Background

- Mefloquine was developed by the U.S. military as an antimalarial drug
  - Origins in the late 1960s during a Vietnam War-era program
- Widespread use in the U.S. military beginning in the early 1990s (e.g. Somalia, SOCOM, OIF/OEF, AFRICOM)
  - Tens (hundreds?) of thousands of veterans have been exposed
- Recently deprioritized for use by DoD
  - Followed U.S. and international “black box” warnings and recognition of chronic psychiatric and neurologic effects
2013 “Drug of Last Resort” Policy Memorandum

“Mefloquine is the drug of last resort for malaria chemoprophylaxis and should only be used in persons with contraindications to chloroquine, doxycycline and atovaquone-proguanil.”
Declining Use of Mefloquine within DoD

Undesirable effects

Lariam may cause long lasting serious mental problems. Due to the long half-life of mefloquine, adverse reactions may occur and persist up to several months after discontinuation of the drug.

Some people who have taken Lariam developed serious neuropsychiatric reactions, including:

- suicidal behaviour
- committing suicide
- severe anxiety
- paranoia
- hallucinations
- depression
- feeling restless
- unusual behaviour
- insomnia & abnormal dreams

Psychiatric symptoms such as insomnia, abnormal dreams/nightmares, acute anxiety, depression, restlessness or confusion have to be regarded as prodromal for a more serious event.

Please complete the ‘Checklist for the prescription, supply or recommendation of mefloquine for malaria chemoprophylaxis’ to assist you in determining your patient’s suitability for this product.

“[Mefloquine] may cause long lasting serious mental problems… Some people who have taken [mefloquine] developed serious neuropsychiatric reactions…”

“Psychiatric symptoms such as insomnia, abnormal dreams/nightmares, acute anxiety, depression, restlessness or confusion have to be regarded as prodromal for a more serious event.”
In a small number of patients, it has been reported that neuropsychiatric reactions (e.g. depression, dizziness, or vertigo and loss of balance) may persist for months or longer, even after discontinuation of the drug.

Neuropathy

Cases of polyneuropathy (based on neurological symptoms such as pain, burning, sensory disturbances or muscle weakness, alone or in combination) have been reported in patients receiving mefloquine.

Mefloquine should be discontinued in patients experiencing symptoms of neuropathy, including pain, burning, tingling, numbness, and/or weakness in order to prevent the development of an irreversible condition.

“... an irreversible condition.”

In this report, an adverse reaction to mefloquine chemoprophylaxis is described characterized by prodromal symptoms of anxiety with subsequent development of psychosis, short-term memory impairment, confusion and personality change accompanied by complaints of disequilibrium and vertigo, with objective findings of central vestibulopathy. It is posited that these effects represent an idiosyncratic neurotoxic syndrome of progressive limbic encephalopathy and multifocal brainstem injury caused by the drug.
“The brain stem structure that we observed to be primarily targeted by mefloquine was the n. gracilis. The n. gracilis is a component of the dorsal column system which transfers proprioceptive signals... Simple clinical neurological exams of humans might also reveal whether the loss of proprioceptive function underpins the vertigo/dizziness seen with some mefloquine-treated patients. It is also important to point out that the mefloquine-induced brain stem injury revealed by silver staining is permanent in nature.”

U.S. Mefloquine Boxed Warning

- Potential signals of vestibular disorder were identified by the FDA Adverse Event Reporting System (AERS) between April - June 2012
- Pharmacovigilance evaluation by the FDA led to July 2013 Boxed Warning:

Mefloquine may cause neuropsychiatric adverse reactions that can persist after mefloquine has been discontinued. Mefloquine should not be prescribed for prophylaxis in patients with major psychiatric disorders. During prophylactic use, if psychiatric or neurologic symptoms occur, the drug should be discontinued and an alternative medication should be substituted (see WARNINGS).

During prophylactic use, the occurrence of psychiatric symptoms such as acute anxiety, depression, restlessness or confusion suggest a risk for more serious psychiatric disturbances or neurologic adverse reactions. In these cases, the drug should be discontinued and an alternative medication should be substituted.
Neurologic Adverse Reactions

Neurologic symptoms such as dizziness or vertigo, tinnitus, and loss of balance have been reported. These adverse reactions may occur early in the course of mefloquine use and in some cases have been reported to continue for months or years after mefloquine has been stopped. Dizziness or vertigo, tinnitus, and loss of balance have been reported to be permanent in some cases. During prophylactic use, if neurologic symptoms occur, the drug should be discontinued and an alternative medication should be substituted.

