.93)	25 (1.7)	42 (2.6)
WR226253	CF_3	Cl	Cl	0.17	30	5.7 (2.1)	18 (2.2)	34 (2.9)
WR007930	Ph	Cl	Cl	0.04	28	3.2 (3.5)	7.8 (4.7)	18 (5.1)
WR073879	CF_3	Me	H	NC	28	8 (0.6)	42 (0.88)	78 (1.2)
Mefloquine	CF_3	CF_3	H	1	25	9.9 (1.0)	33 (1.0)	82 (1.0)
WR122950	OPh-4′-Cl	Me	Me	0.03	23	14 (0.65)	30 (1.0)	65 (1.2)
WR006006	Ph	Cl	H	0.05	18	8.4 (0.85)	24 (0.99)	31 (1.9)
Test set								
WR159314	CF_3	CF_3	OCH_3	0.81	35	NT	NT	NT
WR007936	Ph-4′-Cl	Cl	Cl	1.29	19	NT	NT	NT
WR073898	Ph-4′-Cl	Me	Me	0.03	10	NT	NT	NT
WR062175	Ph	CF_3	H	0.11	10	NT	NT	NT
Conventional quinolines								
Amodiaquine	NA[f]	NA	NA	Active	400	25 (6.3)	6.2 (85)	73 (180)
Halofantrine	NA	NA	NA	Active	55	1.5 (15)	5.0 (15)	60 (30)
Chloroquine	NA	NA	NA	Active	600	500 (0.47)	11 (72)	190 (10)
Quinine	NA	NA	NA	Active	900	320 (1.1)	66 (18)	300 (10)

[a] The in vivo activity of the test compound is expressed in terms of the molar ratio of the 50% curative dose of mefloquine hydrochloride to that of the test compound after a single subcutaneous dose administration in the *P. berghei* mouse model (29). NC, not curative.
[b] This cyclopentyl substituent incorporates positions 2 and 3 of the quinoline ring.
[c] This phenyl substituent incorporates the 7 and 8 positions of the quinoline ring.
[d] The lowest concentration tested in the malaria screening assay was 2.44 ng/ml, at which inhibition was greater than 50%. Therefore, IC_{50}s of these compounds were <2.44 ng/ml. They have been expressed in nanomolar units to facilitate ease of comparison across the table.
[e] Actual therapeutic indices of mefloquine against W2, D6, and TM91C235 were 2,525, 758, and 305, respectively. Numbers in parentheses represent therapeutic indices relative to mefloquine. NT, not tested against malaria parasites.
[f] NA, not applicable.

subcompartments in the brain exceeding 100 μM (2). Since it has long been known that a prolonged disruption of neuronal calcium homeostasis may lead to neuronal cell death and injury (6, 13), it is reasonable to suppose that such events may contribute to the clinical neuropathy of the drug.

Mefloquine remains a useful antimalarial drug for many patients who are able to tolerate the drug or are unable or unwilling to take doxycycline or Malarone. However, the neurotoxicity associated with mefloquine is such that some have questioned its clinical utility as a prophylactic drug (7). There are several approaches to the amelioration of this problem, including (i) administration of neuroprotective drugs such as physostigmine (26), (ii) reformulation of mefloquine as a pure isomer (24), and (iii) reengineering of the mefloquine molecule to yield derivatives that are less neurotoxic but retain their antimalarial activity. Bhattacharjee and Karle (3) earlier showed that the in vivo potency of 4-quinolinecarbinolamines was correlated with key stereoelectronic features, including electrostatic potential and lipophilicity. However, the issues of neurotoxicity and drug resistance were not addressed. In the present report, we show that the antimalarial potential of 4-quinolinecarbinolamines may be limited by their neurotoxicity and cross-resistance of mefloquine-resistant parasites. We also describe the generation of a reliable function-based three-dimensional (3D) quantitative structure activity relationship (QSAR) pharmacophore model for neurotoxicity of this class of compounds which may be useful for selecting new quinoline analog candidates devoid of such toxicity.

MATERIALS AND METHODS

Mefloquine analogs. All of the mefloquine analogs tested were 4-quinolinecarbinolamines and were obtained through the Walter Reed Army Institute of Research chemical inventory system. Their structures have been described in earlier work (3) and are presented in Table 1 and Fig. 1. Related drugs also investigated in the present study were quinine, chloroquine, amodiaquine, and halofantrine. All of these drugs were obtained from the Walter Reed Army Institute of Research chemical inventories except for chloroquine, which was purchased from Sigma. Stock solutions (8×10^{-3} to 40×10^{-3} M in dimethyl sulfoxide [DMSO]) were prepared, and aliquots were frozen at −20°C. Prior to each experiment, aliquots were thawed and diluted appropriately in Locke's neuronal culture medium as previously described (10).

Neurotoxicity assay. The effects of mefloquine analogs on the viability of rat neurons in primary culture were investigated. Neurons were isolated and cultured as previously described (15). Animal care and use was approved by an institutional animal ethics committee in accordance with national guidelines. Neurons were exposed to graded concentrations of the mefloquine analogs for 20 min as previously described (10). Effects of the analogs on neuronal viability were assessed using the colorimetric MTT (thiazolyl blue reduction) assay as previously described (10). Results were expressed as percentages of change in viability

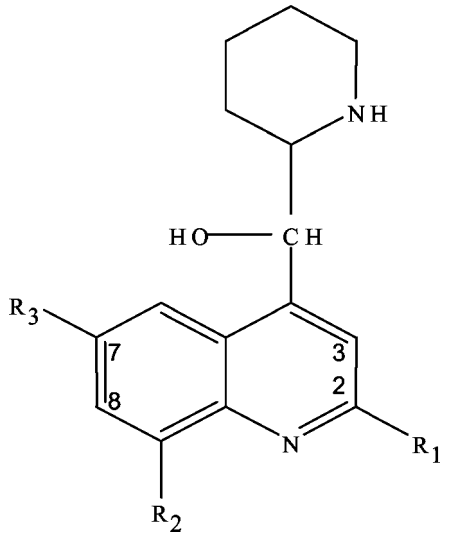

FIG. 1. Core structure of the 4-quinolinecarbinolamines. Substituents at positions R1, R2, and R3 for each analog are listed in Table 1.

compared to appropriate DMSO control results. For most analogs the final DMSO concentration in the cultures was 1 or 2% at the highest concentration tested (usually 200 μM). DMSO concentrations were lower at lower drug concentrations, as dilutions were performed in culture medium with no added DMSO. For quinine and WR187044, the highest starting concentrations were 3.2 and 1.6 mM, respectively, at final DMSO concentrations of 8% (necessary to ensure solubility). In control experiments (data not shown), neuronal viability was unaffected by 20 min of exposure to 8% (or less) DMSO. Viability data were used to plot concentration-effect curves, from which 50% inhibitory concentrations (IC_{50}s) were estimated. Each drug was tested at least in duplicate (triplicate in most cases).

Antimalarial activity. The susceptibility of different malaria strains to the mefloquine analogs was determined using the tritiated hypoxanthine incorporation assay of Desjardins et al. (9), as modified by Milhous et al. (17), except that the drug exposure period was 48 h. IC_{50}s of the drugs were determined using a nonlinear logistic dose response program. The *P. falciparum* clones used were W2, D6, and TM91C235 (19). W2 is a mefloquine-sensitive strain resistant to chloroquine and pyrimethamine. Strains D6 and TM91C235 are both resistant to mefloquine. TM91C235 is a strain from Southeast Asia that is highly resistant to mefloquine and a number of other antimalarials. Therapeutic indices were calculated using the following formula: neurotoxicity of drug (IC_{50} in micromoles)/antimalarial activity of drug (IC_{50} in micromoles). From these data, therapeutic indices relative to mefloquine were calculated using the following formula: therapeutic index of drug/therapeutic index of mefloquine. In vivo efficacy data are expressed as a mefloquine index (MfI). These values were determined using the *Plasmodium berghei* mouse model with a single subcutaneous dose at 640 mg/kg of body weight as the highest dose (29). MfI is defined as the ratio of the molar 50% curative dose of mefloquine to the 50% curative dose of the test compound. The 50% curative dose is that which cures 50% of test animals. These values are considered approximate because of the relatively few animals used in testing (5 mice/dose; six dosing levels).

Confocal microscopy. The effects of some of the analogs on neuronal calcium homeostasis were investigated as previously described (10, 15). The neurons were loaded with the calcium-sensitive dye Fluo 3-AM (5 μM for 1 h), rinsed, and returned to an incubator for 15 min prior to the imaging experiment. Changes in neuronal calcium homeostasis were monitored using a Bio-Rad Radiance 2000 confocal imaging system. Changes in cytoplasmic calcium were recorded as fluctuations in the emitted fluorescence of Fluo-3-complexed calcium at 530 nm (excitation was 488 nM). Sequential image scans of fields containing 5 to 25 neurons were used to construct temporal profiles of the effects of the different analogs. Scans were made at 10-s intervals. To compare the fluorescence levels in different neurons (which were often in slightly different focal planes) on different days, readings at each time point were normalized to the first value measured for each neuron. Drugs (at concentrations of 100 μM or 4× the drug's IC_{50} in 1% DMSO) were added after four scans, and their effects on calcium homeostasis were monitored for 6 min. Each drug was tested at least in triplicate. After subtraction of baseline values (1% DMSO control), the effects of the drugs are expressed as the percentage of increase in Fluo-3 fluorescence over time. For the chloroquine experiments, the drug was prepared in Locke's buffer, which was also used as the baseline control.

Generation of a neurotoxicity pharmacophore. The 3D neurotoxicity pharmacophore model was developed using the HypoGen algorithm of the CATALYST methodology (1). Structures of the 4-quiniolinecarbinolamines were imported into CATALYST to create a training set, and energy was minimized to the closest local minimum with the generalized CHARMM-like force field as implemented in the program. The CATALYST model treats molecular structures as templates comprised of chemical functions localized in space that will bind effectively with complementary functions on the respective binding proteins. The most relevant chemical features are extracted from a small set of compounds that cover a broad range of activity (28). Molecular flexibility is taken into account by

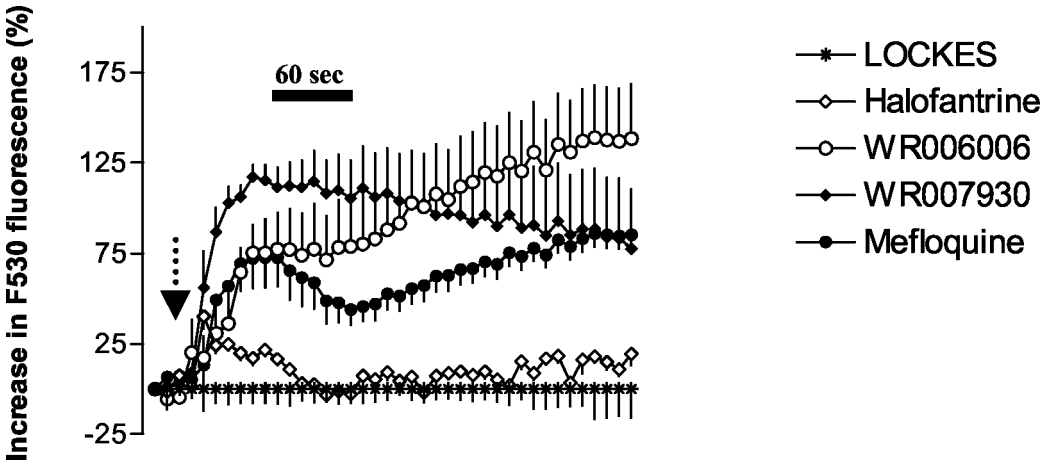

FIG. 2. Effects of 4-quinolinecarbinolamines and halofantrine on neuronal calcium homeostasis. Drugs were added after 30 s as indicated by the arrow, and their effects on neuronal cytoplasmic calcium levels were monitored using confocal microscopy. Data are expressed as the percentages of change (± standard errors of the means [SEM]) in Fluo 3-AM (F530) fluorescence after subtraction of appropriate baseline values (1% DMSO). Mefloquine, WR006006, and WR007930 at concentrations of 100 μM induced sustained elevations in cytoplasmic calcium levels. Halofantrine (100 μM) exhibited a more modest and transient increase in cytoplasmic calcium levels. The concentration of mefloquine used is four times higher than the compound's IC_{50} against embryonic rat neurons and represents the maximum level of accumulation of the drug in the brain after transport across the blood-brain barrier.

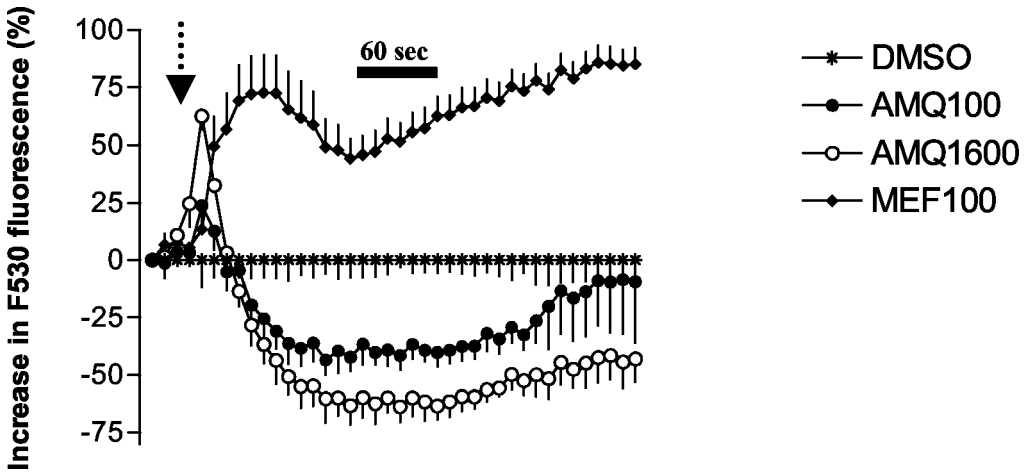

FIG. 3. Effect of amodiaquine on neuronal calcium homeostasis. Drugs were added after 30 s as indicated by the arrow, and their effects on neuronal cytoplasmic calcium levels were monitored using confocal microscopy. Data are expressed as the percentages of change (± SEM) in Fluo 3-AM (F530) fluorescence after subtraction of appropriate baseline values (1% DMSO). Amodiaquine at a concentration of 100 μM (AMQ100) induced a more modest and transient increase in the cytoplasmic calcium concentration than mefloquine (MEF100). At a concentration (1,600 μM [AMQ1600]) equivalent to that used for mefloquine, amodiaquine also induced a sharp, albeit brief, increase in the cytoplasmic calcium concentration that was followed by a decline below the baseline level.

considering each compound as an ensemble of conformers representing different accessible areas in 3D space. The "best searching procedure" was applied to select representative conformers within 10 kcal/mol of the global minimum (12). CATALYST allows the use of structure and activity data for a set of lead compounds to create a hypothesis characterizing the activity of the lead set. HypoGen generates 10 hypotheses for the training set with various costs. The hypotheses are described by a set of functional features such as hydrophobicity, hydrogen bond donor, hydrogen bond acceptor, and positively and negatively ionizable sites distributed over a 3D space. The hydrogen bonding features are vectors, whereas all other functions are points. The statistical relevance of the obtained hypothesis is assessed on the basis of their cost relative to the null hypothesis and their correlation coefficient. The difference between the fixed and null costs in the present study was found to be 68 bits, and the cost range between the first and the 10th hypotheses is about 8 bits. Therefore, it can be expected that for all these hypotheses there is a 75 to 90% chance of representing a true correlation of the data. The validation of statistical significance of a hypothesis is based on Fischer's randomization test as implemented in CATALYST (1). However, the main goal of performing this type of validation is to check whether there is a strong correlation between the chemical structures and biological activity.

Prediction of neurotoxicity of test set members. The neurotoxicity pharmacophore was converted into a 3D-shape-based template. This template was used to predict the neurotoxicity of a test set of compounds including four 4-quinolinecarbinolamines, amodiaquine, chloroquine, halofantrine and quinine. The IC_{50}s of the compounds were estimated by fast-fitting their 3D structures to the template. The analogs were predicted to be neurotoxic when their estimated IC_{50}s were less than 300 μM. This criterion was based on a toxicity threshold of 100 μM (the maximum level to which mefloquine accumulates across the blood-brain barrier) multiplied threefold to account for the error inherent in the pharmacophore model. These criteria are conservative, because we have assumed that mefloquine analogs may accumulate in the CNS to the same degree as mefloquine and that estimates of neurotoxicity will be lower by a factor of

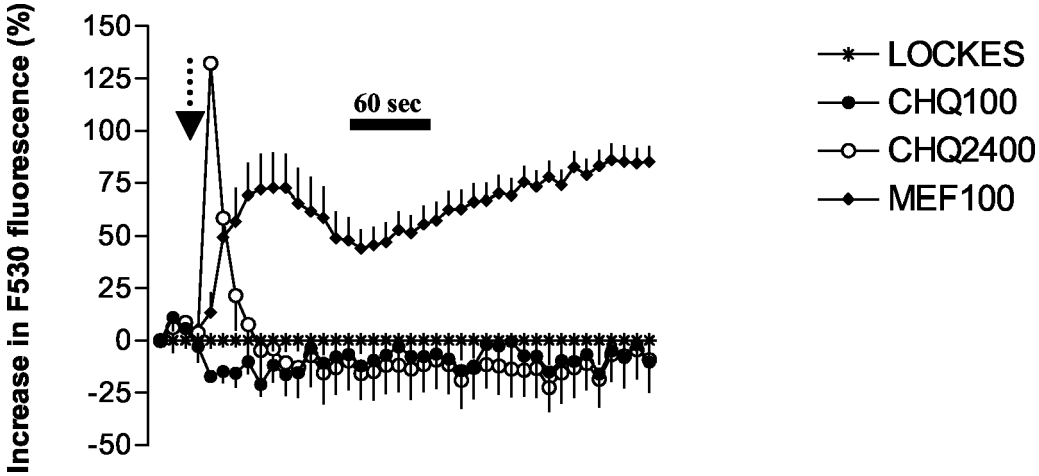

FIG. 4. Effect of chloroquine on neuronal calcium homeostasis. Drugs were added after 30 s as indicated by the arrow, and their effects on neuronal cytoplasmic calcium levels were monitored using confocal microscopy. Data are expressed as the percentages of change (± SEM) in Fluo 3-AM (F530) fluorescence after subtraction of appropriate baseline values (1% DMSO for mefloquine and Locke's buffer for chloroquine). In comparison to mefloquine (100 μM [MEF100]), chloroquine (100 μM [CHQ100]) did not alter calcium homeostasis. At concentrations (2,400 μM [CHQ2400]) equivalent to that used for mefloquine, chloroquine induced a sharp but brief increase in the cytoplasmic calcium concentration that was followed by a decline below the baseline level.

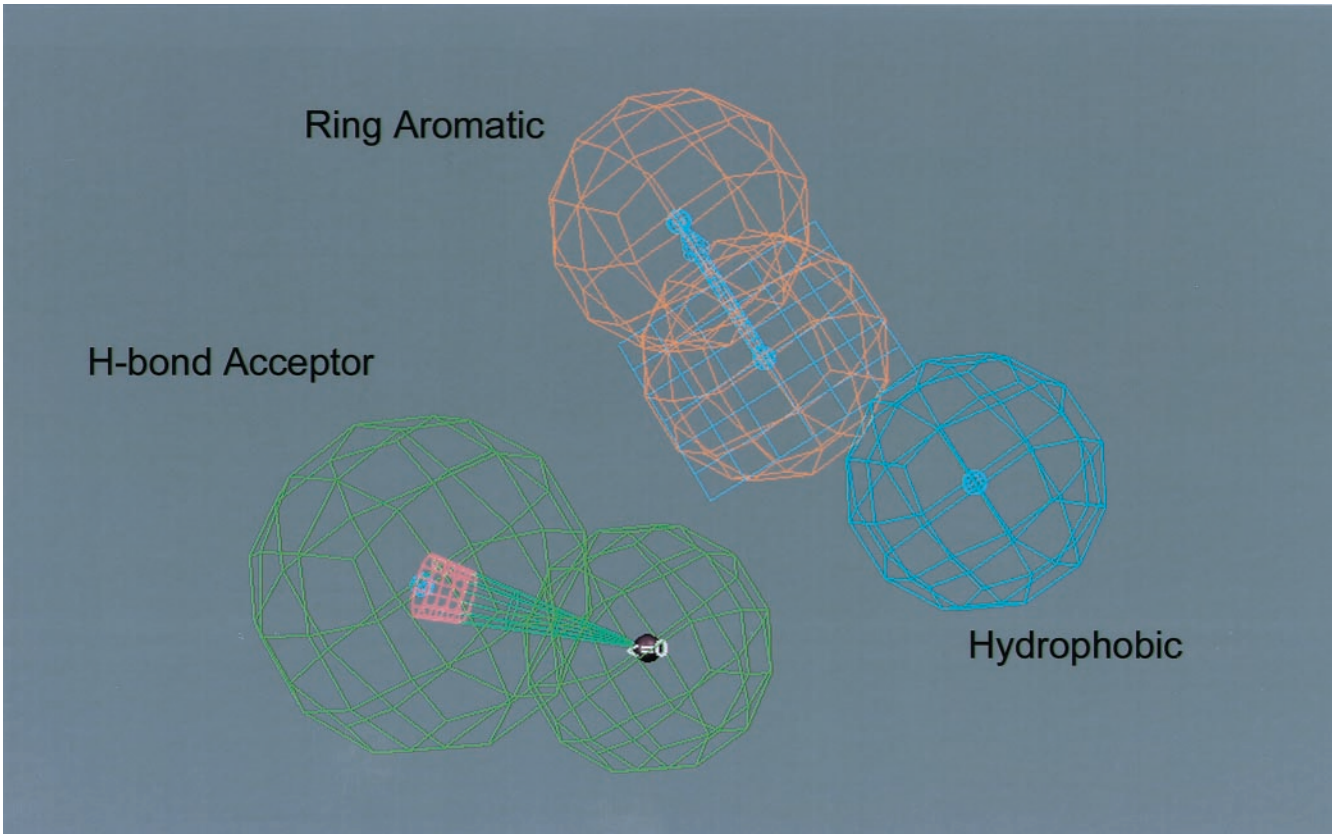

FIG. 5. Neurotoxicity pharmacophore for 4-quinolinecarbinolamines: The pharmacophore for the neurotoxicity of 4-quinolinecarbinolamines is depicted. The key functional features required for neurotoxicity include (i) one lipid type H-bond acceptor function (shown in green with a direction vector), (ii) one ring aromatic function (shown in light magenta), and (iii) one aliphatic hydrophobic function (shown as a blue sphere).

three in every case. The actual IC_{50}s of the test set members were then determined as described above.

RESULTS

Neurotoxicity and antimalarial activity. All the 4-quinolinecarbinolamines tested exhibited a neurotoxic effect on primary rat neurons, with 16 of 18 analogs exhibiting IC_{50}s of less than 100 μM after 20 min of exposure (Table 1). Two analogs, WR073872 and WR0187044, possessed IC_{50}s that were higher than 100 μM for neurons; however, neither of these has a curative antimalarial effect in vivo (Table 1). Twelve analogs were less neurotoxic than mefloquine. Five of these, WR157801, WR073892, WR007333, WR226253, and WR007930, have curative antimalarial activity in vivo, lower IC_{50}s than mefloquine for all the *P. falciparum* strains tested, and higher therapeutic indices than mefloquine against TM91C235 and therefore represent the best candidates for further development (Table 1). Both mefloquine-resistant *P. falciparum* strains appeared to exhibit a degree of cross-resistance to the 4-quinolinecarbinolamines, since in every case IC_{50}s for these strains were higher than for W2 (Table 1). This was not necessarily the case for the other quinolines tested. Among the conventional quinolines, only halofantrine possessed an IC_{50} of less than 100 μM for neurons. The IC_{50}s of halofantrine against the three *P. falciparum* strains were always lower, and the relative therapeutic indices were always higher, than those of the five most promising 4-quinolinecarbinolamines.

Effects of quinolines on neuronal calcium homeostasis. The effects of a number of different quinolines at a concentration of 100 μM on neuronal calcium homeostasis were investigated using confocal microscopy. Treatment of neurons with mefloquine, WR006006, WR007930, halofantrine, and amodiaquine but not with chloroquine increased cytoplasmic calcium concentrations (Fig. 2, 3, and 4). This effect was much more pronounced with the 4-quinolinecarbinolamines (Fig. 2). Halo-

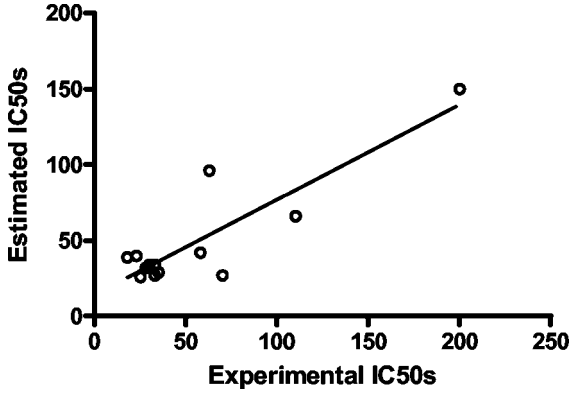

FIG. 6. Correlation ($r = 0.86$; $P < 0.0001$ [Pearson correlation]) of experimental and estimated neurotoxicity (IC_{50}) data for the training set.

