Mefloquine Poisoning and VA Service Connection

Presentation to the State Bar of Texas
Military and Veterans Law Section

March 29, 2019
Salado, Texas

Remington Nevin, MD, MPH, DrPH
Executive Director

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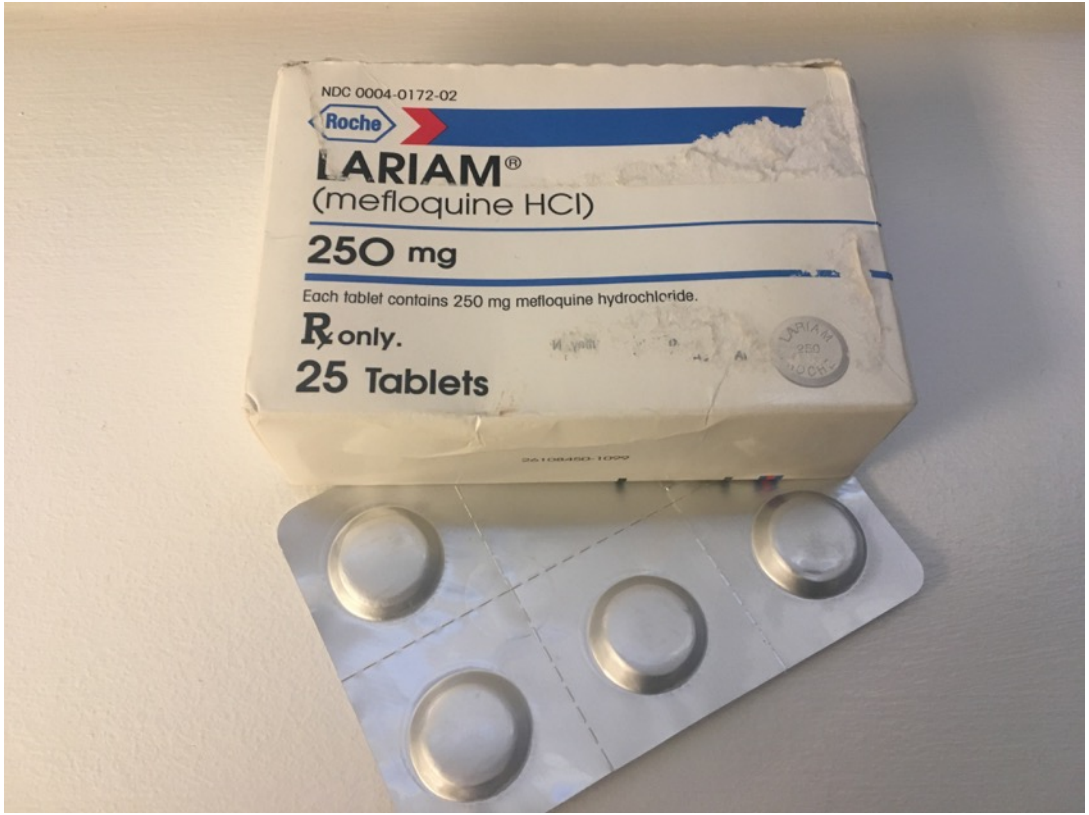

Photo credit: Dr. Remington Nevin

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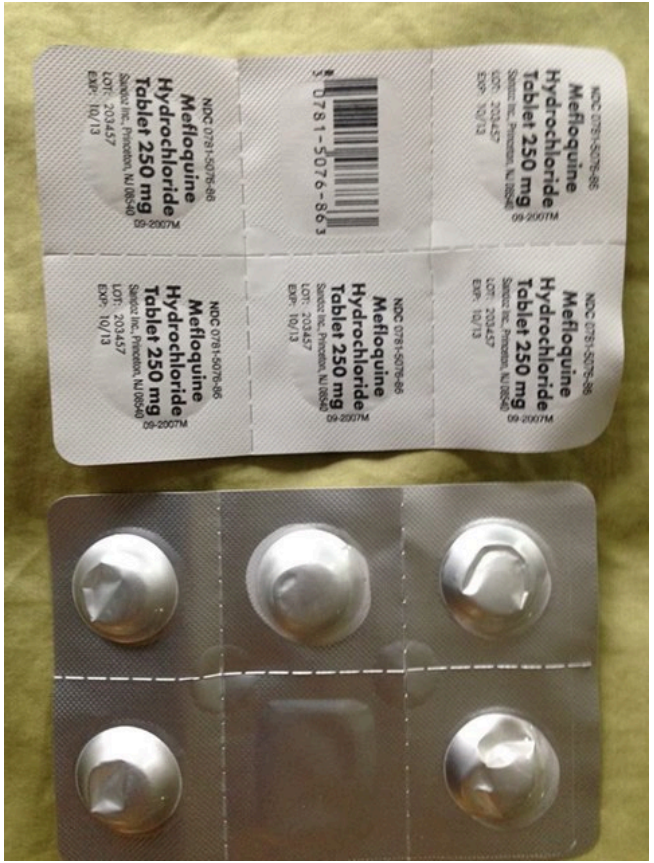

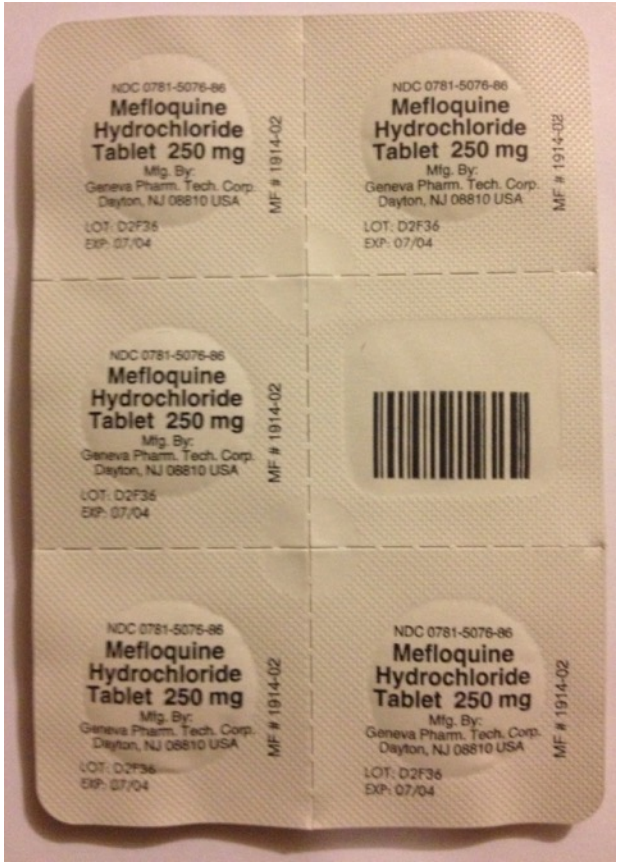

Photo credits: Dr. Remington Nevin

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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**

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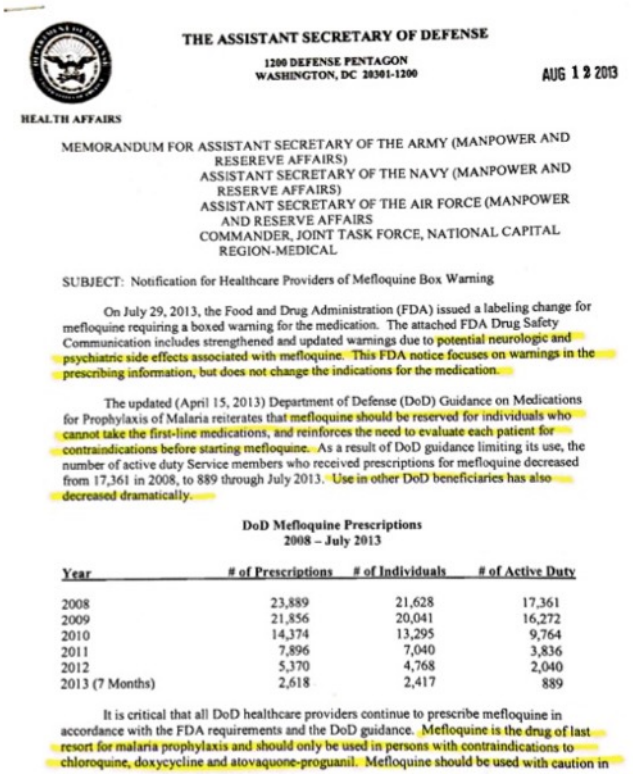
2013 “Drug of Last Resort” Policy Memorandum