Postmarketing

The most frequently reported adverse events are nausea, vomiting, loose stools or diarrhea, abdominal pain, dizziness or vertigo, loss of balance, and neuropsychiatric events such as headache, somnolence, and sleep disorders (insomnia, abnormal dreams). These adverse reactions may occur early in the course of mefloquine use. It has been reported that dizziness or vertigo, tinnitus and hearing impairment, and loss of balance may continue for months after discontinuation of the drug and may be permanent in some cases.

More severe neuropsychiatric disorders have been reported such as: sensory and motor neuropathies (including paresthesia, tremor and ataxia), convulsions, agitation or restlessness, anxiety, depression, mood swings, panic attacks, memory impairment, confusion, hallucinations, aggression, psychotic or paranoid reactions and encephalopathy. Cases of suicidal ideation and suicide have been reported.
FDA Drug Safety Communication: FDA approves label changes for antimalarial drug mefloquine hydrochloride due to risk of serious psychiatric and nerve side effects

[7-29-2013] The U.S. Food and Drug Administration (FDA) is advising the public about strengthened and updated warnings regarding neurologic and psychiatric side effects associated with the antimalarial drug mefloquine hydrochloride. A boxed warning, the most serious kind of warning about these potential problems, has been added to the drug label. FDA has revised the patient Medication Guide dispensed with each prescription and wallet card to include this information and the possibility that the neurologic side effects may persist or become permanent. The neurologic side effects can include dizziness, loss of balance, or ringing in the ears. The psychiatric side effects can include feeling anxious, mistrustful, depressed, or having hallucinations (For a more complete list of potential side effects, see Additional Information for Patients).

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. Patients, caregivers, and health care professionals should watch for these side effects. When using the drug to prevent malaria, if a patient develops neurologic or psychiatric symptoms, mefloquine should be stopped, and an alternate medicine should be used. If a patient develops neurologic or psychiatric symptoms while on mefloquine, the patient should contact the prescribing health care professional. The patient should not stop taking mefloquine before discussing symptoms with the health care professional.
PRECAUTIONS: General: Caution should be exercised with regard to driving, piloting airplanes and operating machines, as dizziness, a disturbed sense of balance or neuropsychiatric reactions have been reported during the use of Lariam. During prophylactic use, if signs of unexplained anxiety, depression, restlessness or confusion are noticed, these may be considered prodromal to a more serious event. In these cases, the drug must be discontinued.

ADVERSE REACTIONS: Clinical: At the doses used for treatment of acute malaria infections, the symptoms possibly attributable to drug administration cannot be distinguished from two serious adverse reactions were cardiopulmonary arrest in one patient shortly after ingesting a single prophylactic dose of mefloquine while concomitantly using propranolol (see WARNINGS and PRECAUTIONS), and encephalopathy of unknown etiology during prophylactic mefloquine administration. The relationship of encephalopathy to drug administration could not be clearly established.

The following additional adverse reactions have been reported during post-marketing surveillance: vertigo, visual disturbances and central nervous system disturbances (e.g. psychotic manifestations, hallucinations, confusion, anxiety and depression).
Acute/Subacute Intoxication
- Vivid Dreams,
- Sleep Disturbance,
- Nightmares, Personality Change, Disinhibition,
  - “Anxiety, Depression, Restlessness or Confusion”,
- Mania, Psychosis,
- Disorientation, Amnesia,
- Neurological Symptoms

Prodrome

Dosing

Time

Severity

Chronic Neurotoxic Effects
- Chronic Neurological Symptoms,
  - Behavioral, Mood, and Cognitive Changes
“A distinct neuropsychiatric syndrome class was identified that was strongly and significantly associated with reports of mefloquine use (odds ratio = 3.92, 95% confidence interval 2.91-5.28), defined by a very high probability of symptoms of deliria (82.7%) including confusion and disorientation, and a moderate probability of other severe psychiatric and neurologic symptoms including dementia and amnesia (18.6%) and seizures (18.1%). The syndrome class was also associated with symptoms that are considered prodromal including anxiety, depression, sleep disturbance, and abnormal dreams, and neurological symptoms such as dizziness, vertigo, and paresthesias”.

Acute and long-term psychiatric side effects of mefloquine: A follow-up on Danish adverse event reports

Åsa Ringqvist a,b,*, Per Bech c,d, Birte Glenthøj d,e, Eskild Petersen f

9/43 (21%) reporting nightmares with use of the drug and 14/42 (33%) reporting cognitive dysfunction with use of the drug reported these persisting for > 3 years.
Symptoms of Chronic Mefloquine Poisoning

- Nightmares, abnormal dreams, insomnia
- Anxiety, panic and depression
- Paranoia and delusions
- Cognitive problems
- Tinnitus and hearing problems
- Dizziness, vertigo, and disequilibrium
- Visual disturbances
- Many others…
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- Visual disturbances
- Many others…

PTSD-like

TBI-like
Mefloquine, PTSD, and TBI

Special Considerations for US Military Deployments

“Neuropsychiatric side effects may confound the diagnosis and management of posttraumatic stress disorder and traumatic brain injury, which makes the continued routine use of mefloquine less desirable.”