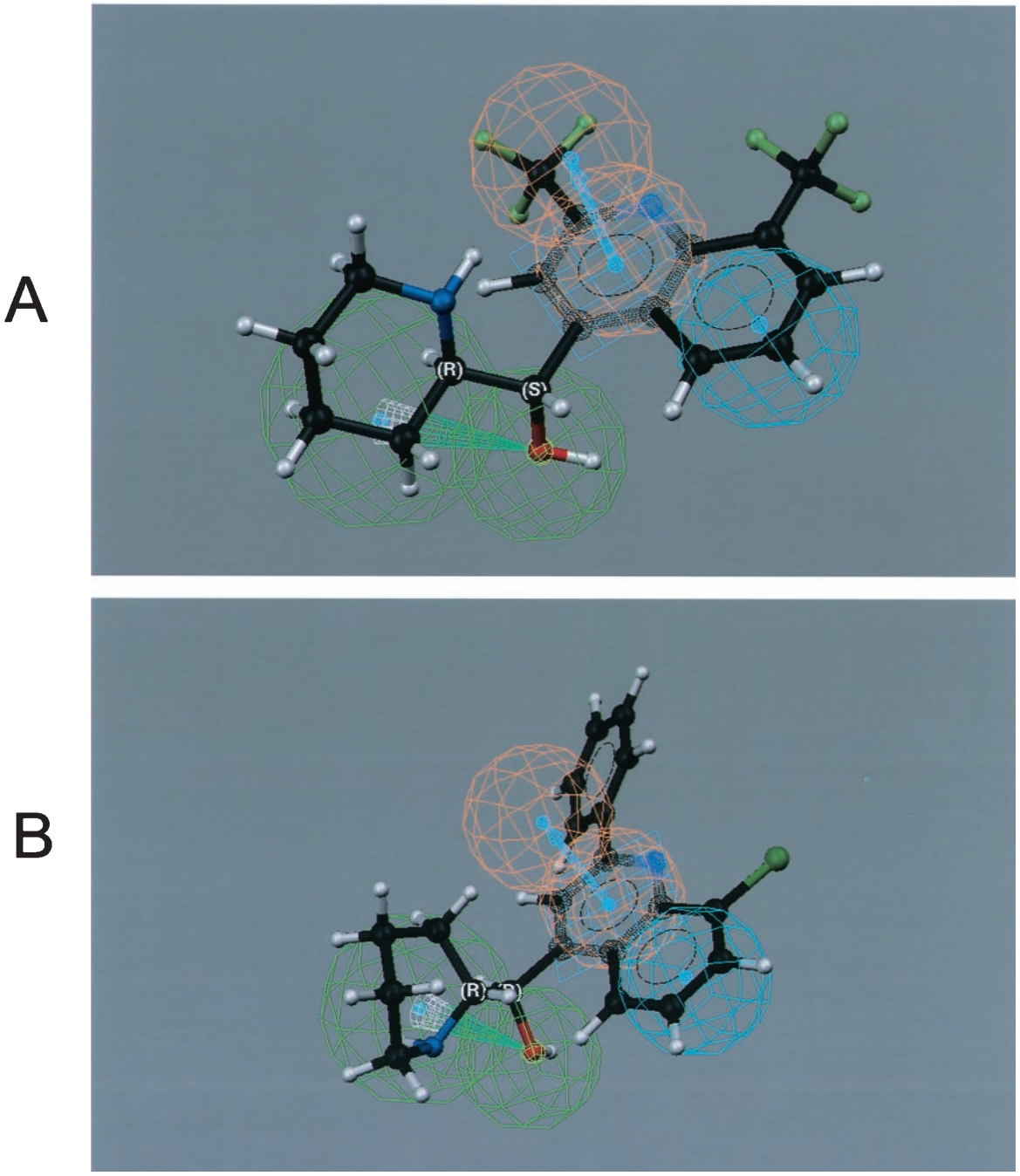

FIG. 7. Mapping of the pharmacophore on two known neurotoxic compounds, mefloquine (A) and WR006006 (B), showing how all the features of the pharmacophore map onto them.

fantrine induced a transient increase in cytosolic calcium concentrations (Fig. 2). This effect was similar in duration and magnitude to that observed at lower mefloquine concentrations (data not shown). At concentrations approximately four times higher than their IC_{50}s, chloroquine and amodiaquine treatment induced a sharp initial increase in intracellular calcium concentration followed by a sharp decline relative to baseline values (Fig. 3 and 4). The effects of chloroquine and amodiaquine were qualitatively different from that of mefloquine at an equivalent concentration (100 μM), as the latter drug induces a more sustained elevation in cytoplasmic calcium concentrations (Fig. 3 and 4).

Development of mefloquine neurotoxicity pharmacophore. The 3D-QSAR pharmacophore model for the neurotoxicity of 4-quinolinecarbinolamines was found to contain one hydrogen bond acceptor (lipid) function, one aliphatic hydrophobic function, and a ring aromatic function at specific geometric orientation in the molecule (Fig. 5). It was developed from a set of 14 structurally diverse 4-quinolinecarbinolamines that included the parent compound mefloquine shown in Table 1. The

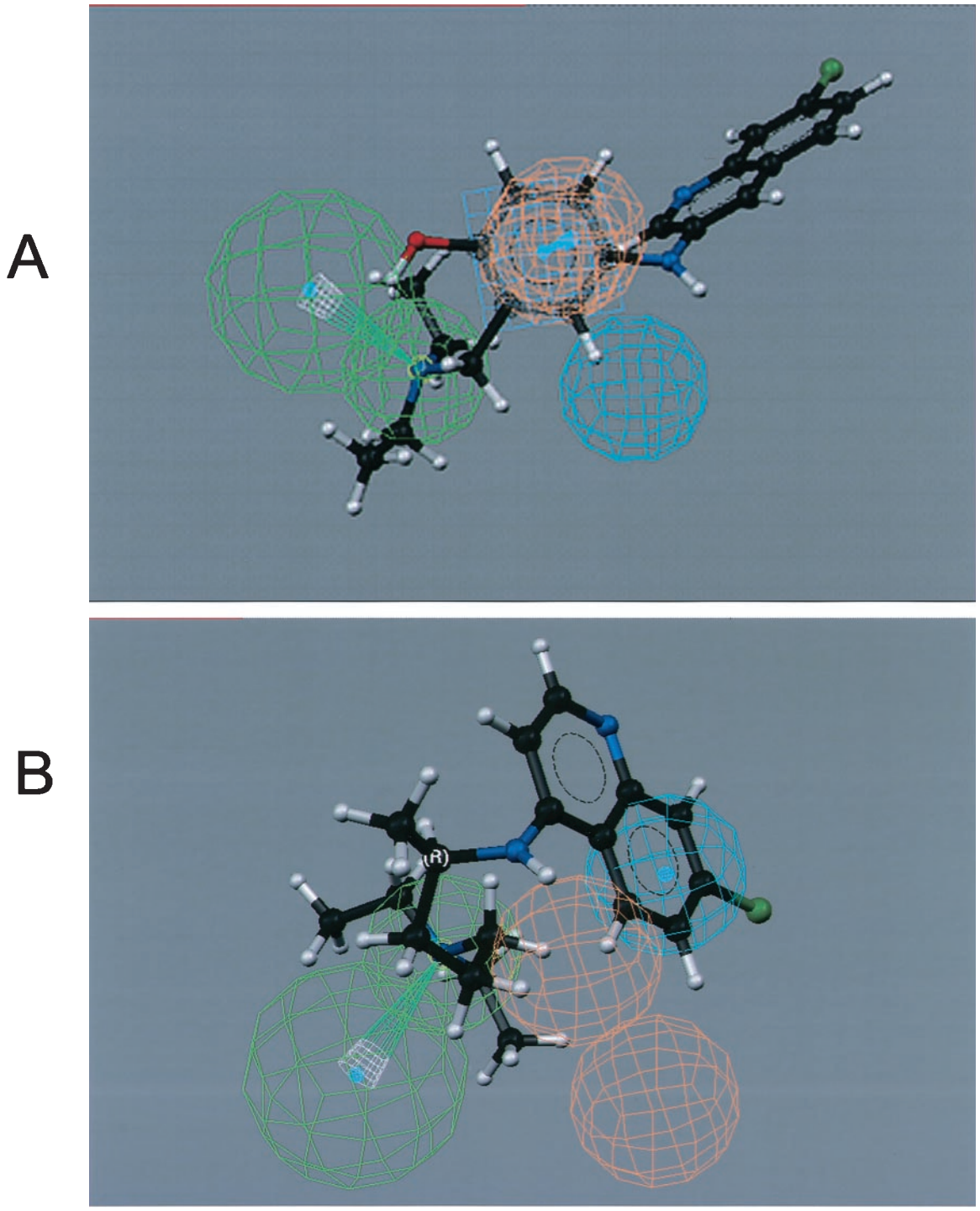

FIG. 8. Mapping of the pharmacophore on two nonneurotoxic compounds, amodiaquine (A) and chloroquine (B), showing how not all of the features of the pharmacophore map onto them.

experimental neurotoxicity data of the 14 analogs covers a range from 18 to 200 μM. The pharmacophore was developed using CATALYST methodology (1) by placing suitable constraints on the number of available features such as aromatic hydrophobic or aliphatic hydrophobic interactions, hydrogen bond donors, hydrogen bond acceptors, hydrogen bond acceptors (lipid), and ring aromatic sites to describe the neurotoxicity of the 4-quinolinecarbinolamines. Earlier reported quantum chemical calculations of the stereoelectronic properties for a few of these compounds (3) provided guidance for selection of these physicochemical features. During pharmacophore development, the molecules were mapped to the features, with their predetermined conformations generated using the fast-fit techniques in the CATALYST methodology. The procedure

TABLE 2. Actual and predicted neurotoxicity of test set compounds

Analog	Predicted value[a]	Neurotoxic?[b]	Good prediction?[c]
Amodiaquine	620	No	Yes
Halofantrine	50	Yes	Yes
Chloroquine	550	No	Yes
Quinine	540	No	Yes
WR062175	110	Yes	Yes
WR159314	140	Yes	Yes
WR007936	64	Yes	Yes
WR073898	54	Yes	Yes

[a] Predicted value for the IC_{50} of the compounds against rat neurons after fast-fit mapping of the compound's structure to the neurotoxicity pharmacophore.

[b] The analog was predicted to be neurotoxic if the predicted IC_{50} was <300 μM (100 μM threshold multiplied threefold for the error constraints of the pharmacophore model).

[c] "Yes" or "No" indicates whether the compound was or was not correctly categorized as being neurotoxic on the basis of the experimental values in Table 1.

resulted in the generation of 10 alternative pharmacophores for antimalarial activity of the compounds and appeared to perform quite well for the training set. Significantly, the best pharmacophore (Fig. 5) is also statistically the most relevant pharmacophore. The estimated activity values, along with the experimentally determined neurotoxicity values of the compounds, are presented in Fig. 6. Experimentally determined IC_{50} values were well correlated with estimated values within a range of uncertainty of 3 ($r = 0.86$; $P < 0.0001$ [Pearson correlation]). The more neurotoxic analogues of the series such as mefloquine and WR006006 map all the functional features of the pharmacophore (Fig. 7), whereas the nonneurotoxic compounds such as amodiaquine and chloroquine do not map all the features (Fig. 8).

Assessment of predictive value of the pharmacophore using the test set. To cross-validate the reliability of the pharmacophore, we searched the in-house chemical inventory system database with the pharmacophore as the template and identified several 4-quinolinecarbinolamines. The test set contains four 4-quinolinecarbinolamines together with the four conventional antimalarials halofantrine, chloroquine, amodiaquine, and quinine. The four 4-quinolinecarbinolamines and halofantrine were predicted to be neurotoxic, whereas quinine, chloroquine, and amodiaquine were not (Table 2). In all cases, the qualitative predictions made about neurotoxicity were accurate (Table 2).

DISCUSSION

The clinical utility of mefloquine or a mefloquine-like drug would be enhanced if measures could be employed to negate the toxicity of the drug. This could be achieved through the use of an intrinsically less neurotoxic analog or by lowering the required dose of a similarly neurotoxic analog. Of the 18 mefloquine analogs tested here, 2, WR187044 and WR073872, possessed IC_{50}s greater than 100 μM. This is a physiologically relevant threshold, since mefloquine crosses the blood-brain barrier and accumulates in the CNS at a level 10- to 30-fold higher relative to plasma levels at therapeutic dose rates, reaching concentrations as high as 100 μM (2, 14, 20). While it is possible that 4-quinolinecarbinolamines do not cross the blood-brain barrier to the same degree as mefloquine, in the absence of specific information to the contrary it is prudent to take a conservative approach and assume that they do. In any case, WR187044 and WR073872 do not represent viable alternative drugs to mefloquine, since they display little in vivo antimalarial activity (Table 1).

The utility of a mefloquine replacement drug could also be improved if the relative dose rate could be reduced. This might be possible if a mefloquine analog were at worst equivalent to mefloquine in terms of neurotoxicity but exhibited a greater relative therapeutic index against mefloquine-resistant strains of malaria. Selection of a particular relative therapeutic index as a threshold is necessarily problematic, because the reduction of dose that would be possible and the degree to which CNS accumulation would be consequently reduced are difficult to predict. Therefore, an empirically derived benchmark is probably the most appropriate. Halofantrine is a conventional quinoline antimalarial that displays some cross-resistance to mefloquine both in vitro (high relative IC_{50}s against D6 and TM91C235; Table 1) and in vivo (5). Halofantrine was the only one of the conventional antimalarials to exhibit neurotoxicity in the same concentration range as the 4-quinolinecarbinolamines, with some mechanistic attributes in common.

Therefore, we propose that the threshold therapeutic index relative to mefloquine should be approximately 30 against TM91C235, the same as that of halofantrine. On this basis, the 4-quinolinecarbinolamines tested here do not exhibit sufficient selective antimalarial activity.

However, this does not mean that other quinolines would not be suitable replacement drugs (11, 27). Three of the conventional antimalarial antimalarials tested here were much less neurotoxic than mefloquine and exhibited qualitatively different mechanisms of action against neurons. Further, not all quinoline antimalarials exhibit the same inherent cross-resistance to mefloquine as halofantrine and the 4-quinolinecarbinolamines (Table 1). Therefore, there are reasonable grounds to propose that there may be other, as-yet-undiscovered quinolines that exhibit much greater selective toxicity than those tested here. One might be able to identify such compounds by developing a reliable 3D pharmacophore and using it for virtual screening of compound databases, since these techniques not only enable predictions of the biological activity of unknown compounds but also provide a basis for custom-designed synthesis of compounds with optimum efficacy that have both the necessary chemical functions and the requisite stereoelectronic properties (4). As a first step in the development of such an in silico screening method for quinoline antimalarials, we have developed a pharmacophore on the basis of the neurotoxicity data for the 4-quinolinecarbinolamines.

The crucial molecular features that appear to correlate with the neurotoxic properties of the 4-quinolinecarbinolamines include (i) one hydrogen bond acceptor (lipid) function, (ii) one aliphatic hydrophobic function, and (iii) a ring aromatic function at specific geometric locations distributed over the 3D space of the molecule. When the pharmacophore was employed as a qualitative in silico screening tool, we observed that the approach was able to correctly predict whether a series of quinolines were neurotoxic (or not) on the basis of the mapping of their 3D structures to the pharmacophore (Table 2 and Fig. 7 and 8). These preliminary data suggest that the approach

has merit. The next step in the process is obviously to develop an appropriate pharmacophore on the basis of the antimalarial activity of quinolines. This approach is presently under investigation in our laboratory.

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DEPARTMENT OF VETERANS AFFAIRS
Veterans Health Administration
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UNDER SECRETARY FOR HEALTH'S INFORMATION LETTER

POSSIBLE LONG-TERM HEALTH EFFECTS FROM THE MALARIAL PROPHYLAXIS MEFLOQUINE (LARIAM)

1. **Purpose.** This Under Secretary for Health's Information Letter provides information to clinicians who examine and provide care to veterans who may have taken mefloquine as a malaria prophylaxis while on active duty in Southwest Asia during Operation Iraqi Freedom (OIF) and Operation Enduring Freedom (OEF).

2. **Background**

a. During OIF and OEF, the United States (U.S.) Department of Defense (DOD) provided mefloquine (Lariam) to some U.S. service members to protect them against endemic malaria.

b. Mefloquine is approved by the U.S. Health and Human Services Food and Drug Administration (FDA) for protection against malaria, and since the late 1980s it has become widely recommended for malaria chemoprophylaxis. Mefloquine can cause common mild side effects including vivid dreams and mild psychiatric symptoms, which can be sufficiently uncomfortable as to affect compliance. In addition, a number of anecdotal and media reports have suggested that mefloquine has caused more serious effects, including violent and suicidal behavior, and symptoms similar to Post-traumatic Stress Disorder (PTSD). These media accounts link reports of such behavior to mefloquine use among returning OIF and OEF veterans, for example, homicides and suicides among five service members returning to Ft. Bragg, NC, in the Summer of 2002. Concerns that mefloquine might cause violent behavior is not new; a Canadian soldier accused of homicide claimed that taking mefloquine, while deployed to Somalia in 1992, had caused his violent behavior.

c. Adding to this concern, the DOD warning label "Information for Clinicians" for mefloquine (taken essentially from the equivalent FDA label), includes the following:

"Rare instances of suicide in patients taking mefloquine have been reported but no studies have demonstrated a statistical association between mefloquine use and suicide, suicidal ideas, suicide attempts, or any other violent behavior. Patients with a history of psychiatric illness may be vulnerable to mefloquine-related psychiatric symptoms, and the package insert recommends against prescribing (it) to patients with a history of psychiatric or alcohol problems. Often, potential neuropsychiatric side effects are the greatest concern for patients. Side effects may include anxiety, paranoia, depression, agitation, restlessness, mood changes, panic attacks, forgetfulness, hallucinations, aggression, and psychotic behavior. Symptoms may continue long after mefloquine use has been stopped. If neuropsychiatric symptoms occur, mefloquine use should be discontinued in favor of other prophylactic medications or

measures. Potential side effects that can impair reaction time and thinking include sensory and motor neuropathies, encephalopathy, convulsions, psychosis, nightmares, dizziness, and confusion. Studies indicate that these may occur in 1 in 2,000 to 1 in 13,000 people who receive prophylactic mefloquine."

d. VHA held a meeting April 13, 2004, to discuss possible responses to this issue. The meeting included representatives from the Office of Public Health and Environmental Hazards and Office of Patient Care Services' Medical-Surgical, Mental Health, and Pharmacy Benefits & Management, and other VHA leaders and experts in neurology, mental health, infectious disease, and toxicology. The group concluded that the Department of Veterans Affairs (VA) needed a well-grounded response to current concerns among veterans, their families, Congress, the media, VA health care providers, and others about possible long-term health effects and disability among OIF and OEF veterans from taking mefloquine. In particular, VHA health care providers will need concise and accurate medical information about mefloquine health effects to answer questions and concerns of veterans who are returning from deployments in Southwest Asia.

e. To develop guidance on possible long-term and chronic health effects from mefloquine, this group conducted a literature review of more than sixty reports that included eight surveys of travelers, 34 case reports of adverse events, two Cochrane reviews, seven epidemiological studies including clinical trials and prospective studies, and nine general reviews of multiple case reports, which included manufacturer and FDA warning label summaries. The most recent Cochrane review (2004) examined ten clinical trials involving 2750 adult participants, five of which were field trials, mainly of male soldiers.

3. Guidance

a. The following summary is to assist VA health care providers when they are providing care to veterans who may have taken mefloquine while on active duty. Since there are no practical tests for mefloquine, nor are there any specific tests that can be recommended specifically for veterans who took mefloquine while on active duty, medical care needs to focus upon occupational health issues: e.g., taking a thorough military and medical history, including taking of mefloquine, along with a basic medical examination that includes appropriate laboratory tests relating to the veteran's complaints and medical findings.

b. Review of available literature (see Att.A for references and summaries) suggests that certain health effects may be associated with mefloquine, some of which may persist after the drug is stopped. Self-reported symptoms in "travelers surveys" include: insomnia, mood impairment, depression, "strange thoughts," altered spatial perception, sleeping disturbances, fatigue, dizziness and other neuropsychiatric effects, lasting in some instances more than 2 months. Clinical trials and epidemiological studies suggest that reported side effects are not common, are self-limiting, and include: depression, panic attacks, anxiety, insomnia, vertigo, nausea and headache, and strange or vivid dreams. However, such studies have only limited power to detect more rare and serious adverse events.

c. The most severe and persistent adverse effects appear in "case reports." In those instances, consistent with the nature of a case report, the relevant signs and symptoms began while mefloquine was being taken, and persisted in some reports for weeks, months or even years after the drug was stopped. ***NOTE:*** *Mefloquine has a long half-life in humans of 15 to 30 days.* Adverse effects that are reported to persist for significant periods after the drug is stopped, or that could be associated with long-term health effects, include the following which lists in decreasing frequency the cases; ***NOTE:*** *The reported number of individual cases and the number of published reports for that health effect are shown in parenthesis; i.e., 16/12 means that there were sixteen reported cases and twelve published reports.*

(1) Anxiety, paranoia, hallucinations, depression, suicidal ideation, cognitive and other neuropsychiatric symptoms (16/12),

(2) Acute and paranoid psychosis (10/9),

(3) Convulsions, grand mal seizures, coma and abnormal electroencephalography (EEG) (9/4),

(4) High frequency sensorineural hearing loss and tinnitus, with partial or no remission (3/1),

(5) Acute lung injury with diffuse alveolar damage (2/1),

(6) Elevated liver function tests or fatty liver (2/2),

(7) Multifocal myoclonus (1/1),

(8) Fatal toxic epidermal necrolysis (1/1),

(9) Trigeminal sensory neuropathy (1/1),

(10) Atrial flutter (1/1), and

(11) Mefloquine overdose induced encephalopathy (1/1).

d. Veterans need to be informed that seeking care for possible mefloquine-related conditions does not constitute a claim for compensation. ***NOTE:*** *Veterans wishing to file a compensation claim need to be referred to a Veterans Benefits Counselor, or advised to contact the appropriate VA Regional Office at 1-800-827-1000.*

4. Contact. Questions regarding this information letter may be addressed to the Environmental Agents Service (131) at (202) 273-8579.

S/ Arthur S. Hamerschlag for
Jonathan B. Perlin, MD, PhD, MSHA, FACP
Acting Under Secretary for Health

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ATTACHMENT A

SUMMARY OF LITERATURE ON POSSIBLE LONG-TERM CHRONIC HEALTH EFFECTS FROM MEFLOQUINE

1. To develop guidance on possible long-term health effects from mefloquine, a Veterans Health Administration (VHA) expert group that included representatives from the Office of Public Health and Environmental Hazards and Office of Patient Care Services' Medical-Surgical, Mental Health, and Pharmacy Benefits & Management, and other VHA leaders and experts in neurology, mental health, infectious disease, and toxicology, conducted a literature review that located seven health surveys of travelers, thirty-four case reports of adverse events, two Cochrane reviews, six epidemiological studies including clinical trials and prospective studies, and nine general reviews of multiple case reports including manufacturer and Food and Drug Administration (FDA) warning label summaries. In addition the two Cochrane reviews (the most recent dated 2004) examined ten clinical trials involving 2750 adult participants. Five of those were field trials, mainly of male soldiers. The following table, sorted by study-type, then by date, summarizes this information.

Title, Authors, Reference	***Date***	***Study Type - Subjects***	***Major Findings***
"Low body mass index is associated with an increased risk of neuropsychiatric adverse events and concentration impairment in women on mefloquine," van Riemsdijk MM, Sturkenboom MC, Ditters JM, Tulen JH, Ligthelm RJ, Overbosch D, Stricker BH; British Journal of Clinical Pharmacology, 2004;57(4):506-12.	2004	Survey of 151 Dutch travelers from 1999 to 2000 before and up to 3 weeks (pre travel) after taking mefloquine	Significant impairment of mood state observed subjects with body mass index (BMI) < or = 20 kg m(-2); Stratification for gender showed that the total mood disturbance in females in the lowest BMI category significantly increased by 8.42 points [95 percent confidence interval (CI) 3.33, 13.50], whereas BMI did not affect the risk in males; Stratification for history of use of mefloquine showed that the risks were highest in first-time users; An sustained attention performance test showed reaction time in women with a BMI < or = 20 kg m(-2) increased significantly by 22.5 ms (95 percent CI 7.80, 37.20), whereas reaction time in men showed a slight and nonsignificant decrease. ***CONCLUSION:*** *Risk factors for mefloquine-associated neuropsychiatric adverse events and concentration impairment are female gender, low BMI, and first-time use. The frequency of neuropsychiatric effects is highest in women with a BMI < or = 20 kg m(-2).*
"Many travelers suffer of side-effects of malaria prophylaxis," Rietz G, Petersson H, Odenholt I; Lakartidningen, 2002 Jun 27;99(26-27):2939-44.	2002	Survey of about 500 Swedish travelers before and after their trip, with 62 percent response rate	Travelers taking any malarial prophylaxis reported greater rate of symptoms compared to controls (59 percent vs. 41 percent), and that their trip had been negatively affected by their symptoms; Neuropsychiatric symptoms most common among mefloquine takers but the difference was not significant; Travelers taking mefloquine more frequently associated their symptoms with that drug; travelers most worried about taking malaria prophylaxis prior to the trip reported symptoms more often than those not feeling any anxiety.