THE ASSISTANT SECRETARY OF DEFENSE
1200 DEFENSE PENTAGON
WASHINGTON, DC 20301-1200

AUG 12 2013

HEALTH AFFAIRS

MEMORANDUM FOR ASSISTANT SECRETARY OF THE ARMY (MANPOWER AND RESEREVE AFFAIRS)
ASSISTANT SECRETARY OF THE NAVY (MANPOWER AND RESERVE AFFAIRS)
ASSISTANT SECRETARY OF THE AIR FORCE (MANPOWER AND RESERVE AFFAIRS
COMMANDER, JOINT TASK FORCE, NATIONAL CAPITAL REGION-MEDICAL

SUBJECT: Notification for Healthcare Providers of Mefloquine Box Warning

On July 29, 2013, the Food and Drug Administration (FDA) issued a labeling change for mefloquine requiring a boxed warning for the medication. The attached FDA Drug Safety Communication includes strengthened and updated warnings due to potential neurologic and psychiatric side effects associated with mefloquine. This FDA notice focuses on warnings in the prescribing information, but does not change the indications for the medication.

The updated (April 15, 2013) Department of Defense (DoD) Guidance on Medications for Prophylaxis of Malaria reiterates that mefloquine should be reserved for individuals who cannot take the first-line medications, and reinforces the need to evaluate each patient for contraindications before starting mefloquine. As a result of DoD guidance limiting its use, the number of active duty Service members who received prescriptions for mefloquine decreased from 17,361 in 2008, to 889 through July 2013. Use in other DoD beneficiaries has also decreased dramatically.

DoD Mefloquine Prescriptions
2008 – July 2013

Year	# of Prescriptions	# of Individuals	# of Active Duty
2008	23,889	21,628	17,361
2009	21,856	20,041	16,272
2010	14,374	13,295	9,764
2011	7,896	7,040	3,836
2012	5,370	4,768	2,040
2013 (7 Months)	2,618	2,417	889

It is critical that all DoD healthcare providers continue to prescribe mefloquine in accordance with the FDA requirements and the DoD guidance. Mefloquine is the drug of last resort for malaria prophylaxis and should only be used in persons with contraindications to chloroquine, doxycycline and atovaquone-proguanil. Mefloquine should be used with caution in

“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.”

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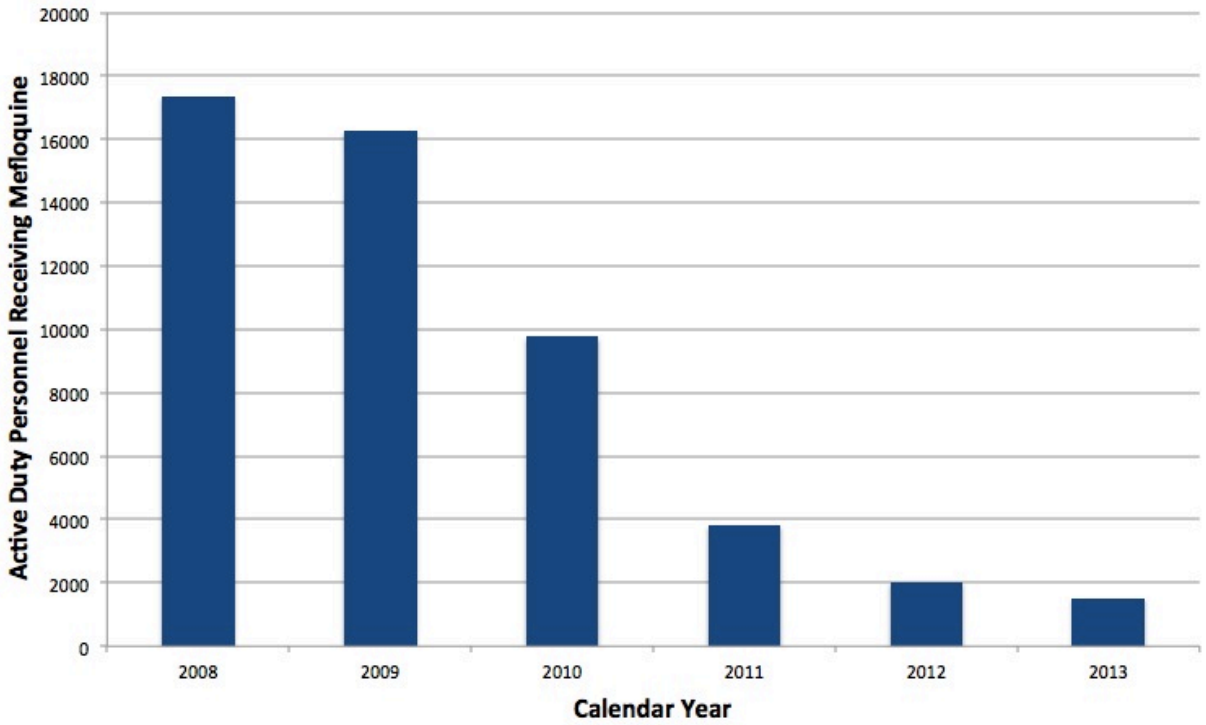
Declining Use of Mefloquine within DoD



Woodson J. Memorandum. Subject: Notification for Healthcare Providers of Mefloquine Box Warning. August 12, 2013. *Emphasis added.*

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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…"

Roche UK. Lariam product documentation, June 2018. *Emphasis added.*

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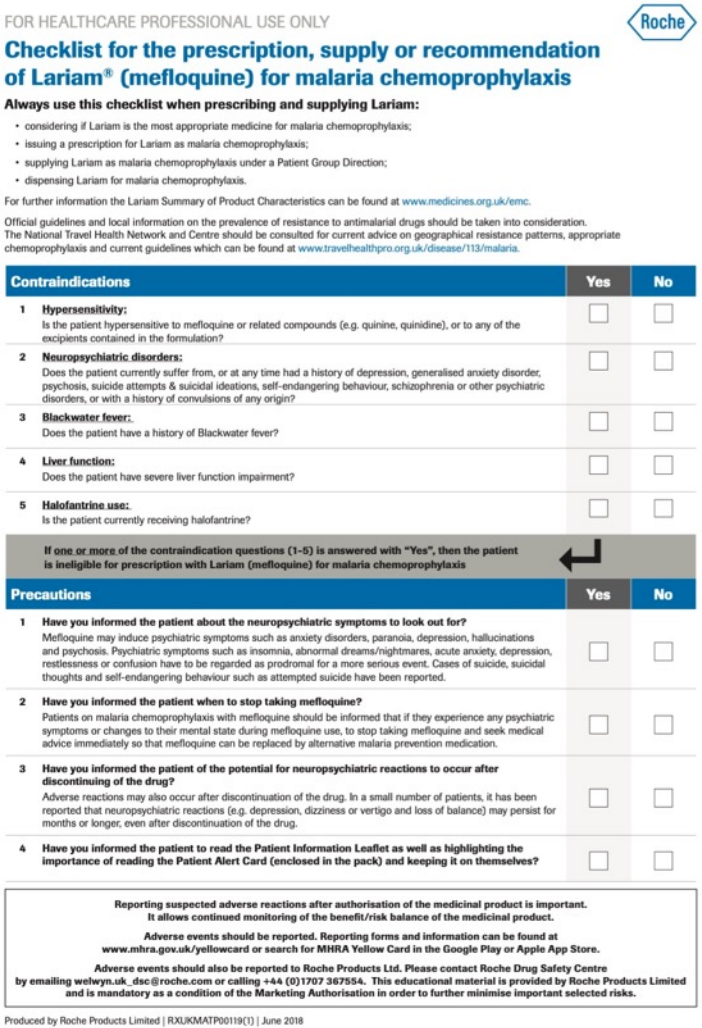

FOR HEALTHCARE PROFESSIONAL USE ONLY

Roche

Checklist for the prescription, supply or recommendation of Lariam® (mefloquine) for malaria chemoprophylaxis

Always use this checklist when prescribing and supplying Lariam:

- considering if Lariam is the most appropriate medicine for malaria chemoprophylaxis;
- issuing a prescription for Lariam as malaria chemoprophylaxis;
- supplying Lariam as malaria chemoprophylaxis under a Patient Group Direction;
- dispensing Lariam for malaria chemoprophylaxis.

