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
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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.

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.*

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.

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).

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.

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.

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.

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***
"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.

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.