Dr. Remington Lee Nevin
Certified in Public Health by the National Board of Public Health Examiners
and Board Certified in Public Health and General Preventive Medicine
by the American Board of Preventive Medicine

rnevin@remingtonnevin.com

Ronan Mulhall
Principal Officer, Litigation Branch
Department of Defence
Station Road, Newbridge
Co. Kildare, W12 AD93, Ireland
Email: ronan.mulhall@defence.ie

February 13, 2016

Dear Mr. Mulhall,

I refer to your correspondence from February 10, 2016 (Attachment 1), in which you advised that a Working Group led by your department is examining issues related to malaria chemoprophylaxis. You had advised further that you would accept material to be considered by the group. I am pleased to submit this brief report for the group's consideration.

1. Credentials and Professional Experience

The following information is provided to briefly establish my credentials and professional experience in this area. A full Curriculum Vitae is enclosed (Attachment 2). I earned a BSc (Honours) in Theoretical Physiology from the University of Toronto, Toronto, Canada; an MD from the Uniformed Services University of the Health Sciences, Bethesda, Maryland, where I was awarded the Captain Richard R. Hooper Award in Preventive Medicine; and an MPH from the Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, where I was elected an Alumni Inductee of the Delta Omega Honor Society, Alpha Chapter and was later recognized with an Outstanding Recent Graduate award. I attended residency training in Preventive Medicine at the Walter Reed Army Institute of Research where I was awarded the George Miller Sternberg Award in Preventive Medicine. I am licensed to practice medicine in the states of New York and Maryland and am board certified in Public Health and General Preventive Medicine by the American Board of Preventive Medicine. I am also Certified in Public Health by the National Board of Public Health Examiners.

In September 2012, I completed a 14 year career in the U.S. military that included overseas service in malaria-endemic areas of Afghanistan and Africa. During this time, I published over 40 scientific and medical publications, including 8 peer-reviewed manuscripts and 11 letters in scientific and medical journals specifically on the topics of mefloquine or malaria. This work, including a manuscript in the journal *Travel Medicine and Infectious Disease* that constituted the first clinical case description of a syndrome of toxic encephalopathy and neurotoxic central nervous system (CNS) injury resulting from prophylactic use of mefloquine, has broadly informed changing U.S. military policy on the use of mefloquine in the prevention of malaria. In June 2012, while on active duty, I testified to the U.S. Senate Appropriations Subcommittee on Defense on issues related to mefloquine CNS toxicity.

Since my leaving the U.S. military, I have co-authored the first manuscript in the psychiatric literature on the forensic application of claims of mefloquine CNS toxicity, which appears in the *Journal of the American Academy of Psychiatry and the Law*. I have also authored a book chapter in the U.S. Army's *Textbook of Military Medicine* series titled *Mefloquine and Posttraumatic Stress Disorder* (Attachment 3), and have co-authored a book chapter titled *The Mefloquine Intoxication Syndrome: A Significant Potential Confounder in the Diagnosis and Management of PTSD and Other Chronic Deployment-Related Neuropsychiatric Disorders*, which appears in the book *Post-Traumatic Stress Disorder and Related Diseases in Combat Veterans*, published by Springer International. In January 2013 I was invited by the Food and Drug Administration to speak to their Center for Drug Evaluation and Research on the clinical presentation and pharmacology of mefloquine CNS toxicity. I have also been extensively quoted in national and international media on topic of mefloquine.

I am presently a consulting physician epidemiologist based in Baltimore, Maryland, and am a doctoral student at the Johns Hopkins Bloomberg School of Public Health, where I have earned the certificate in Pharmacoepidemiology and Drug Safety and have been awarded the Gordis Teaching Fellowship and the Ali Kawi scholarship in the Department of Mental Health. I have taught undergraduate courses in Public Health Studies at the Johns Hopkins University Zanvyl Krieger School of Arts and Sciences and a graduate level course in the Department of Mental Health at the Johns Hopkins Bloomberg School of Public Health, each of which included lectures on mefloquine.