Confounding

Exposure to Traumas

Confounder

assumed causation

independent causation

correlation

Insomnia
Nightmares
Depression
Anxiety
Confounding

Exposure to Traumas

assumed causation

Mefloquine

actual causation

Insomnia
Nightmares
Depression
Anxiety
Disequilibrium
Vertigo

“Especially pertinent to the military population, it demonstrates the difficulty in distinguishing from possible mefloquine-induced toxicity versus PTSD, and raises some questions regarding possible linkages between the two diagnoses”.
Adjusted risk of PTSD diagnosis in a non-deployed subgroup was nearly doubled among those prescribed mefloquine as compared with those prescribed atovaquone-proguanil.
DSM-5 PTSD Criterion H

• The 2012 revision to the DSM added a diagnostic exclusion (“Criterion H”)

• Per Criterion H, the symptoms that would otherwise contribute to a PTSD diagnosis cannot be due to the effects of a medication

• Symptoms such as nightmares or insomnia that first begin with mefloquine use and prior to any trauma should not contribute towards PTSD diagnostic criteria
Psychiatric Side Effects of Mefloquine: Applications to Forensic Psychiatry

Elspeth Cameron Ritchie, MD, MPH, Jerald Block, MD, and Remington Lee Nevin, MD, MPH

Mefloquine is a 4-quinolinoxanthine antimalarial first synthesized in the early 1970s,1,2 it was then extensively evaluated in the United States military’s Water Reed Army Institute of Research (WRAMR).3 The drug development was the culmination of a 15-year drug discovery effort, during which time more than 200,000 compounds were screened for their antimalarial properties.4 Of a handful of compounds active against chloroquine-resistant strains of Plasmodium falciparum that demonstrated promising blood stage toxicity profiles, mefloquine (initially known as WR 13,660) was selected for further development and clinical evaluation in humans.5

To ensure the drug’s commercial manufacture and its continued availability, intellectual property rights and research related to mefloquine were transferred at no cost to Hoffmann-La Roche Ltd. (Basel, Switzerland).6

Dr. Ritchie is Chief Medical Officer, Department of Mental Health, District of Columbia, Department of Health, Washington, DC. Dr. Block is Medical Director, Department of Mental Health, Health Services Administration, Department of Mental Health, Washington, DC. Remington Lee Nevin, MD, MPH, is Co-Chief, Division of Mental Health Services, Department of Mental Health, Washington, DC. The views expressed are those of the authors and do not necessarily reflect the views of the District of Columbia Department of Mental Health, the Department of Veteran Affairs, or the U.S. Government. Ad


MEFLOQUINE AND POSTTRAUMATIC STRESS DISORDER

Chapter 19

INTRODUCTION

THE DEVELOPMENT OF MEFLOQUINE

THE HISTORY OF MEFLOQUINE USE IN US MILITARY POPULATIONS

CLINICAL FEATURES OF MEFLOQUINE INTOXICATION

CHRONIC EFFECTS OF MEFLOQUINE TOXICITY

CONFIRMATION OF DIAGNOSTIC AND STATISTICAL MANUAL OF MENTAL DISORDERS DIAGNOSTIC CRITERIA

FORENSIC APPLICATIONS

SUMMARY

The company pursued regulatory approval and marketed the drug to civilian travelers under the trade name Lariqto® after initial Food and Drug Administration (FDA) experience in 1989.3 Owing to its efficacy, prolonged duration of action, and convenient dose schedule that facilitated prophylactic use, mefloquine was soon identified as the drug of choice7 for use by U.S. travelers to areas of chloroquine-resistant malaria at doses of one 250mg tablet nightly.6

Early prescription studies on mefloquine were conducted predominantly among male prisoners,5,8,10 and subjects in third-world countries.9,11-13 Although irritative and manic symptoms were commonly reported in these early trials, the absence of seizure and unipolar depressive reporting14-16 led to the drug being considered largely free of the severe psychiatric side effects that had characterized the related antimalarial compounds chloroquine5,17 and quinacrine.5,15-16