For further information the Lariam Summary of Product Characteristics can be found at www.medicines.org.uk/emc.

Official guidelines and local information on the prevalence of resistance to antimalarial drugs should be taken into consideration. The National Travel Health Network and Centre should be consulted for current advice on geographical resistance patterns, appropriate chemoprophylaxis and current guidelines which can be found at www.travelhealthpro.org.uk/disease/113/malaria.

Contraindications	Yes	No
1 **Hypersensitivity:** Is the patient hypersensitive to mefloquine or related compounds (e.g. quinine, quinidine), or to any of the excipients contained in the formulation?	☐	☐
2 **Neuropsychiatric disorders:** Does the patient currently suffer from, or at any time had a history of depression, generalised anxiety disorder, psychosis, suicide attempts & suicidal ideations, self-endangering behaviour, schizophrenia or other psychiatric disorders, or with a history of convulsions of any origin?	☐	☐
3 **Blackwater fever:** Does the patient have a history of Blackwater fever?	☐	☐
4 **Liver function:** Does the patient have severe liver function impairment?	☐	☐
5 **Halofantrine use:** Is the patient currently receiving halofantrine?	☐	☐

If one or more of the contraindication questions (1-5) is answered with "Yes", then the patient is ineligible for prescription with Lariam (mefloquine) for malaria chemoprophylaxis

Precautions	Yes	No
1 **Have you informed the patient about the neuropsychiatric symptoms to look out for?** Mefloquine may induce psychiatric symptoms such as anxiety disorders, paranoia, depression, hallucinations and psychosis. Psychiatric symptoms such as insomnia, abnormal dreams/nightmares, acute anxiety, depression, restlessness or confusion have to be regarded as prodromal for a more serious event. Cases of suicide, suicidal thoughts and self-endangering behaviour such as attempted suicide have been reported.	☐	☐
2 **Have you informed the patient when to stop taking mefloquine?** Patients on malaria chemoprophylaxis with mefloquine should be informed that if they experience any psychiatric symptoms or changes to their mental state during mefloquine use, to stop taking mefloquine and seek medical advice immediately so that mefloquine can be replaced by alternative malaria prevention medication.	☐	☐
3 **Have you informed the patient of the potential for neuropsychiatric reactions to occur after discontinuing of the drug?** Adverse reactions may also occur after discontinuation of the drug. 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.	☐	☐
4 **Have you informed the patient to read the Patient Information Leaflet as well as highlighting the importance of reading the Patient Alert Card (enclosed in the pack) and keeping it on themselves?**	☐	☐

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

Adverse events should also be reported to Roche Products Ltd. Please contact Roche Drug Safety Centre by emailing welwyn.uk_dsc@roche.com or calling +44 (0)1707 367554. This educational material is provided by Roche Products Limited and is mandatory as a condition of the Marketing Authorisation in order to further minimise important selected risks.

Produced by Roche Products Limited | RXUKMATP00119(1) | June 2018

"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.**"

Roche UK. Lariam product documentation, June 2018. *Emphasis added.*

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Special warnings and precautions for use

Neuropsychiatric Adverse Reactions:

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

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

Adverse reactions may also occur after discontinuation of the drug. 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.

To minimise the risk for these adverse reactions, mefloquine must not be used for chemoprophylaxis in patients with active or a history of psychiatric disturbances such as depression, anxiety disorders, schizophrenia or other psychiatric disorders.

"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."

Roche UK. Lariam product documentation, June 2018. *Emphasis added.*

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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."

Roche UK. Lariam product documentation, June 2018. *Emphasis added.*

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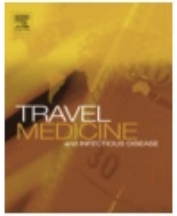
Travel Medicine and Infectious Disease (2012) 10, 144–151

Available online at www.sciencedirect.com

SciVerse ScienceDirect

journal homepage: www.elsevierhealth.com/journals/tmid



CASE REPORT

Limbic encephalopathy and central vestibulopathy caused by mefloquine: A case report☆

Remington L. Nevin*

"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**".

Nevin RL. Limbic encephalopathy and central vestibulopathy caused by mefloquine: A case report. Travel medicine and infectious disease. 2012;10(3):144–51.

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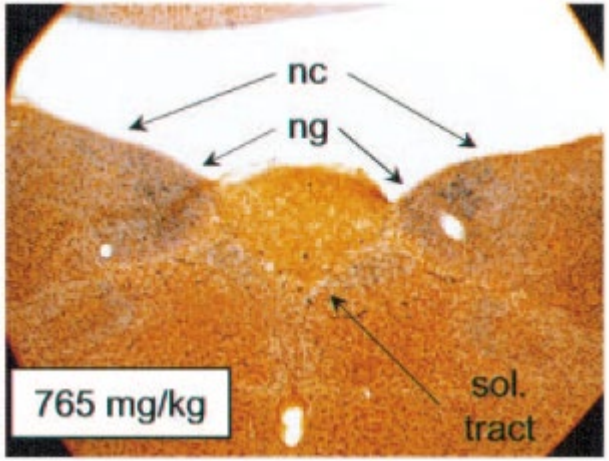

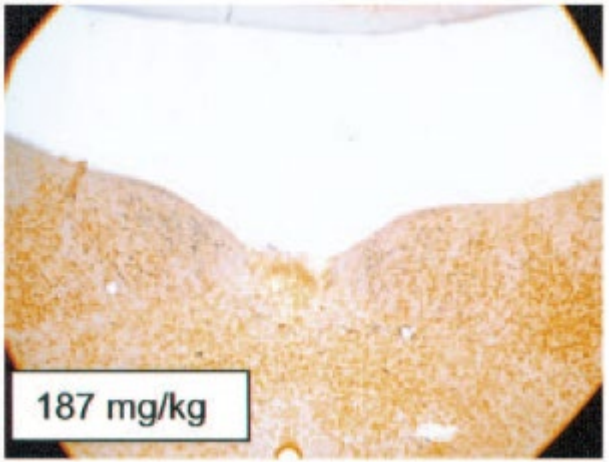

"The brain stem structure that we observed to be primarily targeted by mefloquine was the n. gracilis. The n. gracilis is a component of the dorsal column system which transfers proprioceptive signals… Simple clinical neurological exams of humans might also reveal whether the loss of proprioceptive function 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**."

Dow G, Bauman R, Caridha D, et al. Mefloquine induces dose-related neurological effects in a rat model. Antimicrobial agents and chemotherapy. 2006;50(3):1045-1053.

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.

U.S. Food and Drug Administration. FDA Drug Safety Communication: FDA approves label changes for antimalarial drug mefloquine hydrochloride due to risk of serious psychiatric and nerve side effects. July 29, 2013. http://www.fda.gov/downloads/Drugs/DrugSafety/UCM362232.pdf.

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.

Roxanne Laboratories. Mefloquine Hydrochloride. United States Product Insert. June, 2013.