I am also the principal investigator on a $264,000 U.S. Army Medical Research and Materiel Command research grant entitled "MDR1 polymorphisms and risk of mefloquine anxiogenic adverse events". My current research focuses on the clinical presentation and pharmacology of mefloquine CNS toxicity, including its pathophysiology and genetic epidemiology.

Notwithstanding these affiliations, the opinions expressed in this report are my own and are not necessarily those of the Johns Hopkins University, the Public

Health Studies program of the Zanvyl Krieger School of Arts and Sciences, the Bloomberg School of Public Health, the U.S. Army Medical Research and Materiel Command, or the U.S. Army.

3. Policy Considerations for the Rational Use of Mefloquine in Military Settings

Use of mefloquine in military settings is problematic, and exposes militaries and military personnel to certain risks not encountered during most civilian use of the medication. Mefloquine is an idiosyncratic neurotoxicant and, unlike safer and better tolerated alternatives, exposes those prescribed the drug to a risk of chronic and even permanent neuropsychiatric sequelae resulting from the drug's neurotoxicity. As described in my book chapter *The Mefloquine Intoxication Syndrome: A Significant Potential Confounder in the Diagnosis and Management of PTSD and Other Chronic Deployment-Related Neuropsychiatric Disorders*, and my earlier chapter *Mefloquine and Posttraumatic Stress Disorder* (Attachment 3), these sequelae may confound the diagnosis and management of numerous deployment-related neuropsychiatric disorders, including posttraumatic stress disorder. Furthermore, in order to comply with recent strengthened drug label guidance for the correct use of the medication, militaries that choose to retain mefloquine for use as malaria chemoprophylaxis must ensure policies for use of the medication adhere to a number of requirements which may be impractical to implement and which may not fully eliminate risks associated with the continued use of the medication. Certain militaries, in consideration of these risks and requirements, have chosen to significantly reduce or eliminate use of mefloquine altogether. These considerations are outlined in greater detail in the recent peer-reviewed publication *Rational Risk-Benefit Decision-Making in the Setting of Military Mefloquine Policy* (Attachment 4).

I trust that the publications included as attachments will prove useful to the Working Group during their deliberations. I would be pleased to address specific questions that the group may have in response to this report, or to provide copies to the committee of other publications in my CV, upon written request.

Sincerely,

Remington Lee Nevin, MD, MPH

Attachments: as described

Attachment 1

An Roinn Cosanta
Department of Defence

10th February, 2016.

Dr. Remington Nevin, MD, MPH,
Department of Mental Health,
Johns Hopkins University,
[redacted]

Dear Dr. Nevin,

I refer to correspondence from Mr. Andrew Bryce to the Minister for Defence, in relation to a Working Group led by this Department which is examining issues relating to malaria chemoprophylaxis.

In his correspondence, Mr. Bryce indicated your interest in the work of the group. In that context, I wish to inform you that the working group is open to considering any material you might wish to bring to its attention. You may wish to note that Mr. Bryce did supply details of a number of your published papers and this has been brought to the attention of the group.

I would be grateful if you would indicate by email if you propose to submit any material to the group and in that event, I would ask that material be sent to me by 11th March, 2016.

Yours sincerely,

Ronan Mulhall,
Principal Officer,
Litigation Branch,
Department of Defence,
Station Road,
Newbridge,
Co. Kildare,
W12 AD93,
Ireland.
E-mail: ronan.mulhall@defence.ie

Attachment 2

Remington Lee Nevin, MD, MPH

[redacted]

rnevin@remingtonnevin.com

Current as of February 13, 2016

Education and Professional Training

2012-	Johns Hopkins University Bloomberg School of Public Health Baltimore, MD	DrPH Candidate Department of Mental Health
2012-2014	Johns Hopkins University Bloomberg School of Public Health Baltimore, MD	Certificate in Pharmacoepidemiology and Drug Safety
2003-2005	Walter Reed Army Institute of Research, Washington, DC	Residency in Public Health and General Preventive Medicine
2003-2004	Johns Hopkins University Bloomberg School of Public Health Baltimore, MD	MPH
2002-2003	Womack Army Medical Center Ft. Bragg, NC	Internship
1998-2002	Uniformed Services University of the Health Sciences Bethesda, MD	MD
1995-1998	University of Toronto University College Toronto, Ontario, Canada	BSc (Hon) with High Distinction Majors in Physics & Physiology, Minor in Mathematics