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Title, Authors, Reference	*Date*	*Study Type - Subjects*	*Major Findings*
"Neuropsychiatric events during prophylactic use of mefloquine before traveling," van Riemsdijk MM, Ditters JM, Sturkenboom MC, Tulen JH, Ligthelm RJ, Overbosch D, Stricker BH; European Journal of Clinical Pharmacology, 2002 Sep;58(6):441-5.	2002	Survey 179 Dutch travelers from 1999 to 2000 before and for three weeks after taking mefloquine (prior to traveling)	Females reported adverse events more frequently than males (P=0.005); Small but significant increase in the score on the domain fatigue [0.74 points, 95 percent confidence interval (CI) 0.18, 1.30 exclusively in females and not in males; First-time users increased 2.81 points (95 percent CI 0.70, 4.92) on mood state test, and among those, women showed the largest increase of 4.58 points (95 percent CI 0.74, 8.43). The use of mefloquine was associated with neuropsychiatric adverse effects. Females encountered neuropsychiatric effects more frequently than males, which could be confirmed by validated psychological tests. Neuropsychiatric effects were more common in first-time users than in individuals who had used mefloquine before.
"Reported side effects to chloroquine, chloroquine plus proguanil, and mefloquine as chemoprophylaxis against malaria in Danish travelers," Petersen E, Ronne T, Ronn A, Bygbjerg I, Larsen SO; Journal of Travel Medicine, 2000 Mar-Apr;7(2):79-84.	2000	Survey of self reports among 5, 446 Danish travelers from 1996 to 1998	5, 446 Danish travelers surveyed (76.3 percent response) on drug compliance, hospitalization and premature termination of travel, following use of chloroquine, chloroquine plus proguanil, or mefloquine; Compliance significantly better for mefloquine users (83.3 percent among short term travelers re. 76.3 percent among chloroquine plus proguanil users); 84.8 percent, 59.3 percent and 69.5 percentreported no symptoms using chloroquine, chloroquine plus proguanil, and mefloquine, respectively; 0.6 percent, 1.1 percent and 2.8 percent reported "unacceptable" symptoms, respectively; Compared to chloroquine, mefloquine users had a significantly higher relative risk (RR) of reporting depression, RR 5.06 (95 percent CI 2.71 - 9.45), "strange thoughts," RR 6.36 (95 percent CI 2.52 - 16.05) and altered spatial perception, RR 3.00 (95 percent CI 1.41 - 6.41). ***CONCLUSION**: Overall mefloquine is tolerated at least as well as chloroquine plus proguanil and shows better compliance, however, symptoms related to the central nervous system are more prevalent in mefloquine users and when symptoms develop, they are perceived as more severe.*
"Neuropsychiatric problems in 2,500 long-term young travelers to the tropics," Potasman I, Beny A, Seligmann H;,Journal of Travel Medicine, 2000 Jan;7(1):5-9.	2000	Survey of neuropsychiatric problems and previous psychological consultation of 2,500 young travelers to tropical countries	Out of 1,340 respondents, 151 (11.3 percent) reported they had neuropsychiatric problems (NPP) during travel compared to 2.3 percent who needed psychological consultation before travel (probability (p) <.001); In a follow up, 117 of 151 responded to a study questionnaire (mean age 24.4 years, 54.7 percent female, mean stay abroad 5.3 months) the most common reported NPP were sleeping disturbances (52.1 percent), fatigue (48.7 percent) and dizziness (39.3 percent).; 33 (2.5 percent) reported severe symptoms, 16 (1.2 percent) had symptoms lasting more than 2 months; 7 had pure or mixed depressive symptoms; Consumption of recreational drugs admitted by 22.2 percent; Mefloquine used significantly more often by those who suffered NPP, compared to the entire cohort (98.2 percent vs. 70.7 percent; p<.001); ***CONCLUSIONS:** Long-term travel to the tropics was associated, in this cohort, with a considerable rate of neuropsychiatric symptoms. The majority of the responding travelers were females, used mefloquine as prophylaxis, and at least one fifth used recreational drugs.*

Title, Authors, Reference	*Date*	*Study Type - Subjects*	*Major Findings*
"Adverse effects associated with antimalarial chemoprophylaxis," Corominas N, Gascon J, Mejias T, Caparros F, Quinto L, Codina C, Ribas J, Corachan M.; Medicina Clinica, 1997 May 24;108(20):772-5.	1997	Survey of 1,054 Spanish travelers who traveled from 1992 to 1994	Self reports among 1,054 travelers taking various malarial prophylaxis including mefloquine; 18.4 percent reported adverse reactions including 12.4 percent on chloroquine, 17.2 percent on chloroquine + proguanil, and 20.3 percent on mefloquine (differences not significant); Neuropsychiatric reactions more frequent in the mefloquine group ($p < 0.01$); Gastrointestinal reactions less common in the chloroquine group ($p = 0.04$); Transitory eye disorders more frequent in the chloroquine + proguanil group ($p = 0.01$); Travelers with adverse reactions in mefloquine group had significantly lower weight than those who did not present them ($p < 0.01$); Mefloquine has greater neuropsychiatric toxicity and is worse tolerated in low weight patients.
"Neuro-psychiatric effects of antimalarials," van Riemsdijk MM, van der Klauw MM, van Heest JA, Reedeker FR, Ligthelm RJ, Herings RM, Stricker BH; European Journal of Clinical Pharmacology, 1997;52(1):1-6.	1997	Survey 394 Dutch travelers taking mefloquine, within 14 days of return, compared to travelers taking other malarial prophylaxes	Questionnaire consisted of questions regarding use of alcohol, smoking, general health, medical history, tropical diseases during the trip, and other medicines, and contained an extensive list of general complaints regarding all body systems at four levels of severity. A modified and validated version of the Profile of Mood States was included. **RESULTS:** In the study period, 2541 persons visited the Travel Clinic, of whom 1791 (70 percent) were both eligible and willing to co-operate. Of these 1791, data were obtained from 1501 (84 percent). Insomnia was most frequently encountered in users of mefloquine and mouth ulcers in proguanil users. After adjustment for gender, age, destination, and alcohol use, the relative risk for insomnia to mefloquine versus non-users of antimalarials was 1.6, and the excess risk was 6 per 100 users over an average period of 2 months. There were no significant differences between groups in depression, anxiety, agitation, and confusion. Stratification by gender demonstrated that insomnia was more common in women on mefloquine, but not in men. Also, women more frequently mentioned palpitations as an adverse event. After adjustment for age, destination, and alcohol use in women, the relative risks for insomnia and palpitations to mefloquine versus non-use of antimalarials were 2.4, and 22.5, respectively. When travelers were specifically asked for the adverse reactions they had experienced, anxiety, vertigo, agitation, and nightmares were significantly more frequently mentioned by mefloquine users. ***CONCLUSION:*** *Insomnia was more commonly encountered during use of mefloquine than proguanil or during non-use of antimalarials.*

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Title, Authors, Reference	*Date*	*Study Type - Subjects*	*Major Findings*
"Comparison of adverse events associated with use of mefloquine and combination of chloroquine and proguanil as antimalarial prophylaxis: postal and telephone survey of travelers," Barrett PJ, Emmins PD, Clarke PD, Bradley DJ; British Medical Journal, 1996; 313:528-8.	1996	Survey of 1214 British travelers from 1993 to 1995 who received advice from the travelers telephone health line run by the Medical Advisory Services for Travelers Abroad. Travelers received a questionnaire upon returning from their trip.	27 percent of travelers taking mefloquine reported neuropsychiatric adverse events. The traveler sought medical advice in 2.2 percent of the cases and 0.3 percent required hospital attention. Of those taking chloroquine and proguanil, 16 percent reported neuropsychiatric adverse events with 0.9 percent requiring medical advice and 0.1 percent hospital attention. Of those reporting any adverse event with mefloquine, 5.1 percent discontinued antimalarial prophylaxis and 0.7 percent switched to another agent. The corresponding numbers for chloroquine and proguanil were 6.3 percent and 0.3 percent. Disabling neuropsychiatric adverse events included hallucinations, panic attacks, dissociation from reality, confusion, difficulty concentrating, depression, anxiety, emotional instability depression, anxiety, personality changes, and nightmares.
Centers for Disease Control & Prevention (CDC) National Center for Infectious Diseases, Travelers' Health, Information for the Public: Prescription Drugs for Malaria, accessed 4-21-04 at www.cdc.gov/travel/malariadrugs.htm	2004	Review -- Travelers Advisory from CDC	The most common side effects reported by travelers taking mefloquine include headache, nausea, dizziness, difficulty sleeping, anxiety, vivid dreams, and visual disturbances. Mefloquine has rarely been reported to cause serious side effects, such as seizures, depression, and psychosis. These serious side effects are more frequent with the higher doses used to treat malaria; fewer occurred at the weekly doses used to prevent malaria. Mefloquine is eliminated slowly by the body and thus may stay in the body for a while even after the drug is discontinued. Therefore, side effects caused by mefloquine may persist weeks to months after the drug has been stopped. Most travelers taking mefloquine do not have side effects serious enough to stop taking the drug. Travelers Who Should Not Take Mefloquine. The following travelers should not tak mefloquine and should ask their health care provider for a different antimalarial drug a. Persons with active depression or a recent history of depression b. Persons with a history of psychosis, generalized anxiety disorder, schizophrenia, or other major psychiatric disorder c. Persons with a history of seizures (does not include the type of seizure caused by high fever in childhood) d. Persons allergic to mefloquine Mefloquine is not recommended for persons with cardiac conduction abnormalities (for example, an irregular heartbeat).

Title, Authors, Reference	*Date*	*Study Type - Subjects*	*Major Findings*
CDC National Center for Infectious Diseases, Travelers' Health, Information for Health Care Providers, Prescription Drugs for Malaria, accessed 4-21-04 at www.cdc.gov/travel/malariadrugs2.htm.	2004	Review -- Physicians Advisory put out by CDC	Mefloquine is contraindicated in persons allergic to mefloquine and in persons with active depression or a previous history of depression, generalized anxiety disorder, psychosis, schizophrenia, other major psychiatric disorders, or seizures. Not recommended for persons with cardiac conduction abnormalities. Mefloquine primary prophylaxis should begin 1-2 weeks before travel to malarious areas. It should be continued once a week, on the same day each week, during travel to malarious areas, and for 4 weeks after the traveler leaves such areas. Mefloquine has been associated with rare serious adverse reactions (including psychoses or seizures) at prophylactic doses; these reactions are more frequent with the higher doses used for treatment. Other side effects that occur with prophylactic doses include gastrointestinal disturbance, headache, insomnia, abnormal dreams, visual disturbances, depression, anxiety disorder, and dizziness. Mefloquine is contraindicated for use by travelers with a known hypersensitivity to mefloquine and in persons with active depression or a history of depression, or in persons with generalized anxiety disorder, psychosis, schizophrenia, or other psychiatric disturbances. Mefloquine is contraindicated in persons with a history of seizures (not including the type of seizure caused by high fever in childhood). Mefloquine is not recommended for persons with cardiac conduction abnormalities.
U.S. Department of Health & Human Services, U.S. Food and Drug Administration, FDA News, P03-52, July 9, 2003, "FDA Creates Medication Guide for Lariam." Accessed 4-21-04 at www.fda.gov/bbs/topics/NEWS/2003/NEW00921.html	2004	Review -- FDA Medication Guide	FDA developed the Lariam (mefloquine) Medication Guide in collaboration with the drug's manufacturer, Roche Pharmaceuticals of Nutley, NJ, to help ensure patients understand the risks of malaria, and the rare but potentially serious psychiatric adverse events associated with use of Lariam. Sometimes these psychiatric adverse events may persist even after stopping the medication. Some rare reports have claimed that Lariam users think about killing themselves. There have been rarer reports of suicides, although FDA does not know if Lariam use was related to these suicides.

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Title, Authors, Reference	*Date*	*Study Type - Subjects*	*Major Findings*
"Mefloquine for preventing malaria in non-immune adult travelers, Review," The Cochrane Database of Systematic Reviews, Copyright 2004 The Cochrane Library, Volume (1), Croft, AMJ; Garner, P.	2004	Review – Cochrane review of We included 10 trials involving 2750 non-immune adult participants. Five were field trials, mainly male soldiers. Also reviewed 516 published case reports of mefloquine adverse effects, 63 percent involved tourists and business travelers	Mefloquine prevents malaria, but has adverse effects that limit its acceptability. Evidence from non-randomised studies shows mefloquine has potentially harmful effects in tourists and business travellers. No-one knows if mefloquine is well or poorly tolerated. Many of the standard textbooks of tropical medicine assert that mefloquine is well tolerated in prophylaxis and that the only side effects of importance are neuropsychiatric reactions or seizures, experienced by around one in 10,000 users. This much-cited estimate of the frequency of neuropsychiatric side effects from mefloquine is based not on experimental data, but on spontaneous reports of severe adverse events in mefloquine users, and undoubtedly under-estimates the true incidence of undramatic but nevertheless unpleasant side effects from mefloquine. The main problem with mefloquine is that its tolerability is a major concern of the public, with questions raised repeatedly in the news media. Yet evidence to reassure the public, or confirm their fears, is not available. Withdrawals during clinical trials of mefloquine group were consistently higher in four placebo controlled trials (odds ratio 3.56, 95 percent confidence interval 1.67 to 7.60). In five trials comparing mefloquine with other chemoprophylaxis, no difference in tolerability was detected. There were four fatalities attributed to mefloquine.
Roche Pharmaceuticals "Dear Healthcare Professional" letter about mefloquine side effects, "Copyright © 2003 by Roche Laboratories Inc. All rights reserved," at www.fda.gov/cder/foi/label/2003/19591s19lbl_Lariam.pdf.	2003	Review -- Manufacturer's warning letter to clinicians	"Lariam can rarely cause serious mental problems in some patients. The most frequently reported side effects with Lariam, such as nausea, difficulty sleeping, and bad dreams are usually mild and do not cause people to stop taking the medicine. However, people taking Lariam occasionally experience severe anxiety, feelings that people are against them, hallucinations (seeing or hearing things that are not there, for example), depression, unusual behavior, or feeling disoriented. It has been reported that sometimes, in some patients, these side effects continue after Lariam is stopped. Some patients taking Lariam think about killing themselves, and there have been rare reports of suicides. We do not know if Lariam was responsible for these suicides. Do not take Lariam to prevent malaria if you have 1) depression or had depression recently; 2) recent mental illness or problems, including anxiety disorder, schizophrenia or psychosis; 3) seizures; 4) allergic to quinine or quinidine 5) Heart disease; 6) Pregnancy; 7) Breast feeding; or 8) Liver problems."
"Adverse effects of the antimalaria drug, mefloquine: due to primary liver damage with secondary thyroid involvement?" Croft AM, Herxheimer A; BioMed Central Public Health, 2002 Mar 25;2(1):6.	2002	Review of 516 published case reports – Cochrane Review	Postulate many mefloquine adverse effects are a post-hepatic syndrome caused by primary liver damage; "Mefloquine syndrome" presents in a variety of ways including headache, gastrointestinal disturbances, nervousness, fatigue, disorders of sleep, mood, memory and concentration, and occasionally frank psychosis. Previous liver or thyroid disease, and concurrent insults to the liver (such as from alcohol, dehydration, an oral contraceptive pill, recreational drugs, and other liver-damaging drugs) may be related to the development of severe or prolonged adverse reactions to mefloquine.

Title, Authors, Reference	*Date*	*Study Type - Subjects*	*Major Findings*
"Drug interactions with antimalarial agents," Griffin JP; Adverse Drug Reactions and Toxicological Reviews, 1999 Mar;18(1):25-43.	1999	Review of case reports	Case reports enumerates "common" side effects including nausea, vomiting, dizziness and vertigo, loss of balance, headache, sleep disorders, diarrhea and abdominal pain; More rare serious side effects include: 1) psychiatric effects as including depression, anxiety, confusion, psychosis, paranoia, aggression and agitation; 2) Neurological effects including convulsions, sensory and motor neuropathy, paraesthesia, tinnitus, tremor, ataxia and visual disturbances, and encephalopathy has been reported; 3) Cardiovascular effects including blood pressure changes, syncope, bradycardia, extrasystoles, cardiac conduction defects including atrioventricular block; 4) Skin rashes including urticarial rashes, pruritis, hair loss and Stevens-Johnson syndrome; 5) Hematological effects including leucopenia and thrombocytopenia; and 6) Liver enzyme changes. *No discussion of how long these effects might last after the drug is stopped.*
"Dermatological Adverse Effects with the Antimalarial Drug Mefloquine: a Review of 74 Published case Reports," Smith HR, Croft AM, Black MM; Clinical and Experimental Dermatology, 1999, 24; 249-254.	1999	Review of 74 case reports on mefloquine dermatological effects published between 1983 and 1997	There is good circumstantial evidence that mefloquine can cause mild and occasionally severe adverse dermatological effects in health travelers and in hospital patients with malaria. These effects are mostly self-limiting and rarely require treatment. Pruritus is the most frequent dermatological reaction and maculopapular rash is also common. Stevens-Johnson syndrome and toxic epidermal necrolysis have all been associated with mefloquine. The incidence of dermatological adverse effects with mefloquine may be between 4 to 10 percent for short-term use and as high as 30 percent for prolonged use.
"CNS adverse events associated with antimalarial agents. Fact or fiction?;" Phillips-Howard PA, ter Kuile FO; Drug Safety : An International Journal of Medical Toxicology and Drug Experience, 1995 Jun;12(6):370-83.	1995	Review	Mefloquine therapy causes dose-related transient dizziness; and serious central nervous system (CNS) events occur in 1:1200 Asians and 1:200 Caucasians/Africans; Risk factors include dosage, concomitant drug use/interactions, previous history of a CNS event and disease severity; Retreatment (within a month) increases the risk in Asians 7-fold; Irreversible effects are extremely rare and usually associated with overdosing or prior history of a serious CNS event.
"Mefloquine prophylaxis: an overview of spontaneous reports of severe psychiatric reactions and convulsions," Bem JL, Kerr L, Stuerchler D; The Journal of Tropical Medicine and Hygiene, 1992 Jun;95(3):167-79.	1992	Review of adverse reaction reports since 1991 (about 1 year) by the manufacturer Hoffmann-La Roche	59 serious neurologic and psychiatric adverse reaction reports reviewed: 26 convulsions, 12 depressions, 20 psychotic episodes, and one toxic encephalopathy; none were fatal; Only patient population identified at increased risk of developing these serious reactions are persons with a history of seizures or manic-depressive illness.
"Neuropsychiatric side effects after the use of mefloquine," Weinke T, Trautmann M, Held T, Weber G, Eichenlaub D, Fleischer K, Kern W, Pohle HD; Am The Journal of Tropical Medicine and Hygiene, 1991 Jul;45(1):86-91.	1991	Review of case reports	Reviewed neuropsychiatric side effects in German patients after treatment with mefloquine; Reactions consisted mainly of seizures, acute psychoses, anxiety neurosis, and major disturbances of sleep-wake rhythm; Effects occurred after both therapeutic and prophylactic intake; Estimated that one of 8,000 mefloquine users suffers from such reactions (one of 215 among therapeutic users, one of 13,000 among prophylaxis users).

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Title, Authors, Reference	*Date*	*Study Type - Subjects*	*Major Findings*
"The acute neurotoxicity of mefloquine may be mediated through a disruption of calcium homeostasis and ER function in vitro," Dow GS, Hudson TH, Vahey M, Koenig ML; Malaria Journal, 2003 Jun 12;2(1):14.	2003	Mechanistic study	Investigated the possibility that the acute in vitro neurotoxicity of mefloquine might be mediated through a disruptive effect of the drug on endoplasmic reticulum (ER) calcium homeostasis. Mefloquine was found to disrupt neuronal calcium homeostasis and induce an ER stress response at physiologically relevant concentrations, effects that may contribute, at least in part, to the neurotoxicity of the drug in vitro
"The risk of severe depression, psychosis or panic attacks with prophylactic antimalarials," Meier CR, Wilcock K, Jick SS; Drug Safety : An International Journal of Medical Toxicology and Drug Experience, 2004;27(3):203-13.	2004	Epidemiologic study. A population-based observational study using a database of medical records to quantify and compare the risk of psychiatric disorders during or after use of mefloquine with the risk during use of proguanil and/or chloroquine, or doxycycline	The study population was drawn from the large UK-based General Practice Research Database (GPRD). Subjects were aged from 17-79 years and were exposed to mefloquine, proguanil, chloroquine or doxycycline (or a combination of these drugs) at some time between 1990 and 1999. We performed a person-time and a nested case-control analysis to assess the risk of developing a first-time diagnosis of depression, psychosis or panic attack during or after use of these antimalarial drugs. **RESULTS:** Within the study population of 35 370 subjects (45.2 percent males), we identified 580 subjects with a first-time diagnosis of depression (number of subjects (n) = 505), psychosis (n = 16) or panic attack (n = 57) and two subjects committed suicide. The incidence rates of first-time diagnoses of depression during current use of mefloquine, proguanil and/or chloroquine, or doxycycline, adjusted for age, gender and calendar year, were 6.9 (95 percent CI 4.5-10.6), 7.6 (95 percent CI 5.5-10.5) and 9.5 (95 percent CI 3.7-24.1)/1000 person-years, respectively. The incidence rates of psychosis or panic attacks during current mefloquine exposure were 1.0/1000 person-years (95 percent CI 0.3-2.9) and 3.0/1000 person-years (95 percent CI 1.6-5.7), respectively, approximately 2-fold higher (statistically nonsignificant) than during current use of proguanil and/or chloroquine, or doxycycline. The nested case-control analysis encompassed 505 cases with depression and 3026 controls, 16 cases with psychosis and 96 controls, and 57 cases with a panic attack and 342 controls. Current use of mefloquine was not associated with an elevated risk of developing depression. In a comparison between patients currently using mefloquine with all past users of antimalarials combined, the risk estimate was elevated for current users of mefloquine for both psychosis (odds ratio (OR) 8.0, 95 percent CI 1.0-62.7; $p < 0.05$) and panic attacks (OR 2.7, 95 percent CI 1.1-6.5; $p < 0.05$). ***CONCLUSION:*** *The absolute risk of developing psychosis or panic attack appears low with all the antimalarials tested. No evidence was found in this large observational study that mefloquine use increased the risk of first-time diagnosis of depression when compared with the use of other antimalarials investigated in this study.*

Title, Authors, Reference	*Date*	*Study Type - Subjects*	*Major Findings*
"Atovaquone plus chloroguanide versus mefloquine for malaria prophylaxis: a focus on neuropsychiatric adverse events," van Riemsdijk MM, Sturkenboom MC, Ditters JM, Ligthelm RJ, Overbosch D, Stricker BH; Clinical Pharmacology and Therapeutics, 2002 Sep;72(3):294-301.	2002	Epidemiologic study, prospective, double-blind, randomized study on neuropsychiatric adverse events and concentration impairment during prophylactic use of mefloquine or atovaquone plus chloroguanide	119 Subjects (mean age 35 years) followed from baseline screening to 7 days after leaving malaria area, measuring changes in mood disturbance and neurobehavioral indices including sustained attention, coding speed, and visuomotor accuracy; Significant deterioration in depression, anger, fatigue, vigor, and total mood disturbance domains occurred during use of mefloquine but not during use of atovaquone plus chloroguanide; Stratification on sex showed between-treatment differences in female patients but not in male patients; In both treatment groups, sustained attention deteriorated after travel, especially with increased duration of stay. ***CONCLUSIONS:*** *Prophylactic use of mefloquine was associated with significantly higher scores on scales for depression, anger, and fatigue and lower scores for vigor than prophylactic use of atovaquone plus chloroguanide.*
"Neurological, cardiovascular and metabolic effects of mefloquine in healthy volunteers: a double-blind, placebo-controlled trial," Davis TM, Dembo LG, Kaye-Eddie SA, Hewitt BJ, Hislop RG, Batty KT; British Journal of Clinical Pharmacology, 1996 Oct;42(4):415-21.	1996	Epidemiologic study, Double-blind, randomized, placebo-controlled trial -- 106 healthy adult subjects over 4 weeks	Mefloquine did not alter calcium homoeostasis but produced a mean 0.5 mmol l-1 fall in serum glucose over the study period ($p < 0.001$) and relative hyperinsulinaemia; Symbol digit modalities, and digit forwards and backwards test scores similar in active and placebo groups across the three assessments, as were lying/standing blood pressure and high-tone hearing loss; Electrocardiographic QTc interval prolongation and diarrhea were mild but transient side-effects of mefloquine ($p < 0.01$); Neurological symptoms comparable in two groups throughout study; No evidence of drug toxicity in eleven subjects who withdrew. Concluded mefloquine prophylaxis does not appear to produce low-grade but debilitating neurological symptoms or to alter the results of sensitive tests of cerebral function, but it might contribute to hypoglycaemia and cardiac dysrhythmias.