U.S. Food and Drug Administration
Protecting and Promoting Your Health

Drug Safety Communications

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.

U.S. Food and Drug Administration. FDA Drug Safety Communication: FDA approves label changes for antimalarial drug mefloquine hydrochloride due to risk of serious psychiatric and nerve side effects. July 29, 2013. http://www.fda.gov/downloads/Drugs/DrugSafety/UCM362232.pdf.

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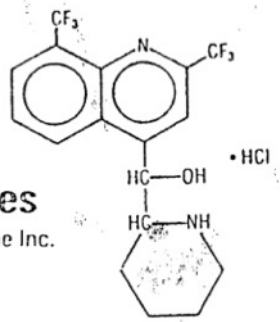
LARIAM®
(mefloquine hydrochloride)
TABLETS



Roche Laboratories
a division of Hoffmann-La Roche Inc.
340 Kingsland Street
Nutley, New Jersey 07110-1199

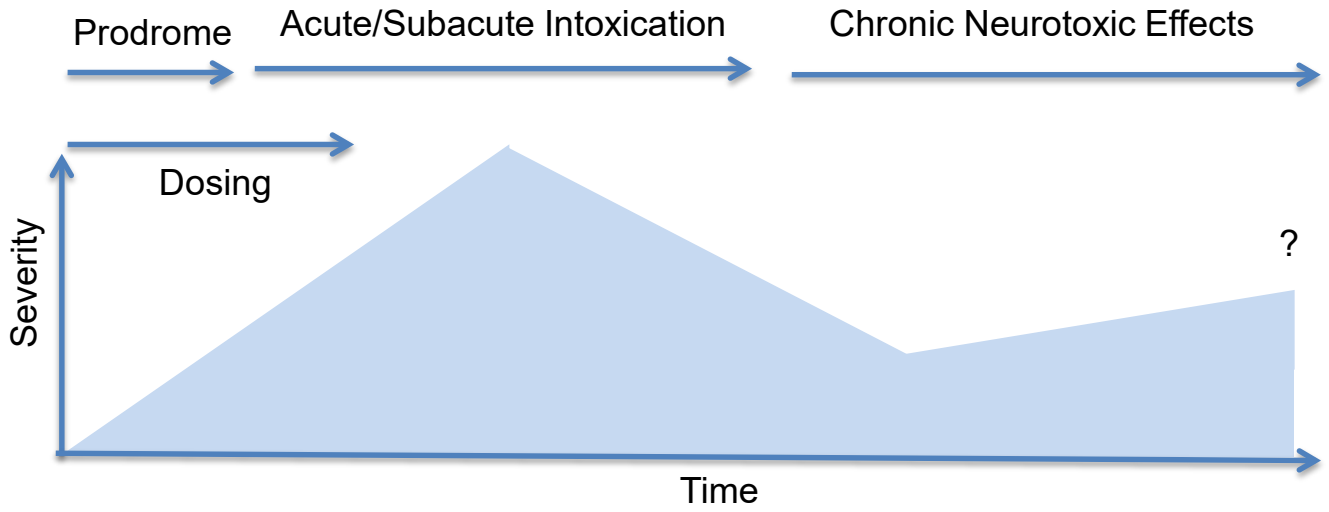
PRECAUTIONS: *General:* Caution should be exercised with regard to driving, piloting airplanes and operating machines, as dizziness, a disturbed sense of balance or neuropsychiatric reactions have been reported during the use of Lariam. During prophylactic use, if signs of unexplained anxiety, depression, 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).

F. Hoffmann-La Roche. Lariam Product Insert, USA. 1989.



Vivid Dreams, Sleep Disturbance, Nightmares, Personality Change, Disinhibition, "Anxiety, Depression, Restlessness or Confusion", Mania, Psychosis, Disorientation, Amnesia, Neurological Symptoms

Chronic Neurological Symptoms, Behavioral, Mood, and Cognitive Changes

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Drugs R D (2017) 17:199–210
DOI 10.1007/s40268-016-0167-3

ORIGINAL RESEARCH ARTICLE

Identification of a Syndrome Class of Neuropsychiatric Adverse Reactions to Mefloquine from Latent Class Modeling of FDA Adverse Event Reporting System Data

Remington L. Nevin[1] · Jeannie-Marie Leoutsakos[2,3]

"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**".

Nevin RL, Leoutsakos J-M. Identification of a Syndrome Class of Neuropsychiatric Adverse Reactions to Mefloquine from Latent Class Modeling of FDA Adverse Event Reporting System Data. *Drugs R D*. 2017;17(1):199-210.

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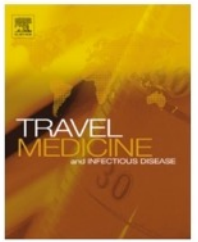
Travel Medicine and Infectious Disease (2015) 13, 80–88



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.**

Ringqvist Å, Bech P, Glenthøj B, Petersen E. Acute and long-term psychiatric side effects of mefloquine: A follow-up on Danish adverse event reports. *Travel Med Infect Dis*. 2015;13(1):80-88.

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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

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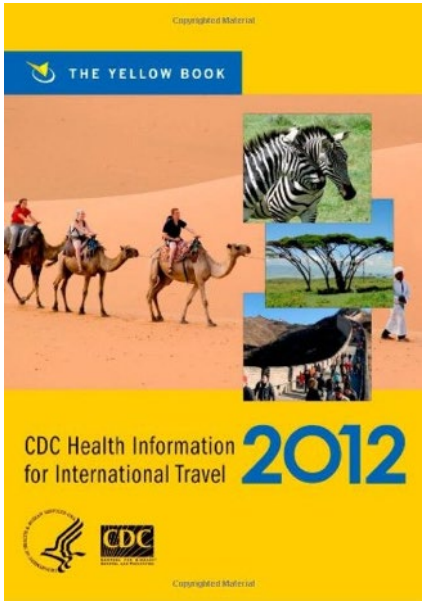
Mefloquine, PTSD, and TBI



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."

Magill A, Cersovsky S, DeFraites R. Special Considerations for US Military Deployments. In: Brunette GW, ed. CDC Health Information for International Travel: The Yellow Book 2012. New York, NY: Oxford University Press; 2012:561-565. Emphasis added.