Professional Licensure

2012-	Medicine and Surgery	Maryland State License #D73583
2003-	Medicine and Surgery	New York State License #229259

Board Certification

2015-	Certified in Public Health	National Board of Public Health Examiners
2006-	Public Health and General Preventive Medicine	American Board of Preventive Medicine

Academic Awards and Honors

2014 Outstanding Recent Graduate Award
Johns Hopkins University Alumni Association

Dr. Ali Kawi Scholarship, Department of Mental Health
Johns Hopkins University, Bloomberg School of Public Health

Gordis Teaching Fellowship
Johns Hopkins University, Zanvyl Krieger School of Arts and Sciences

2013 Dr. Ali Kawi Scholarship, Department of Mental Health
Johns Hopkins University, Bloomberg School of Public Health

Gordis Teaching Fellowship
Johns Hopkins University, Zanvyl Krieger School of Arts and Sciences

2012 Dr. Ali Kawi Scholarship, Department of Mental Health
Johns Hopkins University, Bloomberg School of Public Health

2011 Alumni Inductee, Delta Omega Honor Society, Alpha Chapter
Johns Hopkins University, Bloomberg School of Public Heath

2005 George Miller Sternberg Medal in Preventive Medicine
Walter Reed Army Institute of Research

2002 Captain Richard R. Hooper Award in Preventive Medicine
Uniformed Services University of the Health Sciences

2000 Distinguished Academic Performance Award in Preventive Medicine
Uniformed Services University of the Health Sciences

1997 R. L. Burton Scholarship in Mathematics and Physical Sciences
University of Toronto, University College

Teaching

2016 Johns Hopkins University, Zanvyl Krieger School of Arts and Sciences
Public Health and U.S. Military Policy. AS.280.213 (Winter Intersession).

2015 Johns Hopkins University, Bloomberg School of Public Health
Current Issues in Military Mental Health (with Peter Zandi).
PH.330.659 (Summer Institute).

2014 Johns Hopkins University, Zanvyl Krieger School of Arts and Sciences
U.S. Military Policy and Public Health. AS.280.406 (Fall Term).

Johns Hopkins University, Bloomberg School of Public Health
Current Issues in Military Mental Health (with Peter Zandi).
PH.330.659 (Summer Institute).

Johns Hopkins University, Zanvyl Krieger School of Arts and Sciences
U.S. Military Policy and Public Health. AS.280.406 (Spring Term).

2013 Johns Hopkins University, Zanvyl Krieger School of Arts and Sciences
U.S. Military Policy and Public Health: The Consequences of Conflict.
AS.280.406 (Fall Term).

Academic Committee Service

2014-2015 **DrPH Executive Committee**
Johns Hopkins University, Bloomberg School of Public Health.

Military Service

2010-2012 **Preventive Medicine Physician**
Bayne-Jones Army Community Hospital, Fort Polk, LA.

2008-2009 **Preventive Medicine Officer**
360th Civil Affairs Brigade, United States Africa Command, Combined Joint Task Force Horn of Africa (CJTF-HOA), Camp Lemonnier, Djibouti.

2008 **Preventive Medicine Officer**
18th Medical Command, US Army Garrison Yongsan, Seoul, Korea.

2007-2008 **Preventive Medicine Officer**
Armed Forces Health Surveillance Center, Silver Spring, MD.

2007 **Preventive Medicine Officer**
International Security and Assistance Force (ISAF) Regional Command East (RC-E), Combined Joint Task Force 82 (CJTF-82), Bagram Airfield, Afghanistan.

2005-2006 **Preventive Medicine Officer**
Army Medical Surveillance Activity, Directorate of Epidemiology and Disease Surveillance, US Army Center for Health Promotion and Preventive Medicine, Washington, DC.