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Title, Authors, Reference	*Date*	*Study Type - Subjects*	*Major Findings*
"Tolerability of malaria chemoprophylaxis in non-immune travellers to sub-Saharan Africa: multicentre, randomised, double blind, four arm study," Schlagenhauf P, Tschopp A, Johnson R, Nothdurft HD, Beck B, Schwartz E, Herold M, Krebs B, Veit O, Allwinn R, Steffen R; British Medical Journal., 2003 Nov 8;327(7423):1078.	2003	Clinical trial; randomized, double blind, with placebo, 623 subjects receiving various malaria prophylaxis including mefloquine	Many subject reported adverse events (even in the initial placebo group); none were serious; Chloroquine and proguanil trial had highest mild to moderate adverse events; followed by mefloquine (64/153; 42 percent, 34 percent to 50 percent), doxycycline, and atovaquone and proguanil (p = 0.048 for all); Mefloquine and combined chloroquine and proguanil arms had the highest proportion of more severe events (n = 19; 12 percent, 7 percent to 18 percent and n = 16; 11 percent, 6 percent to 15 percent, respectively), whereas the combined atovaquone and proguanil and doxycycline arms had the lowest (n = 11; 7 percent, 2 percent to 11 percent and n = 9; 6 percent, 2 percent to 10 percent, respectively: p = 0.137 for all); Mefloquine arm had the highest proportion of moderate to severe neuropsychological adverse events, particularly in women (n = 56; 37 percent, 29 percent to 44 percent versus chloroquine and proguanil, n = 46; 30 percent, 23 percent to 37 percent; doxycycline, n = 36; 24 percent, 17 percent to 30 percent; and atovaquone and proguanil, n = 32; 20 percent, 13 percent to 26 percent: p = 0.003 for all); Highest proportion of moderate or severe skin problems were reported in the chloroquine and proguanil arm (n = 12; 8 percent, 4 percent to 13 percent versus doxycycline, n = 5; 3 percent, 1 percent to 6 percent; atovaquone and proguanil, n = 4; 2 percent, 0 percent to 5 percent; mefloquine, n = 2; 1 percent, 0 percent to 3 percent: P = 0.013). ***CONCLUSIONS:*** *Combined atovaquone and proguanil and doxycyline are well tolerated antimalarial drugs; Broader experience with both agents is needed to accumulate reports of rare adverse events.*
"Unexpected frequency, duration and spectrum of adverse events after therapeutic dose of mefloquine in healthy adults," Rendi-Wagner P, Noedl H, Wernsdorfer WH, Wiedermann G, Mikolasek A, Kollaritsch H; Acta Tropica, 2002 Feb;81(2):167-73.	2002	Clinical trial; 22 healthy volunteers monitored 21 days with *therapeutic* mefloquine (750 and 500 mg at 6 hour (h) intervals)	Unexpected high frequency of side effects of any grade reported by all 22 subjects; Most common were vertigo (96 percent), nausea (82 percent) and headache (73 percent); Subjects with severe vertigo (73 percent) required bed rest and specific medication for 1 to 4 days; More females than males reported severe adverse reactions; Majority (77.3 percent) participants (f: 8/12, m: 9/10) showed symptom resolution within 3 weeks (510 h) after drug administration; Biochemical and hematological findings stayed within the normal range of values, but showed nevertheless a significant rise of Na, Cl, Ca, bilirubin, GGT and LDH.

Title, Authors, Reference	*Date*	*Study Type - Subjects*	*Major Findings*
"Atovaquone-proguanil versus mefloquine for malaria prophylaxis in nonimmune travelers: results from a randomized, double-blind study," Overbosch D, Schilthuis H, Bienzle U, Behrens RH et al. Clinical infectious diseases, 2001; 33:1015-21	2001	Clinical trial; randomized, double-blind, with placebo evaluating frequency of adverse events. 976 travelers from the Netherlands, UK, Canada, and S. Africa traveling to malaria endemic areas for up to 28days. Individuals were monitored 7, 28, and 60 days after travel.	Treatment emergent neuropsychiatric events occurred in 29 percent of travelers randomized to mefloquine and in 14 percent randomized to atovaquone-proguanil (p=0.001). Events included strange or vivid dreams, insomnia, dizziness, visual difficulties, anxiety, and depression. Most adverse events were considered mild. Treatment was discontinued due to neuropsychiatric events in nineteen subjects receiving mefloquine, in five receiving mefloquine placebo, and in three receiving atovaquone-proguanil.
"Serious adverse events of mefloquine in relation to blood level and gender," Schwartz E, Potasman I, Rotenberg M, Almog S, Sadetzki S; The American Journal of Tropical Medicine and Hygiene, 2001 Sep;65(3):189-92.	2001	Clinical trial; Mechanistic	Evaluated association between mefloquine serum levels and serious side effects, with seventeen patients presenting to emergency rooms or travel clinics with symptoms suggesting serious adverse effects of mefloquine and twenty-eight controls (healthy people, still taking mefloquine after travel; Mean age patients and controls was 31.5 +/- 11.6 years and 34 +/- 12.2 years, respectively; More women among the patients (76 percent versus 40 percent, respectively; p = 0.03); Most complaints related to central nervous system (13 of 17); five patients interrupted their trip and two were hospitalized; No difference in mefloquine blood levels found comparing patients to control groups; No significant difference found between blood mefloquine levels among men and women; mefloquine blood levels do not correlate with severe adverse events; Women more susceptible than men, despite having similar blood levels of the drug.
"Paranoid psychosis related to mefloquine antimalarial prophylaxis," Fuller SJ, Naraqi S, Gilessi G; Papua and New Guinea Medical Journal, 2002 Sep-Dec;45(3-4):219-21.	2002	Case report – one subject	A 39-year old marine biologist medically evacuated from New Guinea with paranoid ideation and irrational behavior; Taken mefloquine 2 weeks earlier; No history of illicit drug use or other medications; On admission disoriented, speech rambling, agitated and fearful of medical staff; Afebrile; No unusual lab tests; Diagnosed with acute psychosis secondary to mefloquine, which resolved over the next 2 to 3 days; Patient admitted suffered from endogenous depression for 19 years and had taken meds for that.
"Mefloquine-induced paranoid psychosis and subsequent major depression in a 25-year-old student," Dietz A, Frolich L; Pharmacopsychiatry, 2002 Sep;35(5):200-2.	2002	Case report – one subject	Patient developed paranoid psychosis followed by depression after taking mefloquine for a vacation; Recovered fully within 9 months of receiving his first dose of mefloquine.

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Title, Authors, Reference	*Date*	*Study Type - Subjects*	*Major Findings*
"Multifocal Myoclonus Associated with Mefloquine Chemoprophylaxis," Jimenez-Huete, A, Gil-Nagel, A, and Franch O; Clinical Neuropharmacology, 25; 5 243, 2002.	2002	Case report – one subject	Case report of a 54 year old Spanish woman developed multifocal myoclonus during mefloquine prophylaxis; Presented with abnormal movements in four limbs; Cerivastatin started 10 months earlier for treatment of hypercholesterolemia; 8 weeks previously started prophylactic mefloquine, and two weeks later during a trip noticed sudden brief shock-like irregular muscular contractions that appeared without pattern in all four limbs, and were more intense at the end of the day; Complained of slight frontal headache, dizziness and slowness of thinking; No known exposures including recreational drugs and friends were asymptomatic; Continued taking mefloquine 3 more weeks while symptoms increased until she could not drive a car; On the 6th week treatment stopped mefloquine and symptoms rapidly abated; Neurological exam 2 weeks later showed infrequent irregular non-synchronous brief muscular contractions in her proximal and distal upper limbs, consistent with multifocal myoclonus; No brain lesions by magnetic resonance imaging (MRI) and EEG normal; Blood tests showed only slight hypercholesterolemia; Follow up exam 2 weeks later showed no abnormal signs.
"Pulmonary toxicity with mefloquine," Udry E, Bailly F, Dusmet M, Schnyder P, Lemoine R, Fitting JW; The European Respiratory Journal, 2001 Nov;18(5):890-2.	2001	Case report – two subjects	Case 1: Patient developed acute lung injury within hours following mefloquine treatment for a low-level P. falciparum, which was halofantrine resistant; Extensive microbiological investigation remained negative; Video-assisted thoracoscopic lung biopsy demonstrated diffuse alveolar damage; Progress was favorable without treatment; Case 2: Patient experienced acute lung injury and diffuse alveolar damage related to mefloquine; Glucose-6-phosphate dehydrogenase deficiency was present in the former (but not the later, suggesting that it is not a predisposing condition) case and was thought to contribute to the lung injury.
"Mefloquine-induced trigeminal sensory neuropathy," Watt-Smith S, Mehta K, Scully C; Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and EnDODontics, 2001 Aug;92(2):163-5.	2001	Case report – one subject	Patient with sudden-onset trigeminal sensory neuropathy of the lip associated with taking mefloquine.
"Cognitive and neuropsychiatric side effects of mefloquine,"; Javorsky DJ, Tremont G, Keitner GI, Parmentier AH; The Journal of Neuropsychiatry and Clinical Neurosciences, 2001 Spring;13(2):302.	2001	Case report – one subject	52 year old woman no psychiatric history used mefloquine prophylactically once a week for 3 weeks prior and during a trip to Africa; Previously used mefloquine 4 years without problems; During return flight developed anxiety, paranoia, visual hallucinations, confusion and depressive symptoms; Outpatient treatment continued to show suicidal ideation, other neuropsychiatric symptoms, and cognitive disturbances 3 months after last dose of mefloquine; Hospitalized for inpatient psychiatric treatment; Mildly elevated TSH, positive past exposure to hepatitis A, normal brain MRI, medical history was no help; Drug therapy led to improvement over 4 days; after briefly living with a relative following discharge returned to independent functioning.

Title, Authors, Reference	*Date*	*Study Type - Subjects*	*Major Findings*
"Danger of malaria self-treatment. Acute neurologic toxicity of mefloquine and its combination with pyrimethamine-sulfadoxine," Nicolas X, Granier H, Laborde JP, Martin J, Talarmin F; La Presse medicale, 2001 Sep 29;30(27):1349-50.	2001	Case report – one subject	A patient did not follow the prescribed mefloquine dosage and developed acute neurological disorders after overdosing; Patient developed mefloquine related encephalopathy.
"Bipolar disorder after mefloquine treatment," Even C, Friedman S, Lanouar K; Journal of Psychiatry & Neuroscience, 2001 May;26(3):252-3.	2001	Case report – one subject	50 year old man took mefloquine for a vacation in the Far East, developed after his second 250mg dose depressive symptoms that interrupted his trip; Two weeks later he ended up in a psychiatric hospital with worsening depressive symptoms, suicidal ideation and elusions of guilt and economic ruin (still taking mefloquine); received electroconvulsive therapy over 11 days! He was given drugs for depression for 6 years!
"Prolonged visual illusions induced by mefloquine (Lariam): a case report," Borruat FX, Nater B, Robyn L, Genton B; Journal of Travel Medicine, 2001 May-Jun;8(3):148-9.	2001	Case report – one subject	
[Neuropsychiatric symptoms in preventive antimalarial treatment with mefloquine: apropos of 2 cases]; Lebain P, Juliard C, Davy JP, Dollfus S; L'Encephale, 2000 Jul-Aug;26(4):67-70.	2000	Case report – two subjects	Severe neuropsychiatric reactions in two patients following chemoprophylaxis with mefloquine; Case 1: 43 year old woman developed severe depression with visual and auditive hallucinations and a paranoid delusion; Treated by clomipramine and risperidone; Case 2: 55 year old man presented twice with acute psychosis with confusion following mefloquine prophylaxis; treated with halopridol.
"Mefloquine-induced psychosis," Havaldar PV, Mogale KD; The Pediatric Infectious Disease Journal, 2000 Feb;19(2):166-7.	2000	Case report – one subject	Case report of mefloquine induced psychosis in a 7-year old Indian child. Hospitalized and diagnosed with cerebrial malaria, quinine treatment failed, mefloquine treatment started. On third day of mefloquine treatment he had loss of sleep and irrelevant talk, and the following day had hallucinations, which worsened. All symptoms of psychosis subsided within 24 hours of stopping mefloquine.
"Seizures after antimalarial medication in previously healthy persons," Schiemann R, Coulaud JP, Bouchaud O; Journal of Travel Medicine, 2000 May-Jun;7(3):155-6.	2000	Case report – one subject	Case of a grand mal seizure after chloroquine prophylaxis followed by mefloquine therapy in a 19 year old girl who contracted malaria while on vacation, while taking chloroquine and proguanil; Therapy was with mefloquine 1,500 mg, and on the same day she suffered a grand mal seizure.
"Mefloquine-induced acute hepatitis," Gotsman I, Azaz-Livshits T, Fridlender Z, Muszkat M, Ben-Chetrit E; Pharmacotherapy, 2000 Dec;20(12):1517-9.	2000	Case report – one case	Patient with elevated liver function tests attributed to heart failure experienced acute elevation of liver transaminases 6 weeks after taking mefloquine 250 mg per week; Cessation of the drug caused test results to return to normal.
"Long-lasting neuropsychiatric side-effects following mefloquine prophylaxis. A case after six weeks of initiating and lasting six months,"; Bygbjerg IC, Ronn AM; Ugeskrift for Laeger, 1999 Mar 8;161(10):1422-3.	1999	Case report – one subject	Case of severe neuropsychiatric side-effects arising six weeks after initiating mefloquine prophylaxis, requiring repeated hospitalization, and NOT resolving completely after 6 months, in a previously healthy 30 year-old female.
"Neuropsychiatric side effects of malarial prophylaxis with mefloquine (Lariam),"; Minei-Rachmilewitz T; Harefuah, 1999 Jul;137(1-2):25-7, 87.	1999	Case report – one subject	39-year-old woman who developed acute psychosis after being given mefloquine prophylaxis.

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"Acute paranoid hallucinatory psychosis following mefloquine prophylaxis (Lariam)," Kruger E, Grube M, Hartwich P; Psychiatrische Praxis, 1999 Sep;26(5):252-4.	1999	Case report – one subject	Case-report of a patient suffering for the first time from an acute paranoid psychosis induced by mefloquine prophylaxis.
"Mefloquine and ototoxicity: a report of 3 cases," Fusetti M, Eibenstein A, Corridore V, Hueck S, Chiti-Batelli S; Clinica Terapeutica, 1999;150:379-382.	1999	Case report – 3 subjects	Three cases of high-frequency sensorineural hearing loss and tinnitus following malaria prophylaxis with mefloquine; one patient had partial remission of hearing loss after stopping mefloquine; the remaining two cases the symptomatology remained unchanged; no patients reported improvement of tinnitus.
"Acute fatty liver after malaria prophylaxis with mefloquine," Grieco A, Vecchio FM, Natale L, Gasbarrini G; Lancet, 1999 Jan 23;353(9149):295-6.	1999	Case report – one subject	
"A severe adverse reaction to mefloquine and chloroquine prophylaxis," Lysack JT, Lysack CL, Kvern BL; Australian Family Physician, 1999 Apr;28(4):310.	1998	Case report – one subject	A 23 year old man no history neurological or psychiatric illness ingested three weekly 228 mg doses mefloquine malaria prophylaxis while in India; Experienced increasingly severe adverse reaction after each dose, including symptoms of paranoia, hallucinations, and suicidal ideation; Discontinued mefloquine switched to chloroquine, but symptoms acutely intensified and became debilitating; Severe symptoms persisted for 12 months following the discontinuation of both antimalarial drugs.
"Convulsions during prophylactic use of mefloquine," Heeringa M, Kuster JA, Meyboom RH, Bouvy M; Nederlands Tijdschrift voor Geneeskunde, 1999 Jan 30;143(5):273-4.	1999	Case report – 6 subjects	Six patients reported with convulsions attributed to prophylactic use of mefloquine; five had no neurological history; one had history of epilepsy but had had no convulsion during the preceding 5-years; convulsions occurred 1 to 23 days after mefloquine treatment began, and treatment was discontinued after convulsions; four patients with follow-up showed full recovery from convulsions.
"Case study: neuropsychiatric symptoms associated with the antimalarial agent mefloquine," Clattenburg RN, Donnelly CL; Journal of the American Academy of Child and Adolescent Psychiatry, 1997 Nov;36(11):1606-8.	1997	Case report – one subject	Report on acute neuropsychiatric symptoms in a 10-year-old boy subsequent to his return from travel abroad in Africa, where he had taken the antimalarial agent mefloquine; 4-week course of cognitive-behavioral therapy effectively treated this disorder.
"Fatal toxic epidermal necrolysis associated with mefloquine antimalarial prophylaxis." McBride SR, Lawrence CM, Pape SA, Reid CA; Lancet, 1997 Jan 11;349(9045):101.	1997	Case report – one subject	
"Psychopathological phenomena in long-term follow-up of acute psychosis after preventive mefloquinine (Lariam) administration." Meszaros K, Kasper S; Der Nervenarzt, 1996 May;67(5):404-6.	1996	Case report – one subject	Report long-term observation of a patient suffering for the first time an acute psychosis following mefloquine prophylaxis
"Atrial flutter with 1:1 conduction after administration of the antimalarial drug mefloquine," Fonteyne W, Bauwens A, Jordaens L; Clinical Cardiology, 1996 Dec;19(12):967-8.	1996	Case report – one subject	63-year-old male patient with atrial flutter in whom mefloquine use was associated with 1:1 AV conduction; responded to therapy with digoxin and sotalol; patient had a history of palpitations.

Title, Authors, Reference	*Date*	*Study Type - Subjects*	*Major Findings*
"Acute glomerulonephritis without fever: an unusual presentation of malaria on mefloquine prophylaxis," Martinez-Ocana JC, Serra A, Bonet J, Fernandez-Crespo P, Caralps A; Nephron, 1996;73(2):372.	1996	Case report – one subject	
"Neuropsychiatric reactions with mefloquine chemoprophylaxis," Croft AM, World MJ; Lancet, 1996 Feb 3;347(8997):326.	1996	Case report – summary	
"Acute psychosis after mefloquine. Report of six cases." Sowunmi A, Adio RA, Oduola AM, Ogundahunsi OA, Salako LA; Tropical and Geographical Medicine, 1995;47(4):179-80.	1995	Case report – six subjects	Self-limiting psychosis characterized by acute onset of visual and auditory hallucinations and poor sleep developed in six adults between 8 and 24 hours after oral administration of 750-1500 mg of the antimalarial mefloquine. All patients had no personal or family history of psychosis and were neurologically and mentally normal before mefloquine ingestion.
"Adverse reaction to mefloquine associated with ethanol ingestion," Wittes RC, Saginur R; Canadian Medical Association Journal, 1995 Feb 15;152(4):515-7.	1995	Case report – one subject	A 40 year old man no history of neuropsychiatric illness took one 250-mg tablet mefloquine weekly for malaria prophylaxis while in Tanzania; No adverse reaction following first two doses, but with his third and his fourth dose he consumed about half a litre whisky; On those two occasions he experienced hallucinations, paranoid delusions and suicidal ideation; Subsequently continued taking mefloquine, but abstained from alcohol ethanol and had no recurrence of psychiatric symptoms.
"Mefloquine-induced grand mal seizure during malaria chemoprophylaxis in a non-epileptic subject," Pous E, Gascon J, Obach J, Corachan M; Transactions of the Royal Society of Tropical Medicine and Hygiene, 1995 Jul-Aug;89(4):434.	1995	Case report	
"Acute brain syndrome after mefloquine treatment," Ronn AM, Bygbjerg IC; Ugeskrift for Laeger, 1994 Oct 10;156(41):6044-5.	1994	Case report – one subject, treated for P. falciparum.	Patient rehospitalized 12 days after mefloquine treatment with fever, nausea, dizziness and headache; 15 days after treatment generalized convulsions and coma; EEG severely abnormal; discharged 37 days after mefloquine treatment, but two months before the EEG and patient were normal.
"Acute psychosis after mefloquine: a case report," Sowunmi A; East African Medical Journal, 1994 Dec;71(12):818-9.	1994	Case report – one subject	A self-limiting psychosis characterized by visual and auditory hallucinations and isomnia occurred in a 17-year old male after mefloquine administration for presumed chloroquine resistant falciparum malaria.
"Encephalopathy and memory disorders during treatments with mefloquine," Marsepoil T, Petithory J, Faucher JM, Ho P, Viriot E, Benaiche F; Rev Med Interne. 1993;14(8):788-91.	1993	Case report – two subjects	Cas e1: excessive mefloquine therapy lead to an acute psychotic state that ultimately regressed without treatment; Case 2: Patient suffered a transient memory failure following prophylactic mefloquine treatment.
"Psychotic episode caused by prevention of malaria with mefloquine. A case report," Folkerts H, Kuhs H; Der Nervenarzt, 1992 May;63(5):300-2.	1992	Case report – one subject	Developed psychosis, dizziness, confusion and delusions, which were more intensive and remained longer than previously reported.

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Title, Authors, Reference	*Date*	*Study Type - Subjects*	*Major Findings*
"Recurrent psychiatric manifestations during malaria prevention with mefloquine. A case report," Rodor F, Bianchi G, Grignon S, Samuelian JC, Jouglard J; Therapie, 1990 Sep-Oct;45(5):433-4.	1990	Case report – one subject	A 22 year old woman without psychiatric antecedent took mefloquine for a journey in a chloroquine resistant area; First tablet induced an acute psychiatric syndrome that lasted 5 days; Following the second tablet the patient attempted suicide by drowning.

2. **Summary.** Medical literature, and in particular case reports, indicate that mefloquine may rarely be associated with certain long-term chronic health problems that persist for weeks, months, and even years after the drug is stopped.

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"Acute glomerulonephritis without fever: an unusual presentation of malaria on mefloquine prophylaxis," Martinez-Ocana JC, Serra A, Bonet J, Fernandez-Crespo P, Caralps A; Nephron, 1996;73(2):372.	1996	Case report – one subject	
"Neuropsychiatric reactions with mefloquine chemoprophylaxis," Croft AM, World MJ; Lancet, 1996 Feb 3;347(8997):326.	1996	Case report – summary	
"Acute psychosis after mefloquine. Report of six cases." Sowunmi A, Adio RA, Oduola AM, Ogundahunsi OA, Salako LA; Tropical and Geographical Medicine, 1995;47(4):179-80.	1995	Case report – six subjects	Self-limiting psychosis characterized by acute onset of visual and auditory hallucinations and poor sleep developed in six adults between 8 and 24 hours after oral administration of 750-1500 mg of the antimalarial mefloquine. All patients had no personal or family history of psychosis and were neurologically and mentally normal before mefloquine ingestion.
"Adverse reaction to mefloquine associated with ethanol ingestion," Wittes RC, Saginur R; Canadian Medical Association Journal, 1995 Feb 15;152(4):515-7.	1995	Case report – one subject	A 40 year old man no history of neuropsychiatric illness took one 250-mg tablet mefloquine weekly for malaria prophylaxis while in Tanzania; No adverse reaction following first two doses, but with his third and his fourth dose he consumed about half a litre whisky; On those two occasions he experienced hallucinations, paranoid delusions and suicidal ideation; Subsequently continued taking mefloquine, but abstained from alcohol ethanol and had no recurrence of psychiatric symptoms.
"Mefloquine-induced grand mal seizure during malaria chemoprophylaxis in a non-epileptic subject," Pous E, Gascon J, Obach J, Corachan M; Transactions of the Royal Society of Tropical Medicine and Hygiene, 1995 Jul-Aug;89(4):434.	1995	Case report	
"Acute brain syndrome after mefloquine treatment," Ronn AM, Bygbjerg IC; Ugeskrift for Laeger, 1994 Oct 10;156(41):6044-5.	1994	Case report – one subject, treated for P. falciparum.	Patient rehospitalized 12 days after mefloquine treatment with fever, nausea, dizziness and headache; 15 days after treatment generalized convulsions and coma; EEG severely abnormal; discharged 37 days after mefloquine treatment, but two months before the EEG and patient were normal.
"Acute psychosis after mefloquine: a case report," Sowunmi A; East African Medical Journal, 1994 Dec;71(12):818-9.	1994	Case report – one subject	A self-limiting psychosis characterized by visual and auditory hallucinations and isomnia occurred in a 17-year old male after mefloquine administration for presumed chloroquine resistant falciparum malaria.
"Encephalopathy and memory disorders during treatments with mefloquine," Marsepoil T, Petithory J, Faucher JM, Ho P, Viriot E, Benaiche F; Rev Med Interne. 1993;14(8):788-91.	1993	Case report – two subjects	Cas e1: excessive mefloquine therapy lead to an acute psychotic state that ultimately regressed without treatment; Case 2: Patient suffered a transient memory failure following prophylactic mefloquine treatment.
"Psychotic episode caused by prevention of malaria with mefloquine. A case report," Folkerts H, Kuhs H; Der Nervenarzt, 1992 May;63(5):300-2.	1992	Case report – one subject	Developed psychosis, dizziness, confusion and delusions, which were more intensive and remained longer than previously reported.