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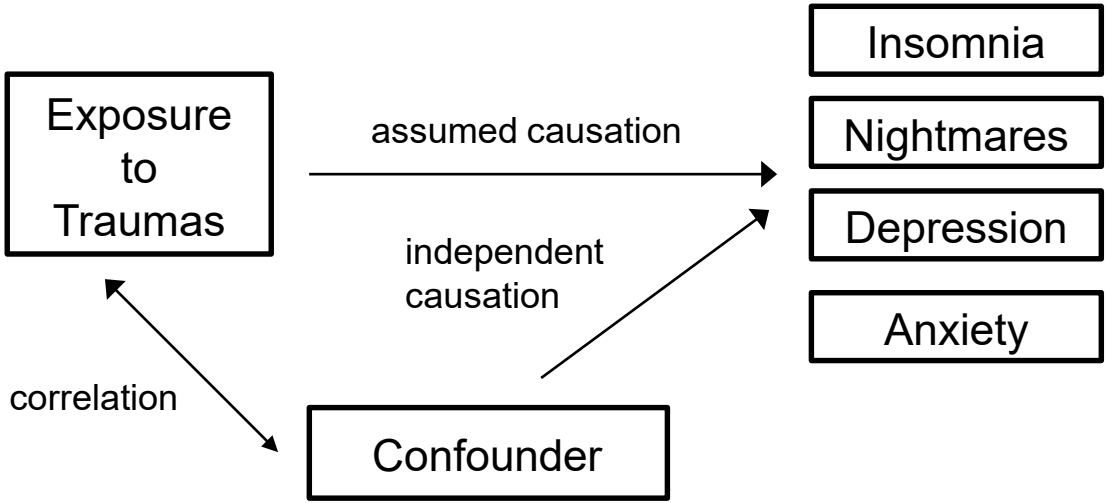
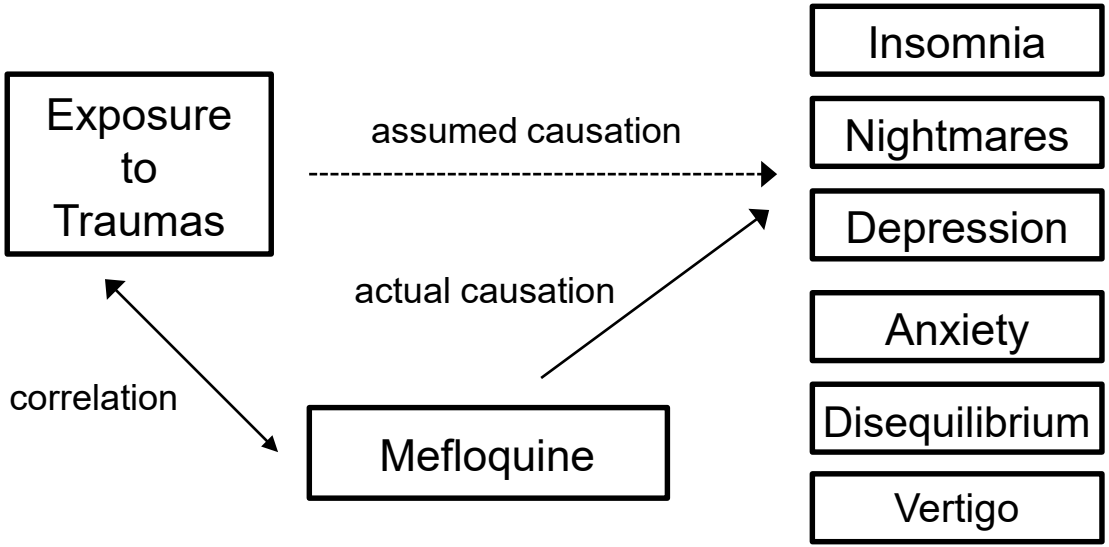
Confounding



Confounding



Nevin RL. Mefloquine Exposure May Confound Associations and Limit Inference in Military Studies of Posttraumatic Stress Disorder. Military Medicine. 2017;182(11/12):1757.

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Drug Saf - Case Rep (2016)3:7
DOI 10.1007/s40800-016-0030-z

CASE REPORT

Prolonged Neuropsychiatric Symptoms in a Military Service Member Exposed to Mefloquine

Jeffrey Livezey[1] · Thomas Oliver[2] · Louis Cantilena[2]

"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".

Livezey J, Oliver T, Cantilena L. Prolonged Neuropsychiatric Symptoms in a Military Service Member Exposed to Mefloquine. Drug Saf Case Reports. 2016;3(1):7. *Emphasis added.*

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Am. J. Trop. Med. Hyg., 96(1), 2017, pp. 159–166
doi:10.4269/ajtmh.16-0390

Neuropsychiatric Outcomes after Mefloquine Exposure among U.S. Military Service Members

Angelia A. Eick-Cost,[1]* Zheng Hu, Patricia Rohrbeck,[1] and Leslie L. Clark[1]
[1]*Epidemiology and Analysis Section, Armed Forces Health Surveillance Branch, Defense Health Agency, Silver Spring, Maryland*

Abstract. Mefloquine was widely prescribed to U.S. military service members until 2009 when use was limited to personnel with contraindications to doxycycline and no contraindications to mefloquine. The need to estimate the occurrence of neuropsychiatric outcomes (NPOs) in service members prescribed mefloquine warranted a comprehensive evaluation of this issue. Active component service members filling a prescription for mefloquine, doxycycline, or atovaquone/proguanil (A/P) between January 1, 2008 and June 30, 2013, were included in the analysis. The risk of developing incident NPOs and the risk of subsequent NPOs among subjects with a history of the condition were assessed. A total of 367,840 individuals were evaluated (36,538 received mefloquine, 318,421 received doxycycline, and 12,881 received A/P). Among deployed individuals prescribed mefloquine, an increased risk of incident anxiety was seen when compared with doxycycline recipients (incidence rate ratio [IRR] = 1.12 [1.01–1.24]). Among nondeployed mefloquine recipients, an increased risk of posttraumatic stress disorder (PTSD) was seen when compared with A/P recipients (IRR = 1.83 [1.07–3.14]). An increased risk of tinnitus was seen for both deployed and nondeployed mefloquine recipients compared with A/P recipients (IRR = 1.81 [1.18–2.79]), 1.51 (1.13–2.03), respectively). Six percent of the mefloquine cohort had an NPO in the year before receiving mefloquine. When comparing individuals with a prior neuropsychiatric history to those without, the ratio of relative risks for adjustment disorder, anxiety, insomnia, and PTSD were higher (not statistically significant) for mefloquine compared with doxycycline. These findings emphasize the continued need for physicians prescribing mefloquine to conduct contraindication screening.

Adjusted **risk of PTSD diagnosis in a non-deployed subgroup was nearly doubled among those prescribed mefloquine** as compared with those prescribed atovaquone-proguanil.

Eick-Cost AA, Hu Z, Rohrbeck P, Clark LL. Neuropsychiatric Outcomes After Mefloquine Exposure Among U.S. Military Service Members. Am J Trop Med Hyg. 2017;96(1):159-166.

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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

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REGULAR ARTICLE

Psychiatric Side Effects of Mefloquine: Applications to Forensic Psychiatry

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

Mefloquine (previously marketed in the United States as Lariam®) is an antimalarial medication with potent psychotropic potential. Severe psychiatric side effects due to mefloquine intoxication are well documented, including anxiety, panic attacks, paranoia, persecutory delusions, dissociative psychosis, and anterograde amnesia. Exposure to the drug has been associated with acts of violence and suicide. In this article, we discuss the history of mefloquine use and describe plausible mechanisms of its psychotropic action. Mefloquine intoxication has not yet been successfully advanced in legal proceedings as a defense or as a mitigating factor, but it appears likely that it eventually will be. Considerations for the application of claims of mefloquine intoxication in forensic settings are discussed.

J Am Acad Psychiatry Law 41:224–35, 2013

Mefloquine is a 4-quinolinemethanol antimalarial first synthesized in the early 1970s[1] by researchers affiliated with the United States military's Walter Reed Army Institute of Research (WRAIR).[2] The drug's development was the culmination of a 10-year drug discovery effort, during which time more than 300,000 compounds were screened for their antimalarial properties.[2] Of a handful of compounds active against chloroquine-resistant strains of *Plasmodium falciparum* malaria that demonstrated seemingly favorable toxicity profiles,[2] mefloquine (initially known as WR 142490) was selected for further development and testing in humans.[3]

To secure the drug's commercial manufacture and its continued availability, intellectual property rights and research related to mefloquine were transferred at no cost to F. Hoffman-La Roche Ltd. (Roche).[4] The company pursued regulatory approval and marketed the drug to civilian travelers in the United States under the trade name Lariam® after its initial Food and Drug Administration (FDA) licensure in 1989.[5] Owing to its efficacy, presumed safety, and convenient dose schedule that facilitated prophylactic use, mefloquine was soon identified as the drug of choice[6,7] for use by U.S. travelers to areas of chloroquine-resistant malaria at a dose of one 250-mg tablet weekly.[8,9]

Early prelicensure studies on mefloquine were conducted predominantly among male prisoners,[2,10] military personnel,[5,11,12] and subjects in third-world countries.[11,13,14] Although vertigo and nausea were commonly reported in these early trials, in the absence of sensitive and unbiased prospective reporting[15] the drug was considered to be largely free of the severe psychiatric side effects that had characterized the related antimalarial compounds chloroquine[16,17] and quinacrine.[18,19]