Public Testimony

2015 UK Parliament. Defence Committee. *An Acceptable Risk? The Use of Lariam for Military Personnel*. Tuesday, December 8, 2015. The Wilson Room, Portcullis House, London, UK.

2012 U.S. Senate. Appropriations Defense Subcommittee. *Outside Witnesses: Mefloquine Research*. Wednesday, June 6, 2012. Dirksen Senate Office Building Room 162, Washington, DC.

Grants and Research Funding

2010	$264K	Department of Defense Fiscal Year 2010 Defense Medical Research Development Program, *MDR1 Polymorphisms and Risk of Anxiogenic Mefloquine Adverse Events. MRMC* #D61-I-10-J5-121
2006	$1.919M	Department of Defense Global Emerging Infectious Disease Surveillance and Response System (DoD-GEIS), *Pandemic Influenza Surveillance Supplemental Funding.*
	$20K	Department of Defense Military Vaccine Agency, *Measles/Mumps/Rubella Immunity Concordance.*
2005	$4.5K	Department of Defense Military Vaccine Agency, *Mumps Screening Cost-Effectiveness*.
	$20K	Department of Defense Military Vaccine Agency, *Hepatitis A Seroprevalence.*

Peer Review

2016 **Journal Reviewer**: American Journal of Tropical Medicine and Hygiene; Disaster Medicine and Public Health Preparedness.

2015 **Journal Reviewer**: American Journal of Infection Control; American Journal of Preventive Medicine; American Journal of Public Health; American Journal of Tropical Medicine and Hygiene; Clinical Case Reports; Journal of Cerebral Blood Flow & Metabolism. **Abstract Reviewer**: American College of Preventive Medicine, 2016 Annual

Meeting; International Society for Pharmacoepidemiology 2016 Mid-Year Meeting.

2014 **Journal Reviewer**: American Journal of Bioethics Neuroscience; American Journal of Infection Control; American Journal of Public Health; Military Medicine. **Abstract Reviewer**: American College of Preventive Medicine, 2015 Annual Meeting.

2013 **Journal Reviewer:** American Journal of Infection Control; American Journal of Tropical Medicine and Hygiene; Military Medicine; Paediatrics and International Child Health. **Abstract Reviewer**: American College of Preventive Medicine, 2014 Annual Meeting.

2012 **Journal Reviewer**: American Journal of Infection Control; American Journal of Public Health; Journal of the Neurological Sciences; Military Medicine. **Abstract Reviewe**r: American College of Preventive Medicine, 2013 Annual Meeting.

2011 **Journal Reviewer**: American Journal of Infection Control; Journal of Infection and Public Health.

2010 **Journal Reviewer**: American Journal of Infection Control; American Journal of Tropical Medicine and Hygiene; BMC Medical Research Methodology; Emerging Infectious Diseases; The Lancet; Lancet Infectious Diseases.

2009 **Journal Reviewer:** American Journal of Public Health; American Journal of Tropical Medicine and Hygiene; Clinical Nursing Research; Military Medicine.

2008 **Journal Reviewer**: American Journal of Infection Control; American Journal of Public Health; American Journal of Tropical Medicine and Hygiene; Military Medicine.

2007 **Journal Reviewer**: American Journal of Public Health; Journal of Adolescent Health.

2006 **Abstract Reviewer**: International Society of Pharmacoeconomics and Outcomes Research, 11th International Meeting.

Peer-Reviewed Publications

2016 Sutcliffe S, **Nevin RL**, Pakpahan R, Elliot DJ, Langston ME, De Marzo AM, Gaydos CA, Isaacs WB, Nelson WG, Sokoll LJ, Walsh PC, Zenilman JM, Cersovsky SB, Platz EA. Infectious Mononucleosis, Other Infections, and Prostate-Specific Antigen Concentration as a Marker of Prostate Involvement During Infection. *Int J Cancer.* 2016. *In press.*

Wicken C, **Nevin RL**, Ritchie EC. U.S. Military Surveillance of Mental Health Disorders, 1998-2013. *Psychiatr Serv.* 2016;67(2):248-251.