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Title, Authors, Reference	*Date*	*Study Type - Subjects*	*Major Findings*
"Acute paranoid hallucinatory psychosis following mefloquine prophylaxis (Lariam)," Kruger E, Grube M, Hartwich P; Psychiatrische Praxis, 1999 Sep;26(5):252-4.	1999	Case report – one subject	Case-report of a patient suffering for the first time from an acute paranoid psychosis induced by mefloquine prophylaxis.
"Mefloquine and ototoxicity: a report of 3 cases," Fusetti M, Eibenstein A, Corridore V, Hueck S, Chiti-Batelli S; Clinica Terapeutica, 1999;150:379-382.	1999	Case report – 3 subjects	Three cases of high-frequency sensorineural hearing loss and tinnitus following malaria prophylaxis with mefloquine; one patient had partial remission of hearing loss after stopping mefloquine; the remaining two cases the symptomatology remained unchanged; no patients reported improvement of tinnitus.
"Acute fatty liver after malaria prophylaxis with mefloquine," Grieco A, Vecchio FM, Natale L, Gasbarrini G; Lancet, 1999 Jan 23;353(9149):295-6.	1999	Case report – one subject	
"A severe adverse reaction to mefloquine and chloroquine prophylaxis," Lysack JT, Lysack CL, Kvern BL; Australian Family Physician, 1999 Apr;28(4):310.	1998	Case report – one subject	A 23 year old man no history neurological or psychiatric illness ingested three weekly 228 mg doses mefloquine malaria prophylaxis while in India; Experienced increasingly severe adverse reaction after each dose, including symptoms of paranoia, hallucinations, and suicidal ideation; Discontinued mefloquine switched to chloroquine, but symptoms acutely intensified and became debilitating; Severe symptoms persisted for 12 months following the discontinuation of both antimalarial drugs.
"Convulsions during prophylactic use of mefloquine," Heeringa M, Kuster JA, Meyboom RH, Bouvy M; Nederlands Tijdschrift voor Geneeskunde, 1999 Jan 30;143(5):273-4.	1999	Case report – 6 subjects	Six patients reported with convulsions attributed to prophylactic use of mefloquine; five had no neurological history; one had history of epilepsy but had had no convulsion during the preceding 5-years; convulsions occurred 1 to 23 days after mefloquine treatment began, and treatment was discontinued after convulsions; four patients with follow-up showed full recovery from convulsions.
"Case study: neuropsychiatric symptoms associated with the antimalarial agent mefloquine," Clattenburg RN, Donnelly CL; Journal of the American Academy of Child and Adolescent Psychiatry, 1997 Nov;36(11):1606-8.	1997	Case report – one subject	Report on acute neuropsychiatric symptoms in a 10-year-old boy subsequent to his return from travel abroad in Africa, where he had taken the antimalarial agent mefloquine; 4-week course of cognitive-behavioral therapy effectively treated this disorder.
"Fatal toxic epidermal necrolysis associated with mefloquine antimalarial prophylaxis." McBride SR, Lawrence CM, Pape SA, Reid CA; Lancet, 1997 Jan 11;349(9045):101.	1997	Case report – one subject	
"Psychopathological phenomena in long-term follow-up of acute psychosis after preventive mefloquinine (Lariam) administration." Meszaros K, Kasper S; Der Nervenarzt, 1996 May;67(5):404-6.	1996	Case report – one subject	Report long-term observation of a patient suffering for the first time an acute psychosis following mefloquine prophylaxis
"Atrial flutter with 1:1 conduction after administration of the antimalarial drug mefloquine," Fonteyne W, Bauwens A, Jordaens L; Clinical Cardiology, 1996 Dec;19(12):967-8.	1996	Case report – one subject	63-year-old male patient with atrial flutter in whom mefloquine use was associated with 1:1 AV conduction; responded to therapy with digoxin and sotalol; patient had a history of palpitations.

Title, Authors, Reference	*Date*	*Study Type - Subjects*	*Major Findings*
"Danger of malaria self-treatment. Acute neurologic toxicity of mefloquine and its combination with pyrimethamine-sulfadoxine," Nicolas X, Granier H, Laborde JP, Martin J, Talarmin F; La Presse medicale, 2001 Sep 29;30(27):1349-50.	2001	Case report – one subject	A patient did not follow the prescribed mefloquine dosage and developed acute neurological disorders after overdosing; Patient developed mefloquine related encephalopathy.
"Bipolar disorder after mefloquine treatment," Even C, Friedman S, Lanouar K; Journal of Psychiatry & Neuroscience, 2001 May;26(3):252-3.	2001	Case report – one subject	50 year old man took mefloquine for a vacation in the Far East, developed after his second 250mg dose depressive symptoms that interrupted his trip; Two weeks later he ended up in a psychiatric hospital with worsening depressive symptoms, suicidal ideation and elusions of guilt and economic ruin (still taking mefloquine); received electroconvulsive therapy over 11 days! He was given drugs for depression for 6 years!
"Prolonged visual illusions induced by mefloquine (Lariam): a case report," Borruat FX, Nater B, Robyn L, Genton B; Journal of Travel Medicine, 2001 May-Jun;8(3):148-9.	2001	Case report – one subject	
[Neuropsychiatric symptoms in preventive antimalarial treatment with mefloquine: apropos of 2 cases]; Lebain P, Juliard C, Davy JP, Dollfus S; L'Encephale, 2000 Jul-Aug;26(4):67-70.	2000	Case report – two subjects	Severe neuropsychiatric reactions in two patients following chemoprophylaxis with mefloquine; Case 1: 43 year old woman developed severe depression with visual and auditive hallucinations and a paranoid delusion; Treated by clomipramine and risperidone; Case 2: 55 year old man presented twice with acute psychosis with confusion following mefloquine prophylaxis; treated with halopridol.
"Mefloquine-induced psychosis," Havaldar PV, Mogale KD; The Pediatric Infectious Disease Journal, 2000 Feb;19(2):166-7.	2000	Case report – one subject	Case report of mefloquine induced psychosis in a 7-year old Indian child. Hospitalized and diagnosed with cerebrial malaria, quinine treatment failed, mefloquine treatment started. On third day of mefloquine treatment he had loss of sleep and irrelevant talk, and the following day had hallucinations, which worsened. All symptoms of psychosis subsided within 24 hours of stopping mefloquine.
"Seizures after antimalarial medication in previously healthy persons," Schiemann R, Coulaud JP, Bouchaud O; Journal of Travel Medicine, 2000 May-Jun;7(3):155-6.	2000	Case report – one subject	Case of a grand mal seizure after chloroquine prophylaxis followed by mefloquine therapy in a 19 year old girl who contracted malaria while on vacation, while taking chloroquine and proguanil; Therapy was with mefloquine 1,500 mg, and on the same day she suffered a grand mal seizure.
"Mefloquine-induced acute hepatitis," Gotsman I, Azaz-Livshits T, Fridlender Z, Muszkat M, Ben-Chetrit E; Pharmacotherapy, 2000 Dec;20(12):1517-9.	2000	Case report – one case	Patient with elevated liver function tests attributed to heart failure experienced acute elevation of liver transaminases 6 weeks after taking mefloquine 250 mg per week; Cessation of the drug caused test results to return to normal.
"Long-lasting neuropsychiatric side-effects following mefloquine prophylaxis. A case after six weeks of initiating and lasting six months,"; Bygbjerg IC, Ronn AM; Ugeskrift for Laeger, 1999 Mar 8;161(10):1422-3.	1999	Case report – one subject	Case of severe neuropsychiatric side-effects arising six weeks after initiating mefloquine prophylaxis, requiring repeated hospitalization, and NOT resolving completely after 6 months, in a previously healthy 30 year-old female.
"Neuropsychiatric side effects of malarial prophylaxis with mefloquine (Lariam),"; Minei-Rachmilewitz T; Harefuah, 1999 Jul;137(1-2):25-7, 87.	1999	Case report – one subject	39-year-old woman who developed acute psychosis after being given mefloquine prophylaxis.

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Title, Authors, Reference	*Date*	*Study Type - Subjects*	*Major Findings*
"Multifocal Myoclonus Associated with Mefloquine Chemoprophylaxis," Jimenez-Huete, A, Gil-Nagel, A, and Franch O; Clinical Neuropharmacology, 25; 5 243, 2002.	2002	Case report – one subject	Case report of a 54 year old Spanish woman developed multifocal myoclonus during mefloquine prophylaxis; Presented with abnormal movements in four limbs; Cerivastatin started 10 months earlier for treatment of hypercholesterolemia; 8 weeks previously started prophylactic mefloquine, and two weeks later during a trip noticed sudden brief shock-like irregular muscular contractions that appeared without pattern in all four limbs, and were more intense at the end of the day; Complained of slight frontal headache, dizziness and slowness of thinking; No known exposures including recreational drugs and friends were asymptomatic; Continued taking mefloquine 3 more weeks while symptoms increased until she could not drive a car; On the 6th week treatment stopped mefloquine and symptoms rapidly abated; Neurological exam 2 weeks later showed infrequent irregular non-synchronous brief muscular contractions in her proximal and distal upper limbs, consistent with multifocal myoclonus; No brain lesions by magnetic resonance imaging (MRI) and EEG normal; Blood tests showed only slight hypercholesterolemia; Follow up exam 2 weeks later showed no abnormal signs.
"Pulmonary toxicity with mefloquine," Udry E, Bailly F, Dusmet M, Schnyder P, Lemoine R, Fitting JW; The European Respiratory Journal, 2001 Nov;18(5):890-2.	2001	Case report – two subjects	Case 1: Patient developed acute lung injury within hours following mefloquine treatment for a low-level P. falciparum, which was halofantrine resistant; Extensive microbiological investigation remained negative; Video-assisted thoracoscopic lung biopsy demonstrated diffuse alveolar damage; Progress was favorable without treatment; Case 2: Patient experienced acute lung injury and diffuse alveolar damage related to mefloquine; Glucose-6-phosphate dehydrogenase deficiency was present in the former (but not the later, suggesting that it is not a predisposing condition) case and was thought to contribute to the lung injury.
"Mefloquine-induced trigeminal sensory neuropathy," Watt-Smith S, Mehta K, Scully C; Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and EnDODontics, 2001 Aug;92(2):163-5.	2001	Case report – one subject	Patient with sudden-onset trigeminal sensory neuropathy of the lip associated with taking mefloquine.
"Cognitive and neuropsychiatric side effects of mefloquine,"; Javorsky DJ, Tremont G, Keitner GI, Parmentier AH; The Journal of Neuropsychiatry and Clinical Neurosciences, 2001 Spring;13(2):302.	2001	Case report – one subject	52 year old woman no psychiatric history used mefloquine prophylactically once a week for 3 weeks prior and during a trip to Africa; Previously used mefloquine 4 years without problems; During return flight developed anxiety, paranoia, visual hallucinations, confusion and depressive symptoms; Outpatient treatment continued to show suicidal ideation, other neuropsychiatric symptoms, and cognitive disturbances 3 months after last dose of mefloquine; Hospitalized for inpatient psychiatric treatment; Mildly elevated TSH, positive past exposure to hepatitis A, normal brain MRI, medical history was no help; Drug therapy led to improvement over 4 days; after briefly living with a relative following discharge returned to independent functioning.

Title, Authors, Reference	*Date*	*Study Type - Subjects*	*Major Findings*
"Atovaquone-proguanil versus mefloquine for malaria prophylaxis in nonimmune travelers: results from a randomized, double-blind study," Overbosch D, Schilthuis H, Bienzle U, Behrens RH et al. Clinical infectious diseases, 2001; 33:1015-21	2001	Clinical trial; randomized, double-blind, with placebo evaluating frequency of adverse events. 976 travelers from the Netherlands, UK, Canada, and S. Africa traveling to malaria endemic areas for up to 28days. Individuals were monitored 7, 28, and 60 days after travel.	Treatment emergent neuropsychiatric events occurred in 29 percent of travelers randomized to mefloquine and in 14 percent randomized to atovaquone-proguanil (p=0.001). Events included strange or vivid dreams, insomnia, dizziness, visual difficulties, anxiety, and depression. Most adverse events were considered mild. Treatment was discontinued due to neuropsychiatric events in nineteen subjects receiving mefloquine, in five receiving mefloquine placebo, and in three receiving atovaquone-proguanil.
"Serious adverse events of mefloquine in relation to blood level and gender," Schwartz E, Potasman I, Rotenberg M, Almog S, Sadetzki S; The American Journal of Tropical Medicine and Hygiene, 2001 Sep;65(3):189-92.	2001	Clinical trial; Mechanistic	Evaluated association between mefloquine serum levels and serious side effects, with seventeen patients presenting to emergency rooms or travel clinics with symptoms suggesting serious adverse effects of mefloquine and twenty-eight controls (healthy people, still taking mefloquine after travel; Mean age patients and controls was 31.5 +/- 11.6 years and 34 +/- 12.2 years, respectively; More women among the patients (76 percent versus 40 percent, respectively; p = 0.03); Most complaints related to central nervous system (13 of 17); five patients interrupted their trip and two were hospitalized; No difference in mefloquine blood levels found comparing patients to control groups; No significant difference found between blood mefloquine levels among men and women; mefloquine blood levels do not correlate with severe adverse events; Women more susceptible than men, despite having similar blood levels of the drug.
"Paranoid psychosis related to mefloquine antimalarial prophylaxis," Fuller SJ, Naraqi S, Gilessi G; Papua and New Guinea Medical Journal, 2002 Sep-Dec;45(3-4):219-21.	2002	Case report – one subject	A 39-year old marine biologist medically evacuated from New Guinea with paranoid ideation and irrational behavior; Taken mefloquine 2 weeks earlier; No history of illicit drug use or other medications; On admission disoriented, speech rambling, agitated and fearful of medical staff; Afebrile; No unusual lab tests; Diagnosed with acute psychosis secondary to mefloquine, which resolved over the next 2 to 3 days; Patient admitted suffered from endogenous depression for 19 years and had taken meds for that.
"Mefloquine-induced paranoid psychosis and subsequent major depression in a 25-year-old student," Dietz A, Frolich L; Pharmacopsychiatry, 2002 Sep;35(5):200-2.	2002	Case report – one subject	Patient developed paranoid psychosis followed by depression after taking mefloquine for a vacation; Recovered fully within 9 months of receiving his first dose of mefloquine.

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Title, Authors, Reference	*Date*	*Study Type - Subjects*	*Major Findings*
"Tolerability of malaria chemoprophylaxis in non-immune travellers to sub-Saharan Africa: multicentre, randomised, double blind, four arm study," Schlagenhauf P, Tschopp A, Johnson R, Nothdurft HD, Beck B, Schwartz E, Herold M, Krebs B, Veit O, Allwinn R, Steffen R; British Medical Journal., 2003 Nov 8;327(7423):1078.	2003	Clinical trial; randomized, double blind, with placebo, 623 subjects receiving various malaria prophylaxis including mefloquine	Many subject reported adverse events (even in the initial placebo group); none were serious; Chloroquine and proguanil trial had highest mild to moderate adverse events; followed by mefloquine (64/153; 42 percent, 34 percent to 50 percent), doxycycline, and atovaquone and proguanil (p = 0.048 for all); Mefloquine and combined chloroquine and proguanil arms had the highest proportion of more severe events (n = 19; 12 percent, 7 percent to 18 percent and n = 16; 11 percent, 6 percent to 15 percent, respectively), whereas the combined atovaquone and proguanil and doxycycline arms had the lowest (n = 11; 7 percent, 2 percent to 11 percent and n = 9; 6 percent, 2 percent to 10 percent, respectively: p = 0.137 for all); Mefloquine arm had the highest proportion of moderate to severe neuropsychological adverse events, particularly in women (n = 56; 37 percent, 29 percent to 44 percent versus chloroquine and proguanil, n = 46; 30 percent, 23 percent to 37 percent; doxycycline, n = 36; 24 percent, 17 percent to 30 percent; and atovaquone and proguanil, n = 32; 20 percent, 13 percent to 26 percent: p = 0.003 for all); Highest proportion of moderate or severe skin problems were reported in the chloroquine and proguanil arm (n = 12; 8 percent, 4 percent to 13 percent versus doxycycline, n = 5; 3 percent, 1 percent to 6 percent; atovaquone and proguanil, n = 4; 2 percent, 0 percent to 5 percent; mefloquine, n = 2; 1 percent, 0 percent to 3 percent: P = 0.013). ***CONCLUSIONS:*** *Combined atovaquone and proguanil and doxycyline are well tolerated antimalarial drugs; Broader experience with both agents is needed to accumulate reports of rare adverse events.*
"Unexpected frequency, duration and spectrum of adverse events after therapeutic dose of mefloquine in healthy adults," Rendi-Wagner P, Noedl H, Wernsdorfer WH, Wiedermann G, Mikolasek A, Kollaritsch H; Acta Tropica, 2002 Feb;81(2):167-73.	2002	Clinical trial; 22 healthy volunteers monitored 21 days with *therapeutic* mefloquine (750 and 500 mg at 6 hour (h) intervals)	Unexpected high frequency of side effects of any grade reported by all 22 subjects; Most common were vertigo (96 percent), nausea (82 percent) and headache (73 percent); Subjects with severe vertigo (73 percent) required bed rest and specific medication for 1 to 4 days; More females than males reported severe adverse reactions; Majority (77.3 percent) participants (f: 8/12, m: 9/10) showed symptom resolution within 3 weeks (510 h) after drug administration; Biochemical and hematological findings stayed within the normal range of values, but showed nevertheless a significant rise of Na, Cl, Ca, bilirubin, GGT and LDH.

Title, Authors, Reference	*Date*	*Study Type - Subjects*	*Major Findings*
"Atovaquone plus chloroguanide versus mefloquine for malaria prophylaxis: a focus on neuropsychiatric adverse events," van Riemsdijk MM, Sturkenboom MC, Ditters JM, Ligthelm RJ, Overbosch D, Stricker BH; Clinical Pharmacology and Therapeutics, 2002 Sep;72(3):294-301.	2002	Epidemiologic study, prospective, double-blind, randomized study on neuropsychiatric adverse events and concentration impairment during prophylactic use of mefloquine or atovaquone plus chloroguanide	119 Subjects (mean age 35 years) followed from baseline screening to 7 days after leaving malaria area, measuring changes in mood disturbance and neurobehavioral indices including sustained attention, coding speed, and visuomotor accuracy; Significant deterioration in depression, anger, fatigue, vigor, and total mood disturbance domains occurred during use of mefloquine but not during use of atovaquone plus chloroguanide; Stratification on sex showed between-treatment differences in female patients but not in male patients; In both treatment groups, sustained attention deteriorated after travel, especially with increased duration of stay. ***CONCLUSIONS:*** *Prophylactic use of mefloquine was associated with significantly higher scores on scales for depression, anger, and fatigue and lower scores for vigor than prophylactic use of atovaquone plus chloroguanide.*
"Neurological, cardiovascular and metabolic effects of mefloquine in healthy volunteers: a double-blind, placebo-controlled trial," Davis TM, Dembo LG, Kaye-Eddie SA, Hewitt BJ, Hislop RG, Batty KT; British Journal of Clinical Pharmacology, 1996 Oct;42(4):415-21.	1996	Epidemiologic study, Double-blind, randomized, placebo-controlled trial -- 106 healthy adult subjects over 4 weeks	Mefloquine did not alter calcium homoeostasis but produced a mean 0.5 mmol l-1 fall in serum glucose over the study period ($p < 0.001$) and relative hyperinsulinaemia; Symbol digit modalities, and digit forwards and backwards test scores similar in active and placebo groups across the three assessments, as were lying/standing blood pressure and high-tone hearing loss; Electrocardiographic QTc interval prolongation and diarrhea were mild but transient side-effects of mefloquine ($p < 0.01$); Neurological symptoms comparable in two groups throughout study; No evidence of drug toxicity in eleven subjects who withdrew. Concluded mefloquine prophylaxis does not appear to produce low-grade but debilitating neurological symptoms or to alter the results of sensitive tests of cerebral function, but it might contribute to hypoglycaemia and cardiac dysrhythmias.

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Title, Authors, Reference	*Date*	*Study Type - Subjects*	*Major Findings*
"The acute neurotoxicity of mefloquine may be mediated through a disruption of calcium homeostasis and ER function in vitro," Dow GS, Hudson TH, Vahey M, Koenig ML; Malaria Journal, 2003 Jun 12;2(1):14.	2003	Mechanistic study	Investigated the possibility that the acute in vitro neurotoxicity of mefloquine might be mediated through a disruptive effect of the drug on endoplasmic reticulum (ER) calcium homeostasis. Mefloquine was found to disrupt neuronal calcium homeostasis and induce an ER stress response at physiologically relevant concentrations, effects that may contribute, at least in part, to the neurotoxicity of the drug in vitro
"The risk of severe depression, psychosis or panic attacks with prophylactic antimalarials," Meier CR, Wilcock K, Jick SS; Drug Safety : An International Journal of Medical Toxicology and Drug Experience, 2004;27(3):203-13.	2004	Epidemiologic study. A population-based observational study using a database of medical records to quantify and compare the risk of psychiatric disorders during or after use of mefloquine with the risk during use of proguanil and/or chloroquine, or doxycycline	The study population was drawn from the large UK-based General Practice Research Database (GPRD). Subjects were aged from 17-79 years and were exposed to mefloquine, proguanil, chloroquine or doxycycline (or a combination of these drugs) at some time between 1990 and 1999. We performed a person-time and a nested case-control analysis to assess the risk of developing a first-time diagnosis of depression, psychosis or panic attack during or after use of these antimalarial drugs. **RESULTS:** Within the study population of 35 370 subjects (45.2 percent males), we identified 580 subjects with a first-time diagnosis of depression (number of subjects (n) = 505), psychosis (n = 16) or panic attack (n = 57) and two subjects committed suicide. The incidence rates of first-time diagnoses of depression during current use of mefloquine, proguanil and/or chloroquine, or doxycycline, adjusted for age, gender and calendar year, were 6.9 (95 percent CI 4.5-10.6), 7.6 (95 percent CI 5.5-10.5) and 9.5 (95 percent CI 3.7-24.1)/1000 person-years, respectively. The incidence rates of psychosis or panic attacks during current mefloquine exposure were 1.0/1000 person-years (95 percent CI 0.3-2.9) and 3.0/1000 person-years (95 percent CI 1.6-5.7), respectively, approximately 2-fold higher (statistically nonsignificant) than during current use of proguanil and/or chloroquine, or doxycycline. The nested case-control analysis encompassed 505 cases with depression and 3026 controls, 16 cases with psychosis and 96 controls, and 57 cases with a panic attack and 342 controls. Current use of mefloquine was not associated with an elevated risk of developing depression. In a comparison between patients currently using mefloquine with all past users of antimalarials combined, the risk estimate was elevated for current users of mefloquine for both psychosis (odds ratio (OR) 8.0, 95 percent CI 1.0-62.7; $p < 0.05$) and panic attacks (OR 2.7, 95 percent CI 1.1-6.5; $p < 0.05$). ***CONCLUSION:*** *The absolute risk of developing psychosis or panic attack appears low with all the antimalarials tested. No evidence was found in this large observational study that mefloquine use increased the risk of first-time diagnosis of depression when compared with the use of other antimalarials investigated in this study.*

Title, Authors, Reference	*Date*	*Study Type - Subjects*	*Major Findings*
"Drug interactions with antimalarial agents," Griffin JP; Adverse Drug Reactions and Toxicological Reviews, 1999 Mar;18(1):25-43.	1999	Review of case reports	Case reports enumerates "common" side effects including nausea, vomiting, dizziness and vertigo, loss of balance, headache, sleep disorders, diarrhea and abdominal pain; More rare serious side effects include: 1) psychiatric effects as including depression, anxiety, confusion, psychosis, paranoia, aggression and agitation; 2) Neurological effects including convulsions, sensory and motor neuropathy, paraesthesia, tinnitus, tremor, ataxia and visual disturbances, and encephalopathy has been reported; 3) Cardiovascular effects including blood pressure changes, syncope, bradycardia, extrasystoles, cardiac conduction defects including atrioventricular block; 4) Skin rashes including urticarial rashes, pruritis, hair loss and Stevens-Johnson syndrome; 5) Hematological effects including leucopenia and thrombocytopenia; and 6) Liver enzyme changes. *No discussion of how long these effects might last after the drug is stopped.*
"Dermatological Adverse Effects with the Antimalarial Drug Mefloquine: a Review of 74 Published case Reports," Smith HR, Croft AM, Black MM; Clinical and Experimental Dermatology, 1999, 24; 249-254.	1999	Review of 74 case reports on mefloquine dermatological effects published between 1983 and 1997	There is good circumstantial evidence that mefloquine can cause mild and occasionally severe adverse dermatological effects in health travelers and in hospital patients with malaria. These effects are mostly self-limiting and rarely require treatment. Pruritus is the most frequent dermatological reaction and maculopapular rash is also common. Stevens-Johnson syndrome and toxic epidermal necrolysis have all been associated with mefloquine. The incidence of dermatological adverse effects with mefloquine may be between 4 to 10 percent for short-term use and as high as 30 percent for prolonged use.
"CNS adverse events associated with antimalarial agents. Fact or fiction?;" Phillips-Howard PA, ter Kuile FO; Drug Safety : An International Journal of Medical Toxicology and Drug Experience, 1995 Jun;12(6):370-83.	1995	Review	Mefloquine therapy causes dose-related transient dizziness; and serious central nervous system (CNS) events occur in 1:1200 Asians and 1:200 Caucasians/Africans; Risk factors include dosage, concomitant drug use/interactions, previous history of a CNS event and disease severity; Retreatment (within a month) increases the risk in Asians 7-fold; Irreversible effects are extremely rare and usually associated with overdosing or prior history of a serious CNS event.
"Mefloquine prophylaxis: an overview of spontaneous reports of severe psychiatric reactions and convulsions," Bem JL, Kerr L, Stuerchler D; The Journal of Tropical Medicine and Hygiene, 1992 Jun;95(3):167-79.	1992	Review of adverse reaction reports since 1991 (about 1 year) by the manufacturer Hoffmann-La Roche	59 serious neurologic and psychiatric adverse reaction reports reviewed: 26 convulsions, 12 depressions, 20 psychotic episodes, and one toxic encephalopathy; none were fatal; Only patient population identified at increased risk of developing these serious reactions are persons with a history of seizures or manic-depressive illness.
"Neuropsychiatric side effects after the use of mefloquine," Weinke T, Trautmann M, Held T, Weber G, Eichenlaub D, Fleischer K, Kern W, Pohle HD; Am The Journal of Tropical Medicine and Hygiene, 1991 Jul;45(1):86-91.	1991	Review of case reports	Reviewed neuropsychiatric side effects in German patients after treatment with mefloquine; Reactions consisted mainly of seizures, acute psychoses, anxiety neurosis, and major disturbances of sleep-wake rhythm; Effects occurred after both therapeutic and prophylactic intake; Estimated that one of 8,000 mefloquine users suffers from such reactions (one of 215 among therapeutic users, one of 13,000 among prophylaxis users).