The purported safety of mefloquine was so well established that when reports of severe psychiatric side effects, including amnesia, confusion and psychosis, first emerged in the literature following the drug's early European licensure,[20–23] these symptoms were frequently dismissed as coincidental[24] or were later attributed by influential authors to the stresses of overseas travel, recreational drug use, or pre-existing or latent mental illness.[25–27] Despite

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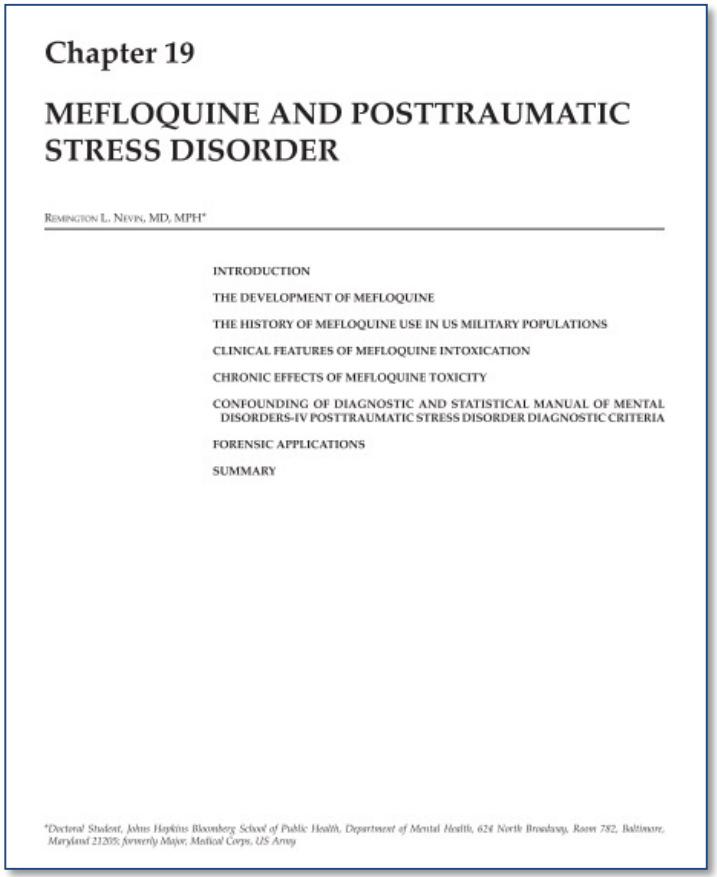
Disclosures of financial or other potential conflicts of interest: Dr. Nevin has served as paid and *pro bono* consultant to attorneys representing litigants advancing claims of harm from exposure to mefloquine.



Chapter 19

MEFLOQUINE AND POSTTRAUMATIC STRESS DISORDER

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Ritchie EC, Block J, Nevin RL. Psychiatric Side Effects of Mefloquine: Applications to Forensic Psychiatry. Journal of the American Academy of Psychiatry and the Law. 2013;41(2):224-235; Nevin RL. Mefloquine and Posttraumatic Stress Disorder. In: Ritchie EC, ed. Textbook of Military Medicine. Forensic and Ethical Issues in Military Behavioral Health. Washington, DC: Borden Institute; 2015.

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The Mefloquine Intoxication Syndrome: A Significant Potential Confounder in the Diagnosis and Management of PTSD and Other Chronic Deployment-Related Neuropsychiatric Disorders

19

Remington Lee Nevin and Elspeth Cameron Ritchie

Acute mefloquine intoxication may produce vivid, hyper-realistic nightmares that may precede a manic, paranoid, dissociative or confusional psychosis, often marked by horrific auditory and visual hallucinations. Courtesy of Allison Stroh Rabin.

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E. C. Ritchie (ed.), *Posttraumatic Stress Disorder and Related Diseases in Combat Veterans*, DOI 10.1007/978-3-319-22985-0_19

Nevin RL, Ritchie EC. The Mefloquine Intoxication Syndrome: A Significant Potential Confounder in the Diagnosis and Management of PTSD and Other Chronic Deployment-Related Neuropsychiatric Disorders. In: Ritchie EC, ed. Posttraumatic Stress Disorder and Related Diseases in Combat Veterans. Cham, Switzerland: Springer International Publishing; 2015:257-278.

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

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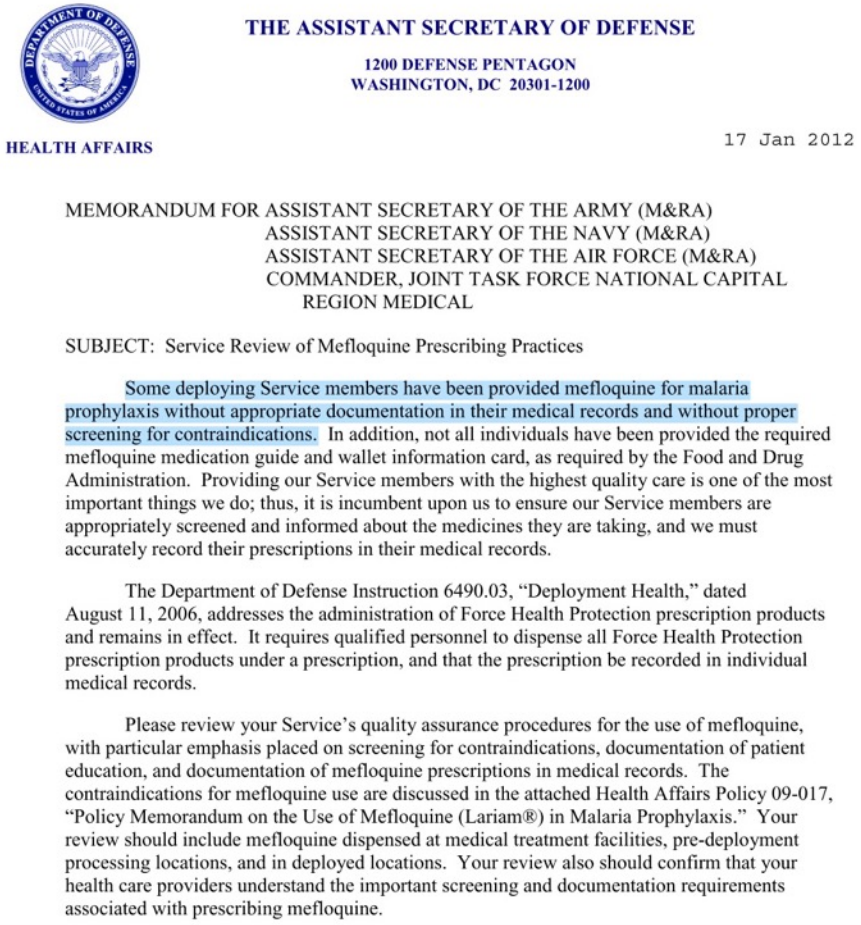

THE ASSISTANT SECRETARY OF DEFENSE

1200 DEFENSE PENTAGON
WASHINGTON, DC 20301-1200

HEALTH AFFAIRS

17 Jan 2012

MEMORANDUM FOR ASSISTANT SECRETARY OF THE ARMY (M&RA)
ASSISTANT SECRETARY OF THE NAVY (M&RA)
ASSISTANT SECRETARY OF THE AIR FORCE (M&RA)
COMMANDER, JOINT TASK FORCE NATIONAL CAPITAL REGION MEDICAL

SUBJECT: Service Review of Mefloquine Prescribing Practices

Some deploying Service members have been provided mefloquine for malaria prophylaxis without appropriate documentation in their medical records and without proper screening for contraindications. In addition, not all individuals have been provided the required mefloquine medication guide and wallet information card, as required by the Food and Drug Administration. Providing our Service members with the highest quality care is one of the most important things we do; thus, it is incumbent upon us to ensure our Service members are appropriately screened and informed about the medicines they are taking, and we must accurately record their prescriptions in their medical records.