2015 **Nevin RL**. Rational Risk-Benefit Decision-Making in the Setting of Military Mefloquine Policy. *J Parasitol Res.* 2015;2015:260106.

Maxwell N, **Nevin RL**, Stahl S, Block J, Shugarts S, Wu A, Dominy S, Solano M, Kappelman-Culver S, Lee-Messer C, Maldonado J, Maxwell A. Prolonged Neuropsychiatric Effects Following Management of Chloroquine Intoxication with Psychotropic Polypharmacy. *Clin Case Rep.* 2015;3(6):379-387.

Chase R, **Nevin RL**. Population Estimates of Undocumented Incident Traumatic Brain Injuries Among Combat-Deployed U.S. Military Personnel. *J Head Trauma Rehabil.* 2015;30(1):E57-64.

2014 **Nevin RL**. A Memoir of Mefloquine Amnesia: A Review of "The Answer to the Riddle is Me" by David Stuart MacLean. *AJOB Neurosci*. 2014;s5(4):88-91.

Nevin RL. Idiosyncratic Quinoline Central Nervous System Toxicity: Historical Insights into the Chronic Neurological Sequelae of Mefloquine. *Int J Parasitol Drugs Drug Resist.* 2014;4(2):118-125.

2013 Cosby MT, Pimentel G, **Nevin RL**, Ahmed SF, Klena JD, Amir E, Younan M, Browning R, Sebeny P. Outbreak of H3N2 influenza at a US military base in Djibouti during the H1N1 pandemic of 2009. *PLOS One*. 2013;8(12):e82089.

Ritchie EC, Block J, **Nevin RL**. Psychiatric Side Effects of Mefloquine: Applications to Forensic Psychiatry. *J Am Acad Psychiatry Law*. 2013:41(2):224-235.

2012 Sutcliffe S, Pakpahan R, Sokoll LJ, Elliot DJ, **Nevin RL**, Cersovsky SB, Walsh PC, Platz EA. Prostate-Specific Antigen Concentration in Young Men: New Estimates and Review of the Literature. *BJU Int.* 2012;110(11):1627-1635.

Nevin RL. Mefloquine Gap Junction Blockade and Risk of Pregnancy Loss. *Biol Reprod.* 2012;87(3):65,1-9.

Nevin RL. Mass administration of the antimalarial drug mefloquine to Guantánamo detainees: A critical analysis. *Trop Med Int Health*. 2012;17(10):1281-1288.

Nevin RL. Limbic encephalopathy and central vestibulopathy caused by mefloquine: A case report. *Travel Med Infect Dis.* 2012;10(3):144-151.

2011 Eick AA, Faix DJ, Tobler SK, **Nevin RL**, Lindler LE, Hu Z, Sanchez JL, MacIntosh VH, Russell KL, Gaydos JC. Serosurvey of Bacterial and Viral Respiratory Pathogens among Deployed U.S. Service Members. *Am J Prev Med.* 2011;41(6):573-580.

Scher AI, Wu H, Tsao JW, Blom HJ, Feit P, **Nevin RL**, Schwab KA. MTHFR C677T Genotype as a Risk factor for Epilepsy Including Post-Traumatic Epilepsy in a Representative Military Cohort. *J Neurotrauma*. 2011;28(9):1739-1745.

Ollivier L, **Nevin RL**, Darar HY, Bougère J, Saleh M, Gidenne S, Maslin J, Anders D, Decam C, Todesco A, Khaireh BA, Ahmed AA. Malaria in the Republic of Djibouti, 1998-2009. *Am J Trop Med Hyg.* 2011;85(3):554-559.

Sutcliffe S, **Nevin RL**, Pakpahan R, Elliott DJ, Cole SR, De Marzo AM, Gaydos CA, Isaacs WB, Nelson WG, Sokoll LJ, Zenilman JM, Cersovsky SB, Platz EA. Prostate involvement during sexually transmitted infections as measured by prostate antigen concentration. *Br J Cancer*. 2011;105(5):602-605.