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Title, Authors, Reference	*Date*	*Study Type - Subjects*	*Major Findings*
"Mefloquine for preventing malaria in non-immune adult travelers, Review," The Cochrane Database of Systematic Reviews, Copyright 2004 The Cochrane Library, Volume (1), Croft, AMJ; Garner, P.	2004	Review – Cochrane review of We included 10 trials involving 2750 non-immune adult participants. Five were field trials, mainly male soldiers. Also reviewed 516 published case reports of mefloquine adverse effects, 63 percent involved tourists and business travelers	Mefloquine prevents malaria, but has adverse effects that limit its acceptability. Evidence from non-randomised studies shows mefloquine has potentially harmful effects in tourists and business travellers. No-one knows if mefloquine is well or poorly tolerated. Many of the standard textbooks of tropical medicine assert that mefloquine is well tolerated in prophylaxis and that the only side effects of importance are neuropsychiatric reactions or seizures, experienced by around one in 10,000 users. This much-cited estimate of the frequency of neuropsychiatric side effects from mefloquine is based not on experimental data, but on spontaneous reports of severe adverse events in mefloquine users, and undoubtedly under-estimates the true incidence of undramatic but nevertheless unpleasant side effects from mefloquine. The main problem with mefloquine is that its tolerability is a major concern of the public, with questions raised repeatedly in the news media. Yet evidence to reassure the public, or confirm their fears, is not available. Withdrawals during clinical trials of mefloquine group were consistently higher in four placebo controlled trials (odds ratio 3.56, 95 percent confidence interval 1.67 to 7.60). In five trials comparing mefloquine with other chemoprophylaxis, no difference in tolerability was detected. There were four fatalities attributed to mefloquine.
Roche Pharmaceuticals "Dear Healthcare Professional" letter about mefloquine side effects, "Copyright © 2003 by Roche Laboratories Inc. All rights reserved," at www.fda.gov/cder/foi/label/2003/19591s19lbl_Lariam.pdf,	2003	Review – Manufacturer's warning letter to clinicians	"Lariam can rarely cause serious mental problems in some patients. The most frequently reported side effects with Lariam, such as nausea, difficulty sleeping, and bad dreams are usually mild and do not cause people to stop taking the medicine. However, people taking Lariam occasionally experience severe anxiety, feelings that people are against them, hallucinations (seeing or hearing things that are not there, for example), depression, unusual behavior, or feeling disoriented. It has been reported that sometimes, in some patients, these side effects continue after Lariam is stopped. Some patients taking Lariam think about killing themselves, and there have been rare reports of suicides. We do not know if Lariam was responsible for these suicides. Do not take Lariam to prevent malaria if you have 1) depression or had depression recently; 2) recent mental illness or problems, including anxiety disorder, schizophrenia or psychosis; 3) seizures; 4) allergic to quinine or quinidine 5) Heart disease; 6) Pregnancy; 7) Breast feeding; or 8) Liver problems."
"Adverse effects of the antimalaria drug, mefloquine: due to primary liver damage with secondary thyroid involvement?" Croft AM, Herxheimer A; BioMed Central Public Health, 2002 Mar 25;2(1):6.	2002	Review of 516 published case reports – Cochrane Review	Postulate many mefloquine adverse effects are a post-hepatic syndrome caused by primary liver damage; "Mefloquine syndrome" presents in a variety of ways including headache, gastrointestinal disturbances, nervousness, fatigue, disorders of sleep, mood, memory and concentration, and occasionally frank psychosis. Previous liver or thyroid disease, and concurrent insults to the liver (such as from alcohol, dehydration, an oral contraceptive pill, recreational drugs, and other liver-damaging drugs) may be related to the development of severe or prolonged adverse reactions to mefloquine.

Title, Authors, Reference	*Date*	*Study Type - Subjects*	*Major Findings*
CDC National Center for Infectious Diseases, Travelers' Health, Information for Health Care Providers, Prescription Drugs for Malaria, accessed 4-21-04 at www.cdc.gov/travel/malariadrugs2.htm.	2004	Review -- Physicians Advisory put out by CDC	Mefloquine is contraindicated in persons allergic to mefloquine and in persons with active depression or a previous history of depression, generalized anxiety disorder, psychosis, schizophrenia, other major psychiatric disorders, or seizures. Not recommended for persons with cardiac conduction abnormalities. Mefloquine primary prophylaxis should begin 1-2 weeks before travel to malarious areas. It should be continued once a week, on the same day each week, during travel to malarious areas, and for 4 weeks after the traveler leaves such areas. Mefloquine has been associated with rare serious adverse reactions (including psychoses or seizures) at prophylactic doses; these reactions are more frequent with the higher doses used for treatment. Other side effects that occur with prophylactic doses include gastrointestinal disturbance, headache, insomnia, abnormal dreams, visual disturbances, depression, anxiety disorder, and dizziness. Mefloquine is contraindicated for use by travelers with a known hypersensitivity to mefloquine and in persons with active depression or a history of depression, or in persons with generalized anxiety disorder, psychosis, schizophrenia, or other psychiatric disturbances. Mefloquine is contraindicated in persons with a history of seizures (not including the type of seizure caused by high fever in childhood). Mefloquine is not recommended for persons with cardiac conduction abnormalities.
U.S. Department of Health & Human Services, U.S. Food and Drug Administration, FDA News, P03-52, July 9, 2003, "FDA Creates Medication Guide for Lariam." Accessed 4-21-04 at www.fda.gov/bbs/topics/NEWS/2003/NEW00921.html	2004	Review -- FDA Medication Guide	FDA developed the Lariam (mefloquine) Medication Guide in collaboration with the drug's manufacturer, Roche Pharmaceuticals of Nutley, NJ, to help ensure patients understand the risks of malaria, and the rare but potentially serious psychiatric adverse events associated with use of Lariam. Sometimes these psychiatric adverse events may persist even after stopping the medication. Some rare reports have claimed that Lariam users think about killing themselves. There have been rarer reports of suicides, although FDA does not know if Lariam use was related to these suicides.

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Title, Authors, Reference	*Date*	*Study Type - Subjects*	*Major Findings*
"Comparison of adverse events associated with use of mefloquine and combination of chloroquine and proguanil as antimalarial prophylaxis: postal and telephone survey of travelers," Barrett PJ, Emmins PD, Clarke PD, Bradley DJ; British Medical Journal, 1996; 313:528-8.	1996	Survey of 1214 British travelers from 1993 to 1995 who received advice from the travelers telephone health line run by the Medical Advisory Services for Travelers Abroad. Travelers received a questionnaire upon returning from their trip.	27 percent of travelers taking mefloquine reported neuropsychiatric adverse events. The traveler sought medical advice in 2.2 percent of the cases and 0.3 percent required hospital attention. Of those taking chloroquine and proguanil, 16 percent reported neuropsychiatric adverse events with 0.9 percent requiring medical advice and 0.1 percent hospital attention. Of those reporting any adverse event with mefloquine, 5.1 percent discontinued antimalarial prophylaxis and 0.7 percent switched to another agent. The corresponding numbers for chloroquine and proguanil were 6.3 percent and 0.3 percent. Disabling neuropsychiatric adverse events included hallucinations, panic attacks, dissociation from reality, confusion, difficulty concentrating, depression, anxiety, emotional instability depression, anxiety, personality changes, and nightmares.
Centers for Disease Control & Prevention (CDC) National Center for Infectious Diseases, Travelers' Health, Information for the Public: Prescription Drugs for Malaria, accessed 4-21-04 at www.cdc.gov/travel/malariadrugs.htm	2004	Review – Travelers Advisory from CDC	The most common side effects reported by travelers taking mefloquine include headache, nausea, dizziness, difficulty sleeping, anxiety, vivid dreams, and visual disturbances. Mefloquine has rarely been reported to cause serious side effects, such as seizures, depression, and psychosis. These serious side effects are more frequent with the higher doses used to treat malaria; fewer occurred at the weekly doses used to prevent malaria. Mefloquine is eliminated slowly by the body and thus may stay in the body for a while even after the drug is discontinued. Therefore, side effects caused by mefloquine may persist weeks to months after the drug has been stopped. Most travelers taking mefloquine do not have side effects serious enough to stop taking the drug. Travelers Who Should Not Take Mefloquine. The following travelers should not tak mefloquine and should ask their health care provider for a different antimalarial drug a. Persons with active depression or a recent history of depression b. Persons with a history of psychosis, generalized anxiety disorder, schizophrenia, or other major psychiatric disorder c. Persons with a history of seizures (does not include the type of seizure caused by high fever in childhood) d. Persons allergic to mefloquine Mefloquine is not recommended for persons with cardiac conduction abnormalities (for example, an irregular heartbeat).

Title, Authors, Reference	*Date*	*Study Type - Subjects*	*Major Findings*
"Adverse effects associated with antimalarial chemoprophylaxis," Corominas N, Gascon J, Mejias T, Caparros F, Quinto L, Codina C, Ribas J, Corachan M.; Medicina Clinica, 1997 May 24;108(20):772-5.	1997	Survey of 1,054 Spanish travelers who traveled from 1992 to 1994	Self reports among 1,054 travelers taking various malarial prophylaxis including mefloquine; 18.4 percent reported adverse reactions including 12.4 percent on chloroquine, 17.2 percent on chloroquine + proguanil, and 20.3 percent on mefloquine (differences not significant); Neuropsychiatric reactions more frequent in the mefloquine group ($p < 0.01$); Gastrointestinal reactions less common in the chloroquine group ($p = 0.04$); Transitory eye disorders more frequent in the chloroquine + proguanil group ($p = 0.01$); Travelers with adverse reactions in mefloquine group had significantly lower weight than those who did not present them ($p < 0.01$); Mefloquine has greater neuropsychiatric toxicity and is worse tolerated in low weight patients.
"Neuro-psychiatric effects of antimalarials," van Riemsdijk MM, van der Klauw MM, van Heest JA, Reedeker FR, Ligthelm RJ, Herings RM, Stricker BH; European Journal of Clinical Pharmacology, 1997;52(1):1-6.	1997	Survey 394 Dutch travelers taking mefloquine, within 14 days of return, compared to travelers taking other malarial prophylaxes	Questionnaire consisted of questions regarding use of alcohol, smoking, general health, medical history, tropical diseases during the trip, and other medicines, and contained an extensive list of general complaints regarding all body systems at four levels of severity. A modified and validated version of the Profile of Mood States was included. **RESULTS:** In the study period, 2541 persons visited the Travel Clinic, of whom 1791 (70 percent) were both eligible and willing to co-operate. Of these 1791, data were obtained from 1501 (84 percent). Insomnia was most frequently encountered in users of mefloquine and mouth ulcers in proguanil users. After adjustment for gender, age, destination, and alcohol use, the relative risk for insomnia to mefloquine versus non-users of antimalarials was 1.6, and the excess risk was 6 per 100 users over an average period of 2 months. There were no significant differences between groups in depression, anxiety, agitation, and confusion. Stratification by gender demonstrated that insomnia was more common in women on mefloquine, but not in men. Also, women more frequently mentioned palpitations as an adverse event. After adjustment for age, destination, and alcohol use in women, the relative risks for insomnia and palpitations to mefloquine versus non-use of antimalarials were 2.4, and 22.5, respectively. When travelers were specifically asked for the adverse reactions they had experienced, anxiety, vertigo, agitation, and nightmares were significantly more frequently mentioned by mefloquine users. ***CONCLUSION:*** *Insomnia was more commonly encountered during use of mefloquine than proguanil or during non-use of antimalarials.*

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Title, Authors, Reference	*Date*	*Study Type - Subjects*	*Major Findings*
"Neuropsychiatric events during prophylactic use of mefloquine before traveling," van Riemsdijk MM, Ditters JM, Sturkenboom MC, Tulen JH, Ligthelm RJ, Overbosch D, Stricker BH; European Journal of Clinical Pharmacology, 2002 Sep;58(6):441-5.	2002	Survey 179 Dutch travelers from 1999 to 2000 before and for three weeks after taking mefloquine (prior to traveling)	Females reported adverse events more frequently than males (P=0.005); Small but significant increase in the score on the domain fatigue [0.74 points, 95 percent confidence interval (CI) 0.18, 1.30 exclusively in females and not in males; First-time users increased 2.81 points (95 percent CI 0.70, 4.92) on mood state test, and among those, women showed the largest increase of 4.58 points (95 percent CI 0.74, 8.43). The use of mefloquine was associated with neuropsychiatric adverse effects. Females encountered neuropsychiatric effects more frequently than males, which could be confirmed by validated psychological tests. Neuropsychiatric effects were more common in first-time users than in individuals who had used mefloquine before.
"Reported side effects to chloroquine, chloroquine plus proguanil, and mefloquine as chemoprophylaxis against malaria in Danish travelers," Petersen E, Ronne T, Ronn A, Bygbjerg I, Larsen SO; Journal of Travel Medicine, 2000 Mar-Apr;7(2):79-84.	2000	Survey of self reports among 5, 446 Danish travelers from 1996 to 1998	5, 446 Danish travelers surveyed (76.3 percent response) on drug compliance, hospitalization and premature termination of travel, following use of chloroquine, chloroquine plus proguanil, or mefloquine; Compliance significantly better for mefloquine users (83.3 percent among short term travelers re. 76.3 percent among chloroquine plus proguanil users); 84.8 percent, 59.3 percent and 69.5 percentreported no symptoms using chloroquine, chloroquine plus proguanil, and mefloquine, respectively; 0.6 percent, 1.1 percent and 2.8 percent reported "unacceptable" symptoms, respectively; Compared to chloroquine, mefloquine users had a significantly higher relative risk (RR) of reporting depression, RR 5.06 (95 percent CI 2.71 - 9.45), "strange thoughts," RR 6.36 (95 percent CI 2.52 - 16.05) and altered spatial perception, RR 3.00 (95 percent CI 1.41 - 6.41). ***CONCLUSION**: Overall mefloquine is tolerated at least as well as chloroquine plus proguanil and shows better compliance, however, symptoms related to the central nervous system are more prevalent in mefloquine users and when symptoms develop, they are perceived as more severe.*
"Neuropsychiatric problems in 2,500 long-term young travelers to the tropics," Potasman I, Beny A, Seligmann H;,Journal of Travel Medicine, 2000 Jan;7(1):5-9.	2000	Survey of neuropsychiatric problems and previous psychological consultation of 2,500 young travelers to tropical countries	Out of 1,340 respondents, 151 (11.3 percent) reported they had neuropsychiatric problems (NPP) during travel compared to 2.3 percent who needed psychological consultation before travel (probability (p) <.001); In a follow up, 117 of 151 responded to a study questionnaire (mean age 24.4 years, 54.7 percent female, mean stay abroad 5.3 months) the most common reported NPP were sleeping disturbances (52.1 percent), fatigue (48.7 percent) and dizziness (39.3 percent).; 33 (2.5 percent) reported severe symptoms, 16 (1.2 percent) had symptoms lasting more than 2 months; 7 had pure or mixed depressive symptoms; Consumption of recreational drugs admitted by 22.2 percent; Mefloquine used significantly more often by those who suffered NPP, compared to the entire cohort (98.2 percent vs. 70.7 percent; p<.001); ***CONCLUSIONS:** Long-term travel to the tropics was associated, in this cohort, with a considerable rate of neuropsychiatric symptoms. The majority of the responding travelers were females, used mefloquine as prophylaxis, and at least one fifth used recreational drugs.*

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ATTACHMENT A

SUMMARY OF LITERATURE ON POSSIBLE LONG-TERM CHRONIC HEALTH EFFECTS FROM MEFLOQUINE

1. To develop guidance on possible long-term health effects from mefloquine, a Veterans Health Administration (VHA) expert group that included representatives from the Office of Public Health and Environmental Hazards and Office of Patient Care Services' Medical-Surgical, Mental Health, and Pharmacy Benefits & Management, and other VHA leaders and experts in neurology, mental health, infectious disease, and toxicology, conducted a literature review that located seven health surveys of travelers, thirty-four case reports of adverse events, two Cochrane reviews, six epidemiological studies including clinical trials and prospective studies, and nine general reviews of multiple case reports including manufacturer and Food and Drug Administration (FDA) warning label summaries. In addition the two Cochrane reviews (the most recent dated 2004) examined ten clinical trials involving 2750 adult participants. Five of those were field trials, mainly of male soldiers. The following table, sorted by study-type, then by date, summarizes this information.

Title, Authors, Reference	*Date*	*Study Type - Subjects*	*Major Findings*
"Low body mass index is associated with an increased risk of neuropsychiatric adverse events and concentration impairment in women on mefloquine," van Riemsdijk MM, Sturkenboom MC, Ditters JM, Tulen JH, Ligthelm RJ, Overbosch D, Stricker BH; British Journal of Clinical Pharmacology, 2004;57(4):506-12.	2004	Survey of 151 Dutch travelers from 1999 to 2000 before and up to 3 weeks (pre travel) after taking mefloquine	Significant impairment of mood state observed subjects with body mass index (BMI) < or = 20 kg m(-2); Stratification for gender showed that the total mood disturbance in females in the lowest BMI category significantly increased by 8.42 points [95 percent confidence interval (CI) 3.33, 13.50], whereas BMI did not affect the risk in males; Stratification for history of use of mefloquine showed that the risks were highest in first-time users; An sustained attention performance test showed reaction time in women with a BMI < or = 20 kg m(-2) increased significantly by 22.5 ms (95 percent CI 7.80, 37.20), whereas reaction time in men showed a slight and nonsignificant decrease. ***CONCLUSION:*** *Risk factors for mefloquine-associated neuropsychiatric adverse events and concentration impairment are female gender, low BMI, and first-time use. The frequency of neuropsychiatric effects is highest in women with a BMI < or = 20 kg m(-2).*
"Many travelers suffer of side-effects of malaria prophylaxis," Rietz G, Petersson H, Odenholt I; Lakartidningen, 2002 Jun 27;99(26-27):2939-44.	2002	Survey of about 500 Swedish travelers before and after their trip, with 62 percent response rate	Travelers taking any malarial prophylaxis reported greater rate of symptoms compared to controls (59 percent vs. 41 percent), and that their trip had been negatively affected by their symptoms; Neuropsychiatric symptoms most common among mefloquine takers but the difference was not significant; Travelers taking mefloquine more frequently associated their symptoms with that drug; travelers most worried about taking malaria prophylaxis prior to the trip reported symptoms more often than those not feeling any anxiety.

c. The most severe and persistent adverse effects appear in "case reports." In those instances, consistent with the nature of a case report, the relevant signs and symptoms began while mefloquine was being taken, and persisted in some reports for weeks, months or even years after the drug was stopped. ***NOTE:*** *Mefloquine has a long half-life in humans of 15 to 30 days.* Adverse effects that are reported to persist for significant periods after the drug is stopped, or that could be associated with long-term health effects, include the following which lists in decreasing frequency the cases; ***NOTE:*** *The reported number of individual cases and the number of published reports for that health effect are shown in parenthesis; i.e., 16/12 means that there were sixteen reported cases and twelve published reports.*

(1) Anxiety, paranoia, hallucinations, depression, suicidal ideation, cognitive and other neuropsychiatric symptoms (16/12),

(2) Acute and paranoid psychosis (10/9),

(3) Convulsions, grand mal seizures, coma and abnormal electroencephalography (EEG) (9/4),

(4) High frequency sensorineural hearing loss and tinnitus, with partial or no remission (3/1),

(5) Acute lung injury with diffuse alveolar damage (2/1),

(6) Elevated liver function tests or fatty liver (2/2),

(7) Multifocal myoclonus (1/1),

(8) Fatal toxic epidermal necrolysis (1/1),

(9) Trigeminal sensory neuropathy (1/1),

(10) Atrial flutter (1/1), and

(11) Mefloquine overdose induced encephalopathy (1/1).

d. Veterans need to be informed that seeking care for possible mefloquine-related conditions does not constitute a claim for compensation. ***NOTE:*** *Veterans wishing to file a compensation claim need to be referred to a Veterans Benefits Counselor, or advised to contact the appropriate VA Regional Office at 1-800-827-1000.*

4. Contact. Questions regarding this information letter may be addressed to the Environmental Agents Service (131) at (202) 273-8579.

S/ Arthur S. Hamerschlag for
Jonathan B. Perlin, MD, PhD, MSHA, FACP
Acting Under Secretary for Health

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measures. Potential side effects that can impair reaction time and thinking include sensory and motor neuropathies, encephalopathy, convulsions, psychosis, nightmares, dizziness, and confusion. Studies indicate that these may occur in 1 in 2,000 to 1 in 13,000 people who receive prophylactic mefloquine."

d. VHA held a meeting April 13, 2004, to discuss possible responses to this issue. The meeting included representatives from the Office of Public Health and Environmental Hazards and Office of Patient Care Services' Medical-Surgical, Mental Health, and Pharmacy Benefits & Management, and other VHA leaders and experts in neurology, mental health, infectious disease, and toxicology. The group concluded that the Department of Veterans Affairs (VA) needed a well-grounded response to current concerns among veterans, their families, Congress, the media, VA health care providers, and others about possible long-term health effects and disability among OIF and OEF veterans from taking mefloquine. In particular, VHA health care providers will need concise and accurate medical information about mefloquine health effects to answer questions and concerns of veterans who are returning from deployments in Southwest Asia.

e. To develop guidance on possible long-term and chronic health effects from mefloquine, this group conducted a literature review of more than sixty reports that included eight surveys of travelers, 34 case reports of adverse events, two Cochrane reviews, seven epidemiological studies including clinical trials and prospective studies, and nine general reviews of multiple case reports, which included manufacturer and FDA warning label summaries. The most recent Cochrane review (2004) examined ten clinical trials involving 2750 adult participants, five of which were field trials, mainly of male soldiers.

3. Guidance

a. The following summary is to assist VA health care providers when they are providing care to veterans who may have taken mefloquine while on active duty. Since there are no practical tests for mefloquine, nor are there any specific tests that can be recommended specifically for veterans who took mefloquine while on active duty, medical care needs to focus upon occupational health issues: e.g., taking a thorough military and medical history, including taking of mefloquine, along with a basic medical examination that includes appropriate laboratory tests relating to the veteran's complaints and medical findings.

b. Review of available literature (see Att.A for references and summaries) suggests that certain health effects may be associated with mefloquine, some of which may persist after the drug is stopped. Self-reported symptoms in "travelers surveys" include: insomnia, mood impairment, depression, "strange thoughts," altered spatial perception, sleeping disturbances, fatigue, dizziness and other neuropsychiatric effects, lasting in some instances more than 2 months. Clinical trials and epidemiological studies suggest that reported side effects are not common, are self-limiting, and include: depression, panic attacks, anxiety, insomnia, vertigo, nausea and headache, and strange or vivid dreams. However, such studies have only limited power to detect more rare and serious adverse events.

DEPARTMENT OF VETERANS AFFAIRS
Veterans Health Administration
Washington DC 20420

IL 10-2004-007
In Reply Refer To: 13

June 23, 2004

UNDER SECRETARY FOR HEALTH'S INFORMATION LETTER

POSSIBLE LONG-TERM HEALTH EFFECTS FROM THE MALARIAL PROPHYLAXIS MEFLOQUINE (LARIAM)

1. **Purpose.** This Under Secretary for Health's Information Letter provides information to clinicians who examine and provide care to veterans who may have taken mefloquine as a malaria prophylaxis while on active duty in Southwest Asia during Operation Iraqi Freedom (OIF) and Operation Enduring Freedom (OEF).