The Department of Defense Instruction 6490.03, "Deployment Health," dated August 11, 2006, addresses the administration of Force Health Protection prescription products and remains in effect. It requires qualified personnel to dispense all Force Health Protection prescription products under a prescription, and that the prescription be recorded in individual medical records.

Please review your Service's quality assurance procedures for the use of mefloquine, with particular emphasis placed on screening for contraindications, documentation of patient education, and documentation of mefloquine prescriptions in medical records. The contraindications for mefloquine use are discussed in the attached Health Affairs Policy 09-017, "Policy Memorandum on the Use of Mefloquine (Lariam®) in Malaria Prophylaxis." Your review should include mefloquine dispensed at medical treatment facilities, pre-deployment processing locations, and in deployed locations. Your review also should confirm that your health care providers understand the important screening and documentation requirements associated with prescribing mefloquine.

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

Woodson J. Memorandum Dated 17 Jan 2012, Subject: Service Review of Mefloquine Prescribing Practices.

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MENTAL HEALTH CARE PRACTICE

Remington L. Nevin, MD, MPH, DrPH

Screening for Symptomatic Mefloquine Exposure Among Veterans With Chronic Psychiatric Symptoms

"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".

Nevin RL. Screening for Symptomatic Mefloquine Exposure Among Veterans With Chronic Psychiatric Symptoms. *Federal Practitioner*. 2017;34(3):12-14. http://www.mdedge.com/sites/default/files/fedprac/0317fp_nevin.pdf.

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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?”

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WRMI-2 Validity

Precautions	Yes	No
1 **Have you informed the patient about the neuropsychiatric symptoms to look out for?** Mefloquine may induce psychiatric symptoms such as anxiety disorders, paranoia, depression, hallucinations and psychosis. Psychiatric symptoms such as insomnia, abnormal dreams/nightmares, acute anxiety, depression, restlessness or confusion have to be regarded as prodromal for a more serious event. Cases of suicide, suicical thoughts and self-endangering behaviour such as attempted suicide have been reported.	☐	☐
2 **Have you informed the patient when to stop taking mefloquine?** Patients on malaria chemoprophylaxis with mefloquine should be informed that if they experience any psychiatric symptoms or changes to their mental state during mefloquine use, to stop taking mefloquine and seek medical advice immediately so that mefloquine can be replaced by alternative malaria prevention medication.	☐	☐

"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]"

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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

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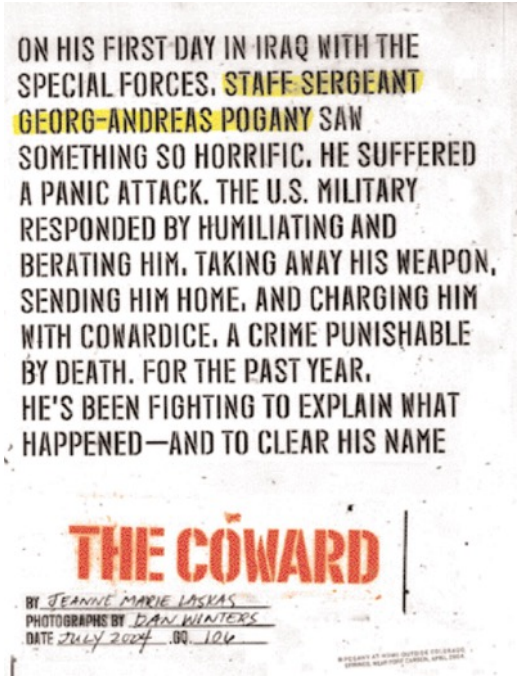

ON HIS FIRST DAY IN IRAQ WITH THE SPECIAL FORCES, STAFF SERGEANT GEORG-ANDREAS POGANY SAW SOMETHING SO HORRIFIC, HE SUFFERED A PANIC ATTACK. THE U.S. MILITARY RESPONDED BY HUMILIATING AND BERATING HIM, TAKING AWAY HIS WEAPON, SENDING HIM HOME, AND CHARGING HIM WITH COWARDICE, A CRIME PUNISHABLE BY DEATH. FOR THE PAST YEAR, HE'S BEEN FIGHTING TO EXPLAIN WHAT HAPPENED—AND TO CLEAR HIS NAME

THE COWARD

BY JEANNE MARIE LASKAS
PHOTOGRAPHS BY DAN WINTERS
DATE JULY 2004 GQ 106

- 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.

Laskas JM. The Coward. Gentleman's Quarterly. July 2004.

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- 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

References: 1. Nevin RL, Ritchie EC. The Mefloquine Intoxication Syndrome: A Significant Potential Confounder in the Diagnosis and Management of PTSD and Other Chronic Deployment-Related Neuropsychiatric Disorders. In: Posttraumatic Stress Disorder and Related Diseases in Combat Veterans. Cham: Springer International Publishing; 2015:257-278; and 2. Nevin RL. Mefloquine and Posttraumatic Stress Disorder. In: Ritchie EC, ed. Textbook of Military Medicine. Forensic and Ethical Issues in Military Behavioral Health. Washington, DC: Borden Institute; 2015:277-296.

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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.**

Reference: Livezey J, Oliver T, Cantilena L. Prolonged Neuropsychiatric Symptoms in a Military Service Member Exposed to Mefloquine. Drug safety - case reports. 2016;3(1):7.

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

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- 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”

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Issue/Contention	Percent (%) Assigned	Effective Date
social anxiety disorder with memory loss (claimed as neurotoxicity, neurological and mental condition)	50%	Feb 28, 2014

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.

Nevin RL, Ritchie EC. FDA Black Box, VA Red Ink? A Successful Service-Connected Disability Claim for Chronic Neuropsychiatric Adverse Effects From Mefloquine. Fed Pract. 2016;33(10):20-24.

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

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Developing a Claim

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

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“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

Nevin RL. Neuropsychiatric Quinism: Chronic Encephalopathy Caused by Poisoning by Mefloquine and Related Quinoline Drugs. In: Ritchie EC, Llorente M, eds. Veteran Psychiatry in the US. Cham, Switzerland: Springer Nature; 2019. doi:10.1007/978-3-030-05384-0. *In press.*

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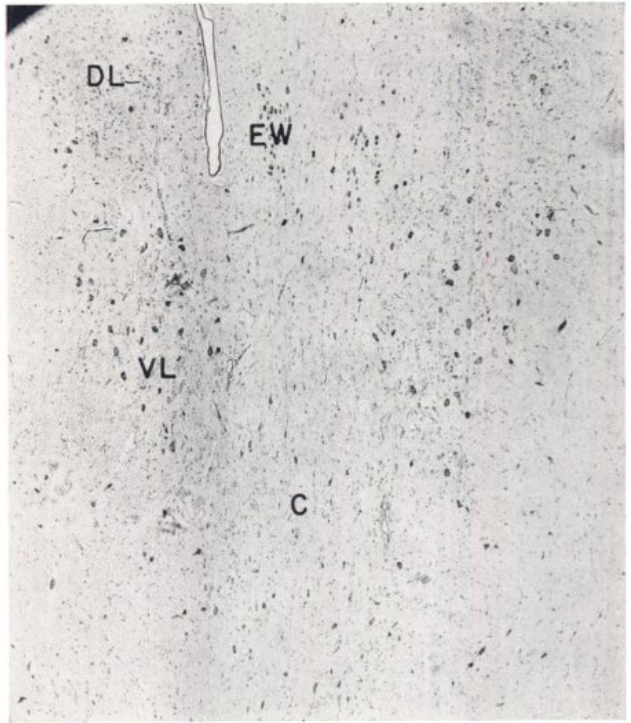

FIG. 4. The oculomotor nucleus, showing reduction in cells of various nuclei, particularly the dorsal lateral, ventral lateral, and central. C, central nucleus of Perlia; DL, dorsal lateral nucleus; EW, Edinger-Westphal nucleus; VL, ventral lateral nucleus. (Cresyl violet, × 45.)