2010 Ollivier L, Decam C, Pommier de Santi V, Darar HY, Dia A, **Nevin RL**, Romand O, Bougère J, Deparis X, Boutin J. Gastrointestinal illnesses

among French forces deployed to the Republic of Djibouti: French military health surveillance, 2005-2009. *Am J Trop Med Hyg.* 2010;83(4):944-950.

Eick A, Ticehurst J, Tobler S, **Nevin R**, Lindler L, Hu Z, MacIntosh V, Jarman RG, Gibbons RV, Myint KSA, Gaydos J. Hepatitis E Seroprevalence and Seroconversion among U.S. Military Service Members Deployed to Afghanistan. *J Infect Dis.* 2010;202(9):1302-1308.

Nevin RL. Mefloquine prescriptions in the presence of contraindications: prevalence among U.S. military personnel deployed to Afghanistan, 2007. *Pharmacoepidemiol Drug Saf*. 2010;19(2):206-210.

2009 **Nevin RL**. Low validity of self-report in identifying recent mental health diagnosis among U.S. service members completing Pre-Deployment Health Assessment (PreDHA) and deployed to Afghanistan, 2007: a retrospective cohort study. *BMC Public Health*. 2009;9:376.

Nevin RL. Epileptogenic potential of mefloquine chemoprophylaxis: a pathogenic hypothesis. *Malar J.* 2009;8:188.

Nevin RL, Means GE. Pain and discomfort in deployed helicopter aviators wearing body armor. *Aviat Space Environ Med*. 2009;80(9):807-810.

Bobo WV, **Nevin R**, Greene E, Lacy TJ. The effect of psychiatric third-year rotation setting on academic performance, student attitudes, and specialty choice. *Acad Psychiatry*. 2009;33(2):105-111.

2008 **Nevin RL**, Carbonell I, Thurmond V. Device-specific rates of needlestick injury at a large military teaching hospital. *Am J Infect Control*. 2008;36(10):750-752.

Nevin RL, Shuping EE, Frick KD, Gaydos JC, Gaydos CA. Cost and effectiveness of chlamydia screening among male military recruits: Markov modeling of complications averted through notification of prior female partners. *Sex Transm Dis*. 2008;35(8):705-713.

Nevin RL, Silvestri JW, Hu Z, Tobler SK, Trotta RF. Suspected pulmonary tuberculosis exposure at a remote U.S. Army camp in northeastern Afghanistan, 2007. *Mil Med.* 2008;173(7):684-688.

Nevin RL, Pietrusiak PP, Caci JB. Prevalence of contraindications to mefloquine use among U.S. military personnel deployed to Afghanistan. *Malar J*. 2008;7:30.

Eick AA, Hu Z, Wang Z, **Nevin RL**. Incidence of mumps and immunity to measles, mumps and rubella among U.S. military recruits, 2000-2004. *Vaccine*. 2008;26(4):494-501.

2007 Knapik JJ, Jones SB, Darakjy S, Hauret K, **Nevin R**, Grier T, Jones B. Injuries and injury risk factors among members of the United States Army Band. *Am J Ind Med.* 2007;50(12):951-961.

Hsu L, **Nevin RL**, Tobler SK, Rubertone MV. Trends in overweight and obesity among 18-year-old applicants to the U.S. military, 1993-2006. *J Adolesc Health*. 2007;41(6):610-612.

Nevin RL, Niebuhr DW. Rising hepatitis A immunity in U.S. military recruits. *Mil Med*. 2007;172(7):787-793.

2006 Grabenstein JD, **Nevin RL**. Mass immunization programs: principles and standards. *Curr Top Microbiol Immunol*. 2006;304:31-51.

Nevin R, Niebuhr D, Frick K, Grabenstein J. Improving soldier care through outcomes research: The Accession Screening and Immunization Program. *U.S. Army Medical Department Journal*. 2006;30-38.

2000 Norwich KH, **Nevin R**. The information of a welcher Weg experiment. *Il Nuovo Cimento*. 2000;115B:1137-1147.

Book Chapters

2015 **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. *Post-Traumatic Stress Disorder and Related Diseases in Combat Veterans*. Basel, Switzerland: Springer; 2015:257-278.