2. **Background**

a. During OIF and OEF, the United States (U.S.) Department of Defense (DOD) provided mefloquine (Lariam) to some U.S. service members to protect them against endemic malaria.

b. Mefloquine is approved by the U.S. Health and Human Services Food and Drug Administration (FDA) for protection against malaria, and since the late 1980s it has become widely recommended for malaria chemoprophylaxis. Mefloquine can cause common mild side effects including vivid dreams and mild psychiatric symptoms, which can be sufficiently uncomfortable as to affect compliance. In addition, a number of anecdotal and media reports have suggested that mefloquine has caused more serious effects, including violent and suicidal behavior, and symptoms similar to Post-traumatic Stress Disorder (PTSD). These media accounts link reports of such behavior to mefloquine use among returning OIF and OEF veterans, for example, homicides and suicides among five service members returning to Ft. Bragg, NC, in the Summer of 2002. Concerns that mefloquine might cause violent behavior is not new; a Canadian soldier accused of homicide claimed that taking mefloquine, while deployed to Somalia in 1992, had caused his violent behavior.

c. Adding to this concern, the DOD warning label "Information for Clinicians" for mefloquine (taken essentially from the equivalent FDA label), includes the following:

"Rare instances of suicide in patients taking mefloquine have been reported but no studies have demonstrated a statistical association between mefloquine use and suicide, suicidal ideas, suicide attempts, or any other violent behavior. Patients with a history of psychiatric illness may be vulnerable to mefloquine-related psychiatric symptoms, and the package insert recommends against prescribing (it) to patients with a history of psychiatric or alcohol problems. Often, potential neuropsychiatric side effects are the greatest concern for patients. Side effects may include anxiety, paranoia, depression, agitation, restlessness, mood changes, panic attacks, forgetfulness, hallucinations, aggression, and psychotic behavior. Symptoms may continue long after mefloquine use has been stopped. If neuropsychiatric symptoms occur, mefloquine use should be discontinued in favor of other prophylactic medications or

McCarthy Supplementary Submission - Attachment 3

U.S. Army Research Office, *Neurotoxicity Associated with Mefloquine, an Anti-Malarial Drug: Small Business Technology Transfer (STTR): Solicitation Topic Number A06-T034 (Army)*, 2006.

In 2006 the U.S. Army Research Office solicited private industry proposals "To define the biological mechanisms of mefloquine neurotoxicity, identify genetic and other predispositions to mefloquine neurotoxicity, and identify whether mefloquine neurotoxicity may extend to other anti-malarials as a class effect."

http://www.acq.osd.mil/osbp/sbir/solicitations/sttr2006/army06.htm

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ARMY

PROPOSAL SUBMITTAL

The United States Army Research Office (ARO), reporting to the Army Research Laboratory (ARL) manages the Army's Small Business Technology Transfer (STTR) Program. The following pages list topics that have been approved for the fiscal year 2006 STTR program. Proposals addressing these areas will be accepted for consideration if they are received no later than the closing date and hour of this solicitation.

The Army anticipates funding sufficient to award one or two STTR Phase I contracts to small businesses with their partner research institutions in each topic area. Awards will be made on the basis of technical evaluations using the criteria contained in the solicitation, within the bounds of STTR funds available to the Army. If no proposals within a given area merit support relative to those in other areas, the Army will not award any contracts for that topic. Phase I contracts are limited to a maximum of $100,000 over a period not to exceed six months.

Based upon progress achieved under a Phase I contract, utilizing the criteria in Section 4.3, a firm may be invited to submit a Phase II proposal (with the exception of Fast Track Phase II proposals - see Section 4.5 of this solicitation). Phase II proposals should be structured as follows: the first 10-12 months (base effort) should be approximately $375,000; the second 10-12 months of funding should also be approximately $375,000. The entire Phase II effort should generally not exceed $750,000. Contract structure for the Phase II contract is at the discretion of the Army's Contracting Officer after negotiations with the small business.

Army STTR Contracts may be fully funded or funded using options or incremental funding.

Please Note!

The Army requires that your entire proposal (consisting of Proposal Cover Sheets, the full Technical Proposal, Cost Proposal (using the template provided), and Company Commercialization Report) must be submitted electronically through the DoD SBIR/STTR Proposal Submission Website. A hardcopy is NOT required. Hand or electronic signature on the proposal is also NOT required.

The DoD-wide SBIR Proposal Submission system (available at http://www.dodsbir.net/submission) will lead you through the preparation and submission of your proposal. Refer to section 3.0 at the front of this solicitation for detailed instructions on Phase I proposal format. You must include a Company Commercialization Report as part of each proposal you submit however, it does not count against the proposal page limit. If you have not updated your commercialization information in the past year, or need to review a copy of your report, visit the DoD SBIR Proposal Submission site. Please note that improper handling of the Commercialization Report may result in the proposal being substantially delayed and that information provided may have a direct impact on the review of the proposal. Refer to section 3.5d at the front of this solicitation for detailed instructions on the Company Commercialization Report.

Be reminded that if your proposal is selected for award, the technical abstract and discussion of anticipated benefits will be publicly released on the Internet therefore, do not include proprietary or classified information in these sections. DoD will not accept classified proposals for the STTR Program. Note also that the DoD web site contains timely information on firm, award, and abstract data for all DoD SBIR/STTR Phase I and II awards going back several years. This information can be viewed on the DoD SBIR/STTR Awards Search website at www.dodsbir.net/awards.

A06-T034 - TITLE: Neurotoxicity Associated with Mefloquine, an Anti-Malarial Drug

TECHNOLOGY AREAS: Biomedical

OBJECTIVE: To define the biological mechanisms of mefloquine neurotoxicity, identify genetic and other predispositions to mefloquine neurotoxicity, and identify whether mefloquine neurotoxicity may extend to other anti-malarials as a class effect.

DESCRIPTION: There are estimated to be 350-500 million clinical cases of malaria and at least a million deaths annually (13). This disease represents a major threat of force reduction for forces deployed to tropical and subtropical regions and is endemic in AORs of all five of the major U.S. commands. Of 290 U.S. Marines deployed to Liberia in 2003 for less than two weeks, 80 developed malaria and five required intensive care, largely due to medication noncompliance. This experience again demonstrated that effective and safe anti-malarial prophylaxis and treatment is not only important in regards to the worldwide burden of disease, but to the specific force protection of deployed U.S. forces.

Currently, mefloquine and chloroquine are the only anti-malarial drugs with a long enough have-life to allow once per week dosing (5). This dosing schedule and its effectiveness against chloroquine-resistant malaria makes it very valuable for deployed forces who may operate under conditions that undermine daily dosing. Unfortunately, as many as 25% of individuals taking mefloquine at prophylactic doses (250 mg per week)and 70% of those taking it at treatment doses (1250 mg over 24 hours) experience neurological or psychiatric adverse effects. While most of these are minor (dizziness, anxiety, nightmares, reduced sleep), serious adverse effects such as psychosis also occur (6-12). The fact that only certain individuals appear to be adversely affected points to a genetic mechanism, possibly a single polynucleotide polymorphism (SNP) that is yet to be identified.

Recent work using a rodent model has demonstrated histologically evident damage in the brainstem of rats given mefloquine that appears to be dose-dependent (2). Neurological and behavioral abnormalities were also observed with likely correlates to the common adverse effects observed in humans (1,2). This work along with previous investigations that include retrospective studies of the effects in humans, form a growing body of evidence of a biological basis of mefloquine neurotoxicity (6-12). The accumulation of mefloquine within the central nervous system is well document and while several possible targets leading to toxicity have been identified, the exact mechanism or mechanisms leading to toxicity remains to be defined (4). Whether this toxicity is related to that observed with other anti-malarials is also unclear (3). If a class effect exist, it is critical that this be elucidated.

PHASE I: As a proof of concept, initial studies will identify the cellular and subcellular mechanisms of neurotoxicity. This will extend beyond work done at WRAIR and other academic institutions that have identified several possible targets leading to toxicity to include the regulation of neuronal cellular calcium, adenosine 2A receptors, and p-glycoproteins. The identification of such specific targets (proteins) will allow investigators to “work backwards” to identify the associated RNA and DNA sequences, likely employing microarray analysis.

PHASE II: Building on Phase I results, these studies will identify the genetic profile, including specific SNPs, which predicts susceptibility to mefloquine-induced neurotoxicity. This will likely involve identifying prior cases of mefloquine toxicity. By identifying a genetic marker for neurotoxic susceptibility, a prototype genetic test can then be developed. Such a test will allow commanders in the future to identify who is at risk for the development of adverse effects. This will allow the safe administration of this valuable drug to the majority of service members while protecting the few with susceptibility via the use of alternative medications.

PHASE III DUAL USE APPLICATIONS: Using commercial partners, the prototype genetic test can be developed into a commercially available test. The reliability of its predictive value can be ascertained in prospective studies. Given the large burden of malaria worldwide and the common use of this medication, a commercial market for this “safety” test is likely.

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KEYWORDS: mefloquine, toxicity, neurotoxicity, malaria, neurological, anti-malarial

McCarthy Supplementary Submission - Attachment 3

Suicide Risk Factors and Mefloquine Side Effects

Box 1 – "Level A" Risk Factors for Suicide (Dunt, 2009)

1. Demographic factors – males aged 30-34, Indigenous, rural and remote populations.
2. Psychopathology & psychiatric hospitalisation – **diagnosis of a mental disorder**, particularly **affective disorders**, substance abuse, **anxiety disorders**, **personality disorders** and **psychiatric comorbidity**.
3. Previous non-fatal suicidal behaviour and **suicidal ideation**.
4. Family history of psychopathology and suicidal behaviour.
5. Physical illness, chronic physical pain.
6. Negative life events and low coping potential.
7. Marital status of divorced, widowed or separated.
8. Low socioeconomic status, unemployment.
9. Neurobiological activity – **hypo-activity of the serotonergic system**.
10. Psychological factors – hopelessness; **high aggression and impulsivity**, lack of reasons for living, **cognitive rigidity**, low ability to solve problems, perfectionism, **psychological pain**.
11. Social isolation and lack of social support.

Box 2 – Mefloquine Side Effects (Roche Australia, 2014)

Relating to Factor 2 above:

- "Common" - anxiety and depression.
- "Uncommon" - hallucinations, bipolar disorder, psychotic disorder including delusional disorder, depersonalisation and mania.

Relating to Factor 3 above:

- "Uncommon" - suicidal ideation.

Relating to Factor 9 above:

- Mefloquine is a 5-HT3 receptor antagonist (serotonin blocker).

Relating to Factor 10 above:

- "Uncommon" - agitation, restlessness, mood swings, panic attacks, confusional state, aggression, depersonalisation and mania and paranoia.

FORENSIC AND ETHICAL ISSUES IN MILITARY BEHAVIORAL HEALTH

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Chapter 19

MEFLOQUINE AND POSTTRAUMATIC STRESS DISORDER

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FOB Warhorse Bunker, by Timothy Lawn, watercolor/ink on paper, Iraq, 2005.
Art: Courtesy of the Army Art Collection, US Army Center of Military History

INTRODUCTION

Mefloquine (previously marketed in the United States as Lariam [F Hoffmann-LaRoche Ltd, Basel, Switzerland]) is a neurotoxic quinoline-derivative originally developed by the US military for treatment and prophylaxis of malaria.[1] Originally the US military's preferred antimalarial drug, mefloquine has been widely used during overseas operations, but recently lost favor because of its association with severe neuropsychiatric side effects. These side effects are now the subject of a "black box" warning, which must appear on the US product label, accompanied by advisories that psychiatric side effects may last years after dosing, and that neurological side effects may be permanent.[2] Recent insights suggest that neuropsychiatric side effects may be considered to be symptomatic of a potentially life-threatening intoxication syndrome (or toxidrome) common to other members of the quinoline class.[3]

Although the drug was originally thought to have few psychiatric effects,[3] symptoms of mefloquine intoxication are now known to affect a majority of users when the drug is administered at treatment doses of 1,250 mg,[4] and at least a sizeable minority when administered at prophylactic doses of 250 mg weekly.[5] Lariam package inserts now warn that "very common" psychiatric symptoms (including abnormal dreams and insomnia) may affect greater than 10% of prophylactic users, and "common" psychiatric symptoms (including anxiety and depression) may affect 1% to 10% of prophylactic users.[6,7] Earlier product inserts emphasized that should certain "prodromal" symptoms develop, including anxiety, depression, restlessness, or confusion, the drug must be discontinued to avoid a "more serious event," which is likely a euphemism for fulminant intoxication and neurotoxicity.[3] Today's Lariam product information expands on this guidance to add nightmares to the list of "prodromal" symptoms[8] and caution that any "change in mental state" is reason to immediately discontinue the medication.[9]

Many of the symptoms of the mefloquine toxidrome, including vivid nightmares, personality and affective change, disordered sleep, irritability, anger, difficulties with concentration, dissociation, and amnesia, may mimic prior *Diagnostic and Statistical Manual of Mental Disorders IV* (*DSM-IV*) criteria B-D, as well as *DSM-5* criteria B-E for posttraumatic stress disorder (PTSD), and may last long after discontinuation of dosing. According to a publication by the Centers for Disease Control and Prevention, these symptoms "may confound the diagnosis and management of posttraumatic stress disorder."[10] As mefloquine has been commonly prescribed to military personnel during combat deployments,[11] risk of intoxication may therefore have frequently coexisted with pervasive exposure to *DSM-IV* and *DSM-5* criterion A stressors, particularly confounding the PTSD diagnosis in military and veteran populations exposed to the drug.

In this chapter, the history of mefloquine's development and its use within the US military are reviewed, and then the clinical features of the mefloquine toxidrome are described with its chronic effects. The chapter then highlights how specific psychiatric symptoms caused by mefloquine may readily confound PTSD diagnostic criteria, particularly those of *DSM-IV*, which unlike *DSM-5* did not specify a diagnostic exclusion for symptoms resulting from a medication's effects. This review ends with a discussion of applications of this information to forensic psychiatry and presents a representative case study illustrating challenges in the diagnosis of mefloquine intoxication among military personnel.

THE DEVELOPMENT OF MEFLOQUINE

Mefloquine, known chemically as bis(trifluoromethyl)-(2-piperidyl)-4-quinolinemethanol, is a 4-methanolquinoline structurally related to quinine. Although the first synthesis of mefloquine was reported in 1969,[12] the drug is closely related to the synthetic compound 4-quinolyl-α-piperidylcarbinol first reported 3 decades earlier in 1938.[13] Mefloquine differs from this previously synthesized compound (later known as SN 2,549)[14(p1062)] solely by adding two trifluromethyl groups (CF_3) at the 2 and 8 positions of the quinoline nucleus, which help to impart antimalarial activity and metabolic stability. The antimalarial utility of the trifluromethyl group was first identified by the Germans, who in 1938 had synthesized what was considered a less toxic version of chloroquine (then known as resochin) featuring the substituent.[14(p1236),15] Trifluoromethylated antimalarial compounds were later extensively studied in the US military's World War II antimalarial drug discovery program, during which time more than 13,000 compounds were investigated[16] for their antimalarial activity, of which 103 were subsequently tested in humans.[17] Of these, many quinoline derivatives demonstrated unacceptable toxicity, causing symptoms of "nervousness," "lassitude," or confusional or paranoid psychosis,[17] and extensive neurotoxic lesions throughout the brainstem and limbic system in humans.[18]

Although 4-methanolquinolines related to mefloquine were initially the subject of significant human testing during the World War II era program, investigation of these compounds as antimalarials appears to have been abandoned in favor of the 4-aminoquinolines,[19] including chloroquine (previously known as SN 7,618), which despite early German concerns of toxicity became the mainstay antimalarial for the next 20 years.[20] By the early 1960s,[21] owing ostensibly to concerns of rising chloroquine resistance, the US military undertook a second large scale drug discovery program,[22] during which time more than 300 4-methanolquinolines were evaluated,[19] including some that had been previously tested from the World War II era program.

Mefloquine (known as WR 142,490) quickly emerged as the favored of these drugs based on the results of limited human testing,[23,24] which indicated the drug was free of the serious psychiatric side effects, including suicide and psychosis, that had characterized related quinoline antimalarials,[25] including chloroquine.[26–28] Soon after its reported first synthesis, mefloquine had been singled out by the US Army for larger scale commercial synthesis, first by the Aerojet Solid Propulsion corporation,[12] and then in anticipation of commercialization, by F Hoffmann-La Roche Ltd.[29] So rapid was the testing of the drug in field settings that one researcher noted, "Phase II clinical trials threatened to outstrip needed Phase I testing."[30]

THE HISTORY OF MEFLOQUINE USE IN US MILITARY POPULATIONS

Although many of the early Phase I and Phase II trials of mefloquine were conducted among prisoners,[31–33] contract employees,[31] and residents of Third World countries,[34] the drug was also tested on US military personnel at various times during the 1980s before its licensure by the Food and Drug Administration (FDA) in 1989.[35] Although details of many of these experimental uses are not available, in one published study from 1988 not listed in the Lariam New Drug Application,[34] 134 soldiers were administered 250 mg of the drug weekly for 4 weeks while on exercises in Thailand.[36]

In the very early years following the drug's FDA licensure in 1989, mefloquine appears to have been used infrequently by the US military, possibly because of concerns for its initially complex and potentially confusing dosing regimen, which recommended every-other-week dosing after the fourth week.[37] For example, there was little mefloquine used among US personnel during the 1990–1991 Persian Gulf War.[38] However, in 1991, mefloquine was the subject of a large randomized trial to assess tolerability during simplified dosing regimens,[37] during which time 203 US Marines were administered the drug.[35] This study noted a high prevalence of prodromal symptoms among subjects. Vivid dreams, described as often "terrifying nightmares with technicolor clarity," occurred in 7% of mefloquine users; irritability in 4%; concentration problems in 5%; anger and moodiness each in an additional 1%; and insomnia in 25%.[35] At the time, the US package insert cautioned to discontinue use of the medication if "anxiety, depression, restlessness, or confusion" developed, but the incidence of these specific symptoms was not assessed, and it appears that this guidance was not consistently communicated or enforced during the trial.[35] For example, 2 of the 203 participants, after failing to discontinue the drug at the onset of severe insomnia, were ultimately hospitalized for severe depression and suicidal thoughts, which were later deemed due to "preexisting" conditions. Despite these findings, the drug was deemed "well tolerated" and recommended for expanded use.[35]

With the seemingly favorable results of these trials and following a change in the package label to recommend once-a-week dosing,[39,40] documented large-scale military use of mefloquine began in earnest in 1992–1993 during Operation Restore Hope in Somalia,[41] where mefloquine sensitivity had been demonstrated in prior field studies.[42,43] Although precise usage figures are uncertain[44] during much of the estimated 163,000 person weeks of deployment time in Somalia,[45] published reports[46] suggest a majority of more than 30,000 US personnel ultimately stationed there[44,47] received mefloquine under command-supervised weekly administration,[44] with some initial users of the alternative drug—doxycycline—switching to mefloquine[48] on command directive.[49] Based on published reports[35] the incidence of discontinuation of mefloquine resulting from prodromal symptoms was exceptionally rare; in one study, only 1 in 344 soldiers discontinued mefloquine.[50] Contrary to today's guidance, soldiers in Somalia reporting vivid dreams or "lightheadedness" (which should be taken to indicate confusion or difficulties in concentration[51]) do not appear to have been directed to discontinue the drug.[50] Although "more serious events" including psychosis or hospitalization were not reported in the definitive published study of mefloquine use among US personnel in Somalia,[44] postmarketing surveillance reports describe a US military member on mefloquine who was hospitalized and experiencing psychosis, confusion, depression, fatigue, hostility, agitation, and paranoia[52]; more than 120 Somalia era veterans later complained of psychiatric symptoms, including flashbacks, night-

mares, paranoia, and suicide attempts,[53] linked to their use of the drug. One soldier later described the effects of the drug as "so much darkness in your brain and so much violence," and reported suffering lasting confusion, paranoia, and suicidal and homicidal ideation.[52]

Despite early concerns for its safety,[54] mefloquine nevertheless became the drug of choice for most US military operations,[55] but its regular use soon attracted further concern. In 1996 officials were informed that family members of US Special Forces soldiers had noted "drastic" changes in mood, impulsivity, and irritability linked to their spouses' use of the drug.[56] Soon after the start of the Afghanistan war in 2001, where the drug was also used frequently,[57] one veteran of early operations in Pakistan complained of hallucinations and delusions while taking the drug and of subsequently suffering "frightening flashes" of anger. Another family member reported his son was hospitalized with hallucinations, anxiety, and depression.[52]

By the summer of 2002, after a rash of homicides and suicides at Fort Bragg had been committed by soldiers returning from Afghanistan, concerns of behavioral toxicity had attracted national media attention.[52,58] Two soldiers murdered their wives and then immediately committed suicide[59]; another soldier murdered his wife and subsequently killed himself in prison the following year.[60] According to family members and acquaintances, the soldier had been experiencing delusions, paranoia, strange behavior, and uncharacteristic fits of rage after returning home.[52,56,61] All three soldiers had taken mefloquine; two had documentation of taking the drug on deployment before the killings[62]; while the third had also been taking the drug,[63] according to unit members, but had stopped some months prior.

In all three cases, there were marital issues; at least one case was suspected of being exacerbated by the drug's behavioral effects.[56] In two cases, the soldiers "returned early from Afghanistan specifically in response to their requests for emergency leave to address perceived marital distress."[62] Numerous barriers to marital counseling and behavioral care at Fort Bragg were identified in the final report of the formal Army investigation, which concluded that "marital discord" was a "major factor" in the killings.[62]

Although the formal Army investigation failed to rule out mefloquine as the cause of violence in at least two cases where unambiguous records of prescribing existed,[52] as a result of no history of mefloquine use in a fourth unrelated case who did not deploy, the report concluded the drug was "unlikely to be the cause of this clustering."[62]

When military operations began in Iraq in 2003, medical intelligence reports had suggested the possibility of chloroquine-resistant malaria.[64] To "err on the side of caution," widespread use of mefloquine was directed throughout the theater.[64,65] Although recordkeeping of prescribing was poor[66] and many prescriptions[67]—particularly those in theater[68]—were never documented,[69] electronic records revealed a sharp increase of documented prescribing to active duty personnel—from 18,704 in 2002 to 36,451 in 2003.[65] Representing a conservative lower estimate of use, for the 12 months ending October 2003[70] electronic records documented approximately 45,000[71] to 49,000 mefloquine prescriptions, comprising more than 1 million 250 mg tablets.[72]

In the summer of 2003, FDA implemented new requirements that all mefloquine prescriptions be accompanied by written warnings specifying that users seek medical attention if prodromal symptoms of intoxication develop.[69] However, surveys indicated that few deploying service members received written or even verbal warnings,[63,65,67] whereas public statements by senior military physicians[73] and formal policy guidance served to undermine awareness of the drug's frequent intoxicating effects. An Army memorandum issued the previous year in 2002 erroneously stated psychiatric symptoms from mefloquine occurred only "at a rate of one per 2,000 to 13,000 persons."[74] This memorandum understated the risk by at least a factor of 100: a randomized clinical trial the year before had demonstrated that prodromal symptoms of anxiety and depression each occurred in 4% of users,[75] whereas the mefloquine package insert continued to make clear that should these prodromal symptoms develop, the drug "must be discontinued."

The awareness was so poor among US forces of mefloquine's written warnings that even fulminant cases of intoxication were misattributed to other causes. One soldier, who received no warnings of the mefloquine's intoxicating effects,[76] suffered panic attacks and hallucinations while taking the drug. On demanding medical attention for his concerns, he was charged with cowardice and later with dereliction of duty for failing to obey orders.[77] Only months later did physicians suspect mefloquine in the etiology of his disorder.