"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.**"

Loken AC, Haymaker W. Pamaquine poisoning in man, with a clinicopathologic study of one case. The American journal of tropical medicine and hygiene. 1949;29(3):341-352. *Emphasis added.*

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JOURNAL OF NEUROPATHOLOGY & EXPERIMENTAL NEUROLOGY

VOLUME 10 JULY 1951 NUMBER 3

NEUROTOXICITY OF THE 8-AMINOQUINOLINES

III. THE EFFECTS OF PENTAQUINE, ISOPENTAQUINE, PRIMAQUINE, AND PAMAQUINE ON THE CENTRAL NERVOUS SYSTEM OF THE RHESUS MONKEY*†

IDA G. SCHMIDT, PH.D.
AND
L. H. SCHMIDT, PH.D.
[*Cincinnati, Ohio*]

"...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…."

Schmidt IG, Schmidt LH. Neurotoxicity of the 8-aminoquinolines. III. The effects of pentaquine, isopentaquine, primaquine, and pamaquine on the central nervous system of the rhesus monkey. Journal of neuropathology and experimental neurology. 1951;10(3):231–56. *Emphasis added.*

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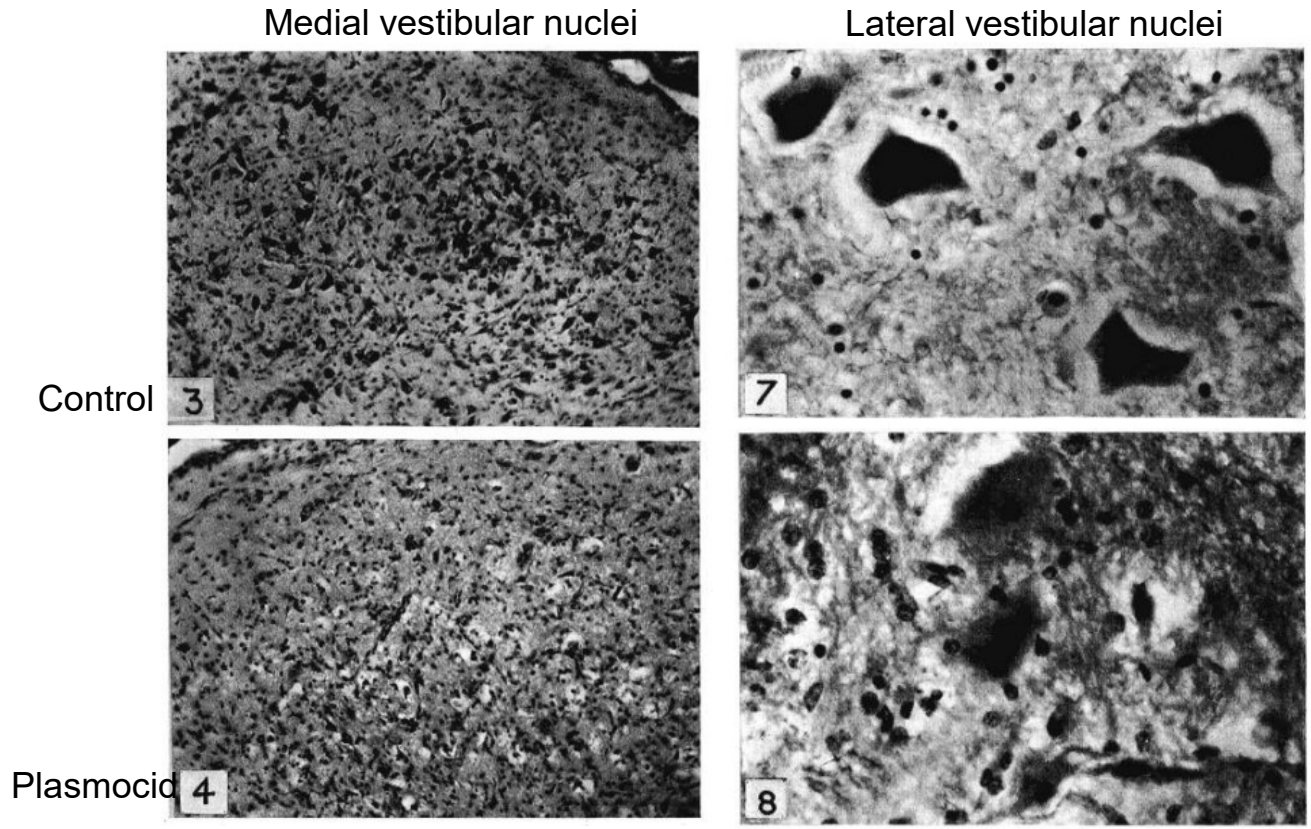

Schmidt IG, Schmidt LH. Neurotoxicity of the 8-aminoquinolines. I. Lesions in the Central Nervous System of the Rhesus Monkey Induced by Administration of Plasmocid. J Neuropathol Exp Neurol. 1948;7(4):368–98.

JOURNAL OF NEUROPATHOLOGY & EXPERIMENTAL NEUROLOGY

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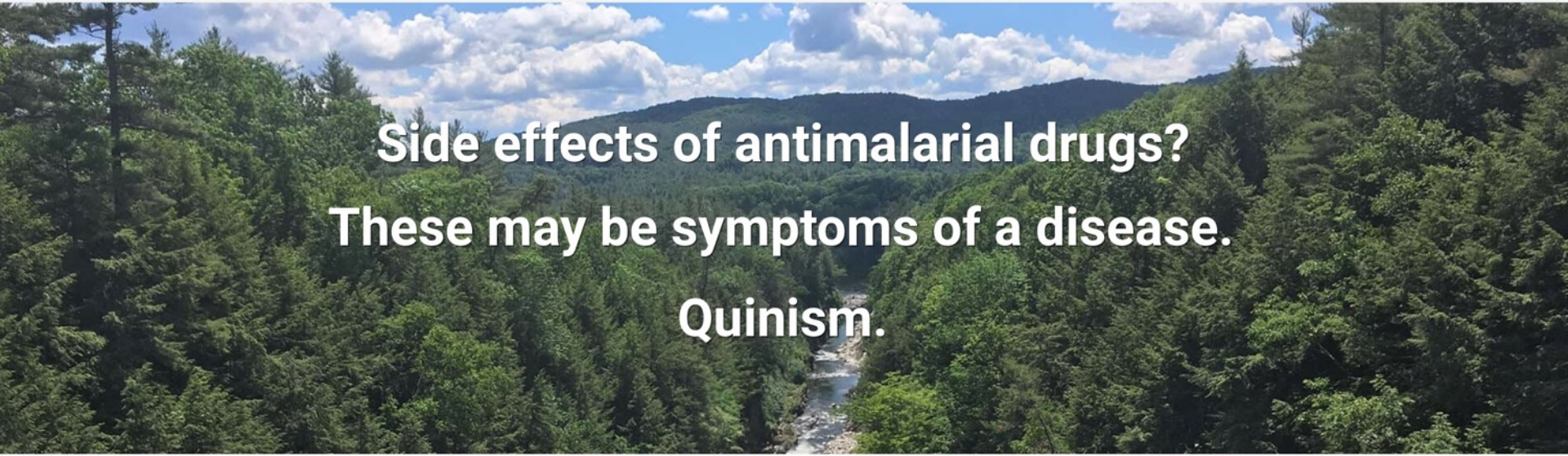
NEUROTOXICITY OF THE 8-AMINOQUINOLINES

III. THE EFFECTS OF PENTAQUINE, ISOPENTAQUINE, PRIMAQUINE, AND PAMAQUINE ON THE CENTRAL NERVOUS SYSTEM OF THE RHESUS 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.

Schmidt IG, Schmidt LH. Neurotoxicity of the 8-aminoquinolines. III. The effects of pentaquine, isopentaquine, primaquine, and pamaquine on the central nervous system of the rhesus monkey. J Neuropathol Exp Neurol. 1951;10(3):231-56.



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.

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