Nevin RL. Mefloquine and Posttraumatic Stress Disorder. In: Ritchie EC, ed. *Forensic and Ethical Issues in Military Behavioral Health. Textbook of Military Medicine*. Washington, DC: Borden Institute Press; 2015:275-296.

Nevin RL. Issues in the Prevention of Malaria Among Women at War. In: Ritchie EC, Naclerio AL, eds. *Women at War.* London, England: Oxford University Press; 2015:93-119.

2006 Engler RJM, Martin BL, **Nevin RL**, Grabenstein JD. Immunizations for military trainees. In: DeKoning B, ed. *Textbook of Military Medicine: Recruit Medicine.* Washington, DC: Borden Institute Press; 2006:205-226.

Grabenstein JD, **Nevin RL**. Mass immunization programs: Principles and standards. In: Plotkin SA, ed. *Mass-Vaccination: Global Aspects – Progress and Obstacles*. Berlin, Germany: Springer-Verlag; 2006:31-51.

Letters

2016 **Nevin RL.** Bias in Military Studies of Mefloquine. *J. Travel Med.* 2016;23(2):tav028.

2015 **Nevin RL**. Unexpected Pharmacological and Toxicological Effects of Tafenoquine. *Occup Med*. 2015;65(5):417.

Nevin RL. Organic Depersonalization as a Chronic Sequela of Mefloquine Intoxication. *Psychosomatics*. 2015;56(1):103.

2013 **Nevin RL**, Ritchie EC. Suicides Among Military Personnel. *JAMA*. 2013;310(23):2563-2564.

Nevin RL. Letter to the Editor regarding: The Incidence of and Risk Factors for Emergence Delirium in U.S. Military Combat Veterans. *J Perianesth Nurs.* 2013;28(6):334-336.

Nevin RL, Caci J. Letter to the Editor regarding: Medical evacuations from Afghanistan during Operation Enduring Freedom, active and reserve components, U.S. Armed Forces, 7 October 2001-31 December 2012. *MSMR*. 2013;20(8):24.

2012 **Nevin RL**. Confounding and Bias in Studies of DMSS Vaccination Data. *Vaccine*. 2012;30(50):7146.

Nevin RL. Falling Rates of Malaria Among U.S. Military Service Members in Afghanistan Substantiate Findings of High Compliance with Daily Chemoprophylaxis. *Am J Trop Med Hyg*. 2012;87(5):957-958.

Nevin RL. Neuropharmacokinetic Heterogeneity of Mefloquine in Treatment of Progressive Multifocal Leukoencephalopathy. *Intern Med*. 2012;51(16):2257.

Nevin RL. Limitations of Post-Marketing Surveillance in the Analysis of Risk of Pregnancy Loss Associated with Maternal Mefloquine Exposure. *Clin Infect Dis.* 2012;55(8):1167-1168.

Nevin RL. Pharmacokinetic considerations in the repositioning of mefloquine for treatment of progressive multifocal leukoencephalopathy. *Clin Neurol Neurosurg.* 2012;114:1204-1205.

Nevin RL. Hallucinations and persecutory delusions in mefloquine-associated suicide. *Am J Forensic Med Pathol.* 2012;33(2):e8.

Nevin RL. Investigating Channel Blockers for the Treatment of Multiple Sclerosis: Considerations with Mefloquine and Carbenoxolone. *J Neuroimmunol*. 2012;243(1-2):106-107.

Nevin RL. Biased Measurement of Neuropsychiatric Adverse Effects of Pediatric Mefloquine Treatment. *Ped Infect Dis J.* 2012;31(1):102.

Nevin RL. Mefloquine Blockade of Connexin 36 and Connexin 43 Gap Junctions and Risk of Suicide. *Biol Psych*. 2012;71(1):e1-2.

2011 **Nevin RL**. Mefloquine Neurotoxicity and Gap Junction Blockade: Critical Insights in Drug Repositioning. *Neurotoxicology*. 2011;32(6):986-987.

Nevin RL. Mefloquine Blockade of Connexin 43 (Cx43) and Risk of Pregnancy Loss. *Placenta*. 2011;32(9):712.