The purported safety of mefloquine was so well established that when reports of seizures were initially reported in German women living in areas where chloroquine-resistant malaria was common, she sought to reduce their exposure to mefloquine.17,18


Strong Evidence of Causation

• “Medication-Induced” Psychiatric Disorders
  – Mood Disorders
  – Anxiety Disorders
  – Psychotic and Sleep Disorders
• Central (i.e. brainstem) Vestibular Disorders
• Central (i.e. brainstem) Visual Disorders
• Tinnitus and Hearing Disorders
Establishing Exposure

- Not all veterans will have evidence of mefloquine in their medical records
- Exposure may be conceded by VA for those with appropriate deployment histories and sworn lay statements
“Clinicians evaluating veterans who are seeking care for lasting psychiatric symptoms should ensure that they screen for prior symptomatic mefloquine exposure… [S]ymptomatic mefloquine exposure is likely to emerge as a significant known confounder in the diagnosis of psychiatric disorders, including PTSD, among the current generation of U.S. veterans”.

WRMI-2

• “Have you ever taken the weekly drug mefloquine (also known as Lariam®) to prevent malaria?"

• If yes, “At any time while taking the drug, did you experience abnormal dreams or nightmares, insomnia, anxiety, depression, restlessness, or confusion?”
“Psychiatric symptoms such as insomnia, abnormal dreams/nightmares, acute anxiety, depression, restlessness or confusion have to be regarded as prodromal for a more serious event [emphasis added]”
Vignette #1

• 33 year old male, army intelligence officer, top secret clearance
• No past medical history
• Deployed to Iraq in 2003 on mefloquine
• Presented acutely in theater to combat stress control after suffering vivid nightmares, visual hallucinations, panic, persecutory delusions, confusion, and dizziness
• Initially diagnosed with combat stress reaction vs. panic attack, attributed to his observing a dead body the day prior

• Charged with cowardice and returned to the U.S.

• Evaluated by ENT and found to have *objective evidence of central vestibular dysfunction*

• Charges dropped

• Medically separated from service for PTSD and vestibular disorder

• **Awarded 30% disability rating for service-connected “vestibular dysfunction” secondary to adverse reaction” to mefloquine**

• **Awarded 30% disability rating for service-connected PTSD “with toxic psychosis secondary” to mefloquine**

Vignette #2

- 32 year old male naval officer
- No past medical history
- Deployed to seas off East Africa in 2009 on mefloquine
- Experienced intense nightmares and anxiety early during deployment
- Subsequently developed disequilibrium and confusion
- Experienced a traumatic event (i.e. enemy gun fire) towards the end of his deployment
• Diagnosed with PTSD following his return home
• Subsequently evaluated for persistent vertigo; found to have normal MRI of the brain, and abnormal vestibular testing deemed consistent with central vestibulopathy
• Suffers persistent insomnia, nightmares, depression, anxiety, dizziness, and poor short-term memory
• Separated from service through a PEB for PTSD secondary to “antimalarial toxicity”, and rated at 70% by the VA.

Vignette #3

- 56 year old non-deployed male submitted a claim to the VA in 2014 for conditions he alleged were due to mefloquine
- In 1991, he had participated in a clinical trial of mefloquine, developing nightmares, abnormal dreams, insomnia, anxiety, depression, cognitive dysfunction, and changes in personality while taking the drug
- The drug was not discontinued and he continued taking the drug for several months while symptomatic
• His psychiatric symptoms persisted after the trial, and through separation from service, and ultimately led to his loss of civilian employment in 2010.

• After becoming aware of the 2013 boxed warning, he sought care for his persistent symptoms.

• His clinician posited his chronic symptoms were most likely a consequence of his earlier use of mefloquine.

• The VA awarded 50% disability for “social anxiety disorder with memory loss”.
<table>
<thead>
<tr>
<th>Issue/Contention</th>
<th>Percent (%) Assigned</th>
<th>Effective Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>social anxiety disorder with memory loss (claimed as neurotoxicity, neurological and mental condition)</td>
<td>50%</td>
<td>Feb 28, 2014</td>
</tr>
</tbody>
</table>