A case report, whose publication was delayed by nearly a decade,[78] described an airman who continued to take mefloquine despite experiencing restlessness, depression, and severe emotional lability. With continued dosing his condition progressed and he was subsequently hospitalized with hallucinations and suicidal ideation.[79] Other media reports highlighted similar cases of hallucination, impulsive aggression, and paranoia in one returned soldier[80]; and anxiety, depression, and paranoia in other soldiers taking the drug.[65] In subsequent congressional testimony, one

soldier who had experienced 3 weeks of nightmares before discontinuing the drug testified that "every soldier I know has problems with it."[73] Military leaders were quick to dismiss such testimony as "perception," cautioning "that perceptions can become realities" should it become "widely held that this medication is widely problematic."[73]

In a prior report, military leaders had been warned that "[a] possible consequence of continued use of mefloquine . . . is that the negative publicity surrounding the drug may lower compliance among deployed personnel."[81] Despite evidence of such lowered adherence,[73] military leaders favored the drug because of its perceived efficacy, weekly dosing schedule, and lower cost relative to better tolerated[75] daily drugs.[81] In August 2003 a group of 225 Marines sent ashore in Liberia were instructed to take mefloquine. Earlier that year, these Marines had served briefly in Iraq and Djibouti where they had also been directed to take mefloquine. Following 10 days ashore in Liberia, an outbreak of febrile illness subsequently affected 80 of the 225 Marines; 36 remained shipboard to be managed empirically, while 44 were medically evacuated for presumed malaria. On epidemiological investigation, 21 of the 44 (45%) endorsed poor medication adherence.[82] Although military physicians had claimed anonymous surveys showed that forgetfulness, not prodromal symptoms, was "overwhelmingly" the cause of poor adherence,[83] later published reports revealed that surveys were not anonymous, raising questions regarding the validity of these responses. The report also speculated that compliance "may have been even lower than reported because some Marines may have overestimated their adherence for fear of administrative sanctions."[82]

Formal meetings were soon convened to discuss rising concerns about the drug, including the problem of low adherence.[84] In prior meetings, leadership had been encouraged to be more "up front about the side effects"[49] to counter low adherence, but better enforcement of directly observed therapy was also proposed. Although expanded use of better tolerated[75] daily drugs had been recommended, concern was expressed at their cost and convenience in directly observed therapy.[49] One presenter, arguing the merits of its weekly dosing, predicted that "[m]ilitary personnel will die of malaria if [mefloquine is] not available.[72]

In spite of continued leadership's support for the drug, these meetings failed to counter overwhelming public and congressional[85] concerns; despite claims of continued safety and efficacy, most first-line use of mefloquine was subsequently discontinued by 2004. Having learned in July 2003 that what little malaria there was in Iraq was sensitive to chloroquine, the US military switched briefly from mefloquine to chloroquine by early 2004[86] before discontinuing chemoprophylaxis altogether by late 2004.[65,84,87] In Afghanistan, forces gradually switched to doxycycline following an official report linking mefloquine to a soldier's suicide.[88] Subsequent US Army policy made doxycycline the drug of choice in Afghanistan, with mefloquine remaining only in limited use, notably in operations in Djibouti and throughout the Horn of Africa.[89]

By 2006, public and congressional focus on the drug had lessened, and partially in response to rising rates of malaria,[90] widespread use of mefloquine in Afghanistan was subsequently resumed. Later analyses of electronic records suggested that nearly 40% of those deployed that year had been prescribed mefloquine before deployment.[11] However, these analyses also revealed widespread problems with prescribing. As preexisting behavioral health conditions, such as anxiety and depression, had been known to confound recognition of developing prodromal symptoms of intoxication, the mefloquine product insert had long noted that the drug should be used with caution in such patients. In subsequent years, this language was strengthened and the drug was formally contraindicated in such patients.[91] Amidst earlier concerns that soldiers with such behavioral health conditions were on occasion being inappropriately deployed,[67] in congressional testimony, military leaders had promised such soldiers would not be prescribed mefloquine[67] and would be offered an alternate medication[92] as previously formalized in Army policy.[74] By 2007, analysis suggested that 1 in 10 deploying soldiers had behavioral health conditions that contraindicated taking the drug; of these, later analysis revealed that 1 in 7 with such behavioral health conditions had been erroneously prescribed the drug, contrary to existing policy and package insert guidance.[11]

With rising recognition of the difficulties in ensuring the drug's proper prescribing, military authors writing for the Centers for Disease Control and Prevention would later note that the "continued routine use of mefloquine" had become "less desirable."[10] A 2009 Army policy memorandum prioritized the use of daily medications and stated that "[m]efloquine should only be used for personnel with contraindications to doxycycline."[93] This policy was extended throughout the Department of Defense later in the year.[94] Although these policies led to widespread prescribing changes in Afghanistan,[95,96] mefloquine was briefly reprioritized for continued use in Africa[97] after the death from malaria of a sailor deployed to Liberia revived concerns about the effectiveness of daily medi-

cations.[98] However, counterbalancing concerns for the risks of mefloquine, particularly when administered under conditions of directly observed therapy,[99] soon also arose after a sailor experienced significant toxicity from the drug.[100] By late 2011, following a meeting of key military stakeholders,[101] deployment guidance even for sub-Saharan Africa had prioritized the use of safer daily medications, including the combination drug atovaquone-proguanil and the broad-spectrum antibiotic doxycycline, and emphasized that mefloquine use "should be restricted to individuals unable to receive either of the other regimens."[102] In early 2012, after concerns arose that some service members were continuing to be prescribed the drug contrary to policy, senior military health officials ordered an additional review of mefloquine prescribing practices, [103] and a prominent editorial called for military officials to better explore "possible alternatives." [104] Further restrictions were formalized in 2013, when mefloquine was declared the "drug of last resort"[105] and reserved only for those "with intolerance or contraindications to both first-line medications" atovaquone-proguanil and doxycycline. [106]

Although falling short of a complete prohibition, policy changes beginning in 2009 served to "casually sideline"[107] what was the last remaining product of the largest drug discovery effort of its time,[107,108] replacing its use in part with a drug that was the military's antimalarial drug of choice 20 years earlier and before mefloquine's 1989 introduction.[50] In the 3 years from 2007–2009, electronic pharmacy records indicate US military facilities issued 48,538 mefloquine prescriptions to active duty personnel; but in the 2 years from 2010–2011 following the policy changes, only 11,494 prescriptions were issued.[109] Popular news reports that cited purchase figures confirmed the substantial decline in the drug's use and concluded that the US Army had effectively pushed mefloquine "to the back of its medicine cabinet."[95] Intriguingly, almost 4 decades earlier, influential authors had cautioned that mefloquine "promises to be broadly useful" to the US military, but noted presciently that "[i]f this promise is not realized, it will doubtless not be for lack of antimalarial activity, but rather because of toxicological attributes not identified in the small-scale studies pursued to date."[19]

CLINICAL FEATURES OF MEFLOQUINE INTOXICATION

As is now understood, the "toxicological attributes" of mefloquine include potent effects on the limbic system and brainstem,[3,99] where the drug may accumulate[110] relative to other areas of the brain.[55,111] Experiments in animal models have demonstrated that at physiological concentrations, mefloquine may induce disruptions in electrical activity in the amygdala[112] and hippocampus,[113,114] with effects on fear conditioning[115] and memory.[116] Mefloquine may also induce disruptions in limbic inhibition[117,118] with resultant effects on mesolimbic dopaminergic tone.[119,120] Mefloquine disrupts autonomic responses in the brainstem[121] and affects electrical activity in the pedunculopontine nucleus,[122,123] striatum,[124] and inferior olive.[125,126] These effects and others may explain the predominance of disturbances in emotion, memory, and sleep, and symptoms of complex neurologic dysfunction commonly observed in cases of mefloquine intoxication.[3]

As noted in the original product insert, certain symptoms, including "anxiety, depression, restlessness, and confusion," should be considered prodromal to a "more serious event," likely a euphemism for fulminant intoxication and neurotoxicity.[3] Such intoxication may manifest with predominant features of restlessness and anxiety[127–129] and may begin with a prodrome of insomnia,[130] nightmares,[79] unease,[99] phobias,[131,132] and a sense of impending doom and restlessness[131]; and it may progress quickly to include outright paranoia,[130,133] persecutory mania,[134] panic attacks,[135] and impulsive aggression.[136] Intoxication may also include features of confusion[133,137] and psychosis, and may begin with a prodrome of vivid dreams[79] and progress quickly to include delusions;[138] magical thinking;[139] dissociation;[140] derealization;[141] and auditory,[142] olfactory,[141] and visual hallucinations[51] and illusions.[143] Hypnopompic states,[77,79] spatiotemporal disorientation,[99] and anterograde amnesia may also occur.[144,145] Significant personality change[99] and depression,[79,133,146] morbid curiosity toward dangerous objects[147] and death,[54] suicidal ideation and attempt,[148] completed suicide,[107,149] and acts of violence[150] are not uncommon.

Many of the symptoms of the mefloquine toxidrome are best understood as a manifestation of an underlying toxic limbic encephalopathy.[99] Toxic encephalopathy (or "acute brain syndrome"[151]) was first noted before the drug's US licensure,[145,152] and a risk of "encephalopathy of unknown etiology" was noted on the original US product inserts. Similar to what is observed with various forms of limbic encephalitis,[3] this toxidrome may also be accompanied by neurological effects including seizures[153–156] and symptoms referable to the midbrain or brainstem nuclei, including paraesthesias,[54,157,158] disequilibrium,[99] parkinsonism[159] and other movement disorders,[128] vertigo,[99,160] visual disturbances,[160] and autonomic dysfunction.[161,162]

CHRONIC EFFECTS OF MEFLOQUINE TOXICITY

Although early product labeling failed to warn of the possibility of chronic effects, by the summer of 2002, after numerous published reports[160,163,164] of chronic symptoms lasting 1 year or more, the US package insert was updated to note that "anxiety, paranoia and depression . . . hallucinations and psychotic behavior" on occasion "have been reported to continue long after mefloquine has been stopped."[58] By 2004 a Veterans Health Administration's informational letter cautioned that use of the drug could be associated with symptoms "that persist for weeks, months, and even years after the drug is stopped."[38,165] Today's US mefloquine product labeling warns that psychiatric side effects may last years after dosing and that neurological side effects may be permanent.[2] The Lariam product information acknowledges a risk of "long lasting serious mental health problems" and warns of a risk of an "irreversible" condition should the medication not be stopped at the onset of certain prodromal symptoms.[8]

Although the chronic effects of mefloquine toxicity had previously been attributed to the long half-life of the drug, as would be expected of a highly lipophilic compound[166] that concentrates in brain and is subject to complex and heterogeneous neuropharmacokinetics,[167] psychiatric effects show little correlation with measurable serum levels.[168,169] With the benefit of current knowledge, many of the chronic effects of mefloquine are best understood as reflecting central nervous system toxicity resulting from the drug's heterogeneous accumulation in the brain,[170] which remains poorly understood but appears subject to multifactorial genetic[171,172] and pharmacologic influences.[173,174]

Evidence of the central nervous system toxicity of mefloquine was noted as early as 1996,[175] and by 2003 the drug had been clearly demonstrated to cause neurotoxic lesions in the brainstem of animal models at physiological concentrations.[176] Authors noted that mefloquine's psychiatric effects could be plausibly due to "[i]mpairment or loss of neurons in specific regions of the brain" and that "[m]efloquine-induced neurotoxicity in the limbic system might be responsible for reported disturbances in emotion."[176]

CONFOUNDING OF DIAGNOSTIC AND STATISTICAL MANUAL OF MENTAL DISORDERS-IV POSTTRAUMATIC STRESS DISORDER DIAGNOSTIC CRITERIA

Given the relatively high prevalence of psychiatric symptoms including nightmares, anxiety, and memory and sleep problems caused by mefloquine, military authors writing for the Centers for Disease Control and Prevention have noted that use of the drug may "confound the diagnosis and management" of PTSD.[10] Unlike many other *DSM-IV* disorders, the diagnostic criteria for PTSD provided no exclusion for symptoms resulting from a medication's direct effects. It is therefore conceivable that patients experiencing mefloquine's toxic effects may have appeared to meet formal PTSD diagnostic criteria, even if the etiology of the symptoms was distinct from the effects of traumatic stress.

How commonly the symptoms of mefloquine intoxication might have complicated the PTSD diagnosis in military settings is unclear. An underpowered[177] retrospective study of US military personnel found an increased risk of hospitalization for diagnosed anxiety disorders and PTSD among those with prior mefloquine exposure as compared to those deployed without mefloquine exposure,[178] but the results of this study were not statistically significant. Despite formal recommendations, no similar study of outpatient encounters has been published,[84] and no long-term studies of veterans have been performed to rule out a higher incidence of such disorders after mefloquine exposure. Anecdotal reports, however, suggest that symptoms caused by mefloquine may be highly comparable to those of PTSD and may have plausibly confounded or complicated diagnosis.[38,165] In one documented case, a soldier prescribed antidepressants and mefloquine on the same day was diagnosed within 5 weeks with anxiety disorder and organic brain disease suggestive of the toxic encephalopathy of mefloquine intoxication. The soldier was subsequently diagnosed with depression, suicide attempt, and PTSD by week 10.[179] Although the actual number of those potentially receiving a PTSD diagnosis under similar circumstances is far from certain, the possibility that at least some diagnosed cases may represent missed diagnoses of mefloquine intoxication seems apparent.

In deployed settings where US military personnel may have been exposed to mefloquine, the ubiquity of potentially traumatic experiences may have had the effect of significantly reducing the specificity of *DSM-IV* diagnostic criteria. For example, in an early study of returning service members from Afghanistan and Iraq, encompassing the period of widespread mefloquine use, between one-quarter and one-half of subjects reported feeling "in great danger of being killed;" more than one-third to one-half reported witnessing individuals wounded or killed,[180] consistent with *DSM-IV* criteria of experiencing, witnessing, or being

confronted by events involving "actual or threatened death or serious injury" (criterion A1). Similarly, intense fear, helplessness, or horror (criterion A2), while seemingly specific to external traumatic stressors, may be readily confounded by the onset of panic attacks or certain symptoms of psychosis,[181] which may solely result from mefloquine's effects but whose specific symptoms may reflect fearful or horrific content that may risk being attributed to an external stressor in the context of military deployment.[77]

Other symptoms of mefloquine intoxication may also closely mimic many criteria B (re-experiencing) and C (avoidant/numbing) symptoms. For example, intrusive recollections (criterion B1), possibly reflecting the effects of daytime or hypnopompal hallucinations,[79] are a common feature of case reports.[77] Similarly, distressing nightmares (criterion B2), frequently described as "vivid" and "terrifying,"[35] are a pervasive feature of intoxication, affecting more than one-third of military users during prophylactic dosing.[5] Similarly, again possibly reflecting the effects of hallucinations, symptoms consistent with flashbacks (criterion B3) are commonly reported with reports of directed actions in response to perceived threats.[65]

As the symptoms of mefloquine intoxication may present independent of a specific external traumatic stressor, individuals suffering from its effects may not exhibit psychological distress or physiological reactivity specifically in response to traumatic reminders (criteria B4 and B5), but instead may experience such reactions unpredictably and without obvious triggers.[79] In certain environments, where traumatic reminders are prevalent or where ascertainment or recall bias may identity these preferentially on examination, such symptoms may be erroneously attributed to traumatic reminders, which confounds diagnosis. Similarly, while the effects of mefloquine intoxication may result in nonspecific avoidance behaviors, these may risk being similarly misattributed to an external traumatic stressor (criteria C1 and C2) on examination. Conversely, because of the lasting effect of mefloquine on memory and its association with anterograde amnesia,[145] the inability of those suffering intoxication to recall specific aspects of a presumed trauma (criterion C3) coincident with dosing may—in some contexts—be erroneously deemed as meeting diagnostic criteria.

Because of the effects of mefloquine on mood and its association with personality change and symptoms of depression,[79,133,146] those suffering from intoxication may exhibit diminished interest in significant activities (criterion C4) or show detachment from others (criterion C5).[79] Similarly, a restricted range of affect (criterion C6) may reflect the direct effects of the drug on affect or be confounded by mild symptoms of confusion,[133,137] dissociation,[140] or derealization.[141] Since those experiencing intoxication from mefloquine may also experience numerous poorly understood somatic and psychiatric complaints, they may experience a sense of foreshortened future (criteria C7).[79]

Criterion D (hyperarousal) symptoms resulting solely from mefloquine may also be problematic to distinguish from those from a specific traumatic etiology and may be highly prevalent in cases of mefloquine intoxication. Sleep problems (criterion D1), a prominent feature, may affect a sizeable minority of prophylactic users,[35] with severe cases of insomnia and "restlessness" commonly reported.[99] Irritability (criterion D2), also a commonly reported symptom,[56] may have multiple etiologies, including reflecting an effect of mefloquine-induced vestibular dysfunction or cognitive impairment.[99] Concentration problems (criterion D3) are also commonly reported in cases of mefloquine intoxication, including problems with executive, visuospatial, and verbal memory, and deficits in orientation and attention.[133] Similarly, symptoms of sensory overload, described as "a whole rush of stuff going into your brain at one time,"[79] may be taken as symptoms of hypervigilance (criterion D4). Lastly, exaggerated startle response (criterion D5), while not commonly reported in the literature, is consistent with persistent heightened anxiety and autonomic dysfunction, and may be expected to co-occur with other lasting symptoms of mefloquine intoxication.

Many symptoms of mefloquine intoxication have been reported to last at least 1 month (criterion E), and case reports describing persistent symptoms lasting a year or more after dosing have been reported.[160,163,164] In some cases, certain psychiatric symptoms, such as irritability, may become relatively more prominent following resolution of acute intoxication.[99] Cases of fulminant intoxication, particularly those featuring panic attacks or symptoms of psychosis, will be likely to cause significant acute distress and functional impairment (criterion F).[79] However, even chronic symptoms, such as memory impairment and irritability, may be significantly functionally impairing, particularly if accompanied by vestibulopathy or disequilibrium or other chronic neurological sequelae.[99]

FORENSIC APPLICATIONS

As a result of the significant similarities among conditions, the forensic psychiatrist may be asked to evaluate a prior PTSD diagnosis for the possible confounding effects of mefloquine intoxication. Such an evaluation may be critical in determining eligibility for disability and adjudicating claims of harm, or in

legal cases where ascertaining the possible effects of the drug may be relevant.[3]

Although this chapter has established that many of the psychiatric symptoms caused by mefloquine may be indistinguishable from those resulting from traumatic exposures, the frequent association of mefloquine intoxication with chronic neurological symptoms—including vertigo, disequilibrium, and certain visual disorders including accommodative dysfunction and photophobia—may permit the effects of mefloquine to be disentangled in forensic evaluation from those resulting from the effects of combat stress.[3]

In particular, mefloquine's previously demonstrated brainstem neurotoxicity, together with the known class effects of related quinoline antimalarials in inducing multifocal neurotoxic lesions throughout the midbrain and brainstem nuclei, may—in some cases where these are clinically significant—provide an opportunity for objective demonstration of injury. Although the neurotoxic lesions produced by the quinolines are typically too small to be visualized on conventional imaging studies, and although routine neurological evaluation is typically nonspecific in such cases, specialty consultation with neuro-optometry, neuro-otology, or ear, nose, and throat specialists with a focus on identifying central nervous system injury may document objective evidence of subtle brainstem dysfunction, and thus prove a valuable component of the forensic psychiatric evaluation. Similarly, as the complex signs and symptoms of mefloquine neurotoxicity may mimic or be mistaken for a malingering diagnosis, or of somatoform, conversion, or personality disorder, such specialty evaluation should be considered essential when these additional diagnoses are under consideration.[3]

Establishing a diagnosis of mefloquine intoxication with or in place of a PTSD diagnosis ultimately requires establishing plausible evidence of mefloquine exposure. However, as mefloquine has been commonly mass prescribed in US military settings[10] without individualized documentation, traditional methods of establishing evidence of exposure may be unavailable. For example, research in Afghanistan in 2006 suggested 30% of soldiers had begun their malaria prophylaxis in theater,[179] where prescribing has traditionally been beyond the capture of electronic medical records systems.[68] Among Army personnel, who comprised the majority of personnel deployed in the period, there were only 6,514 mefloquine prescriptions electronically documented between October 2007 and September 2008 to active duty personnel[179]; and in 2008 there were 8,574 such prescriptions among Army personnel overall.[95] In contrast, during an approximately equal period, a total of 32,404 bottles of 25 mefloquine tablets was delivered to supporting logistics bases overseas in Europe and Southwest Asia, comprising sufficient mefloquine for 16,000 year-long prescriptions or 32,000 6-month refills.[179] A comparison of these figures suggests a significant proportion of these were electronically undocumented. As a result, in US military settings, where individualized documentation is acknowledged to have been poor,[103] presumptive evidence of exposure to mefloquine may rest on the service member demonstrating possession of remaining prescribed mefloquine tablets, or if these are unavailable, reporting a reliable history of taking the drug and being assigned to a military unit to which the drug was issued by policy or procedure. Evidence of this may on occasion be found in individual service records, or in other cases this may be attested to by other unit members or by knowledgeable medical or command authorities.

For illustrative purposes, a representative case of mefloquine intoxication is presented in the accompanying case study. This case demonstrates the characteristic features of intoxication mimicking acute stress reaction and subsequently being diagnosed as PTSD, while demonstrating some of the pathognomonic features of subsequent neurotoxicity. These features permitted a plausible claim of causality to be established despite potentially confounding factors including alcohol use and brain injury. This case illustrates the utility of being able to demonstrate plausible mefloquine exposure and the value of diagnostic insights gleaned from appropriate specialty consultation.

Case Study 19-1: In September 2003, a previously healthy 33-year-old male soldier newly deployed to Iraq presented to a combat stress control unit complaining of the acute onset 4 days earlier of severe anxiety, paranoia, visual and auditory hallucinations, persecutory delusions, and confusion, with worsening physical complaints of dizziness and photophobia. The soldier was a member of a US Army Special Forces unit located at a small team house in the city of Samarra. The night his symptoms began, he reported being jolted awake by a "hyperrealistic" and terrifying nightmare in which his room was exploding in a giant fireball. Believing the team house was under attack and believing he saw the enemy bursting into his room,[64] he grabbed his weapon and quickly donned his combat gear and proceeded to conduct a tactical room-to-room search of the house's sleeping quarters. He was horrified to perceive the sleeping members of his unit as mangled corpses, vividly reminiscent of the corpse of an insurgent he had seen the evening before in conjunction with a mission. With insight that he was hallucinating, he returned to his room anxious, paranoid, and unable to sleep.

The next day, he informed his supervisor of his psychotic symptoms and his fears that he was having a "nervous breakdown." That day, as he interacted with team members, he perceived them as horrific "talking skeletal remains," and he heard nearby muffled voices plotting his death. His persecutory delusions worsened the following day when, after insisting on medical care for his symptoms and fearing for

their safety, his unit members disarmed and confined him while they awaited his transport to a nearby combat stress control unit. Over the next 2 days, as he awaited evaluation, he was repeatedly advised that he had a choice to return to his duties or face legal repercussions for what appeared to be cowardly behavior.

His medical history was significant only for a sports concussion in his mid-teens, for which he was briefly hospitalized and had made a complete recovery. He had no personal or family history of mental illness. He was serving as a human intelligence collector and interrogator, had passed a full background investigation, and had been granted a top secret security clearance.

His only medication was mefloquine, which he had begun approximately 2 weeks before his departure to Iraq. He had taken his third 250 mg weekly dose 2 days before the onset of his symptoms. In the days before his arrival in Iraq he had consumed a modest amount of alcohol with meals while awaiting air transport. Before the acute onset of his psychosis, he had experienced no prodromal symptoms, including vivid dreams, personality change, anxiety, restlessness, depression, or confusion.

At the time of initial evaluation, his psychiatric symptoms were attributed to a combat stress reaction or to a panic attack stemming from his initial encounter with the deceased Iraqi insurgent.[173] An adverse reaction to mefloquine was not suspected. The soldier had been issued the drug months after the FDA first required issuance of the mefloquine medication guide "wallet card;" but despite this requirement, he did not receive either the wallet card or the verbal or other written instructions on under what conditions to discontinue the drug. Unaware of the information contained in this documentation, he continued to take mefloquine for 2 additional weeks after the onset of his symptoms of anxiety and confusion for a total of five doses.

Although combat stress control had recommended local treatment, his unit had elected to initiate legal proceedings. He was swiftly returned to the United States and subsequently charged by the US Army under Article 99 of the Uniformed Code of Military Justice with cowardice, a crime that carries a maximum penalty of death.

On seeking civilian counsel, and based on intense media interest in his case, his legal team became informed that his symptoms might be related to mefloquine and proposed exposure as a defense. The soldier's use of mefloquine was initially challenged by the US Army, owing to lack of documentation of a prescription. However, exposure was conceded when the soldier demonstrated possession of his remaining tablets.

In October 2003, the charge of cowardice was dismissed without explanation and immediately replaced with a charge of willful dereliction of duty. This charge was dismissed in December 2003, after which the soldier spent months while additional charges were considered and his medical concerns were evaluated. During this period, a PTSD diagnosis was assigned. Although his psychiatric symptoms gradually improved, his physical symptoms including vertigo, disequilibrium, photophobia, and accommodative dysfunction became relatively more prominent.

In March 2004, following an independent medical evaluation arranged through his counsel, a military physician concurred that "[b]ased on the [soldier's] historical account of the anxiety symptoms that occurred in Iraq, it is very plausible that the symptoms that he experienced could be related to his use of mefloquine."[173] On subsequent evaluation, an ear, nose, and throat specialist documented nystagmus, and he was diagnosed with a vestibular injury and "likely [mefloquine] toxicity." Brainstem injury was suspected.[173]

Upon being informed of this diagnosis, in June 2004 the US Army terminated all legal action against the soldier, explaining that "[a]dditional information became available over time that indicates that [the soldier] may have medical problems that require treatment."[174]

Although the US Army never formally acknowledged causal attribution to mefloquine, the soldier was temporarily medically retired in April 2005, and he was formally medically retired for his vestibular disorder and a PTSD diagnosis in August 2006. In subsequent years, many of his chronic symptoms of disequilibrium gradually improved following physical and vestibular rehabilitation, but a decade after onset he complains of being occasionally short tempered and irritable and experiencing intermittent vertigo and photophobia.

SUMMARY

In settings where use of the drug cannot be ruled out, symptoms of the mefloquine toxidrome—including nightmares, anxiety, and memory and sleep problems—may plausibly confound a PTSD diagnosis and other stress disorders related to military service. With this chapter, it should be evident that the mefloquine toxidrome—long and previously overlooked—may have significant relevance in military forensic psychiatry, particularly in the evaluation of soldiers and veterans with prior service in Somalia, Iraq, Afghanistan, and other areas of the world where the drug is likely to have been used since its development more than 40 years ago.[182]

In addition to aiding and informing current practice, the observations in this chapter may also suggest the intriguing historical question of whether lasting effects similar to those now attributable to mefloquine may also have occurred from the administration of other closely related quinoline antimalarial drugs, including quinacrine during World War II and chloroquine during the Vietnam War. In this respect, it is intriguing that PTSD evolved considerably as a diagnostic entity in the years following the Vietnam War, mirroring in some ways the greater understanding of stress disorders in the years following World War II.[183,184] The potential for significant confounding of

the effects of intoxication from antimalarial quinolines with those caused by war-related traumatic exposures provides a fascinating glimpse into the complexities and challenges of military forensic psychiatry and points to untapped opportunities for more important research.

DISCLOSURES

Dr Nevin receives consulting fees from attorneys representing clients alleging harm from their exposure to mefloquine, and he has been retained as an expert witness in criminal and civil cases involving civilians and military personnel exposed to the drug.

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