**Explanation**

- We have assigned a 50 percent evaluation for your social anxiety disorder based on: • Difficulty in adapting to stressful circumstances • Panic attacks more than once a week • Occupational and social impairment with reduced reliability and productivity • Chronic sleep impairment • Anxiety.
- The overall evidentiary record shows that the severity of your disability most closely approximates the criteria for a 50 percent disability evaluation.
- A higher evaluation of 70 percent is not warranted unless the evidence shows occupational and social impairment, with deficiencies in most areas, such as work, school, family relations, judgment, thinking, or mood, due to such symptoms as: • Suicidal ideation • Obsessional rituals which interfere with routine activities • Speech intermittently illogical, obscure, or irrelevant • Near-continuous panic or depression affecting the ability to function independently, appropriately, and effectively • Impaired impulse control (such as unprovoked irritability with periods of violence) • Spatial disorientation • Neglect of personal appearance and hygiene • Difficulty in adapting to stressful circumstances (including work or a worklike setting) • Inability to establish and maintain effective relationships.
- VA examiners opined that your condition is at least as likely as not related to Melfoquine testing conducted in service. Rationale is that Melfoquine was administered while in service. There was no treatment for anxiety disorders in service. You were not diagnosed with anxiety disorder until years after service. However, FDA and medical literature note that the onset of behavioral symptoms (anxiety) could occur years after administration of Melfoquine. Therefore, it is at least as likely as not that current social anxiety disorder with memory loss is a result of exposure to testing in service.
Case in Point

FDA Black Box, VA Red Ink?
A Successful Service-Connected Disability Claim for Chronic Neuropsychiatric Adverse Effects From Mefloquine

Remington L. Nevin, MD, MPH, DrPH; and Col (Ret) Elspeth Cameron Ritchie, MD, MPH, USA

More veterans are likely to present to the VA with service-connected claims for adverse effects related to exposure to a prophylactic antimalarial drug commonly used by the military for more than 2 decades.
Claiming “Mefloquine Poisoning”

• Many veterans naively submit a claim for “mefloquine poisoning” or “mefloquine toxicity” after learning of the drug’s effects
  – These cases will likely be denied by the VA

• Mefloquine poisoning is an exposure, not an outcome, and itself provides the nexus connecting military service to the development of one or more disabling conditions
  – Requires an independent medical opinion (i.e. nexus letter) or clinical documentation linking the condition to mefloquine
Developing a Claim

- Psychiatry
- Neurology
- ENT / Neuro-otology
- Neuro-ophthalmology / Neuro-optometry
- Sleep Medicine
- Neuropsychological testing
- Speech-Language Pathology
- Expert Review
“Quinism”

• Historical evidence of common signs and symptoms caused by quinoline drugs
  – Quinine, quinacrine, primaquine, chloroquine, mefloquine, tafenoquine

• Historical evidence of a common etiology and pathophysiology
  – Focal brainstem and limbic neurotoxic injury

"In the oculomotor, trochlear, an abducent nuclei there was considerable dropping out of nerve cells, degenerative changes in many that remained, and moderate proliferation of microglia and oligodendroglia. A representative field from the oculomotor nucleus is illustrated .... Somewhat slighter changes were observed in the vestibular nuclei, especially in the medial vestibular nucleus."

"...in doses well below the lethal level [these drugs] produced striking symptoms of central nervous system injury associated with severe lesions in the principal nuclei of the proprioceptive, visual-reflex, and vestibulo cerebellar pathways...."
NEUROTOXICITY OF THE 8-AMINOQUINOLINES

III. THE EFFECTS OF PENTAQUNE, ISOPENTAQUNE, PRIMAQUE, AND PAMAQUE ON THE CENTRAL NERVOUS SYSTEM OF THE RHESES MONKEY*†

The basic experiments (4), which assisted in establishing the position of the above 8-aminoquinolines in the treatment of relapsing malaria in man, included studies of the reactions of the rhesus monkey to these drugs with special reference to effects on the central nervous system. Interest in the latter effects rested on the observation that the closely related compound, Plasmocid, when administered to rhesus monkeys, evoked a complex group of neurological symptoms, associated with severe and widespread degenerative lesions in various cell groups of the spinal cord, brain stem, and cerebellum (1, 5-7). Whereas intoxication with even multilethal doses of pentaquine, isopentaquine, or primaquine did not evoke similar symptoms, the close structural relations of these compounds to Plasmocid (fig. 1), their high inherent toxicity and capacity to evoke reactions which might mask symptoms of low grade neuronal injury, plus the likelihood of their widespread use in malaria therapy made a detailed search for central nervous system lesions highly desirable.
Side effects of antimalarial drugs?
These may be symptoms of a disease.
Quinism.

The Quinism Foundation is a 501(c)(3) nonprofit charitable organization established January 1, 2018 in White River Junction, Vermont.

The Quinism Foundation promotes and supports education and research on quinism, the family of medical disorders caused by poisoning by mefloquine, tafenoquine, and related quinoline drugs.

Symptoms of neuropsychiatric quinism (also known as chronic quinoline encephalopathy) can mimic those of several psychiatric and neurologic disorders including PTSD and TBI.