Nevin RL. Mental Health Standards for Combat Deployment. *Psychiatr Serv.* 2011;62(7):805.

Nevin RL, Ollivier L. In Reply to: Acute Diarrheas Among French Soldiers in Djibouti. *Am J Trop Med Hyg*. 2011;84(1):175.

2010 **Nevin RL**. Reply to Authors: Active Tuberculosis and Recent Overseas Deployment in the U.S. Military. *Am J Prev Med.* 2010;39(6):e39-40.

2008 **Nevin RL**, Silvestri JW, Hu Z, Tobler SK, Trotta RF. Reply to Authors: Suspected Pulmonary Tuberculosis Exposure at a Remote U.S. Army Camp in Northeastern Afghanistan, 2007. *Mil Med.* 2008;173(12):xviii.

2005 Pablo KR, Rooks PD, **Nevin RL**. Benefits of Screening for Hepatitis B Immunity in Military Recruits. *J Infect Dis.* 2005;192(12):2180-2181.

Technical Publications

2005 **Nevin RL**. *The U.S. Army Accession Screening and Immunization Program.* Edgewood, MD: U.S. Army Center for Health Promotion and Preventive Medicine; November 18, 2005. Technical Guide #310.

Presentation and Poster Awards

2007 Finalist, TRICARE Innovations Awards. Demonstrating the feasibility and cost-effectiveness of serologic screening for recruit immunizations: The U.S. Army Accession Screening and Immunization Program General Leonard Wood Army Community Hospital (GLWACH) pilot implementation. 2007 TRICARE Conference; January 29, 2007; Washington, DC.

2006 Finalist, Captain Gregory Gray Award for Military Operational Research. An economic analysis of serologic screening prior to immunization of Navy enlisted accessions. 45th Navy Occupational and Preventive Medicine Workshop; March 18 to March 23, 2006; Norfolk, VA.

Posters

2014 **Nevin RL**. Historical insights into the neurotoxicity of the 8-aminoquinolines: Implications for the development of tafenoquine and for global malaria control efforts. Poster presented at: Johns Hopkins 2014 World Malaria Day Conference; April 25, 2014; Baltimore, MD.

2013 Maxwell NM, **Nevin RL**, Stahl T, Block J, Shugarts S, Wu A, Dominy S, Blanco M, Kappelman-Culver S, Lee-Messer, C, Maldonado J. A 16 Year old Girl with Acute and Prolonged Mental Status Changes following Chloroquine Toxicity and Polypharmacy: Utility of Personalized Pharmacogenetic Testing. Poster presented at: 2nd International Congress on Personalized Medicine; July 25 to July 28, 2013; Paris, France.

2011 **Nevin R**. Subcortical Encephalopathy and Central Vestibulopathy Associated With Prophylactic Mefloquine Use: A Case Report. Poster presented at: 60th Annual Meeting of the American Society of Tropical Medicine and Hygiene; December 4 to December 8, 2011; Philadelphia, PA.

Scher A, Wu H, Tsao J, Blom H, Feit P, **Nevin R**, Schwab K. MTHFR C677T Genotype as a Risk Factor for Epilepsy in a Representative Military Cohort. Poster presented at: 63rd Annual Meeting of the American Academy of Neurology; April 9 to April 16, 2011; Honolulu, HI.

2009 Jordan N, **Nevin R**, Allen A, Irish V, Gaydos J. Review of sexual health visits and well-woman exams among female military members deployed to Afghanistan. Poster presented at: 18th International Society for STD Research Meeting; June 28 to July 1, 2009; London, UK.

Jacobsmuhlen T, Gaydos C, Meyers M, Gaydos J, **Nevin R**, Foster A. Surveillance for Chlamydia trachomatis among female military personnel newly assigned to U.S. Forces Korea. Poster presented at: 18th International Society for STD Research Meeting; June 28 to July 1, 2009; London, UK.

2008 Eick A, Hu Z, **Nevin R**, Tobler S. Seroprevalence of influenza H1 and H3 antibody among U.S. military accessions. [Poster 32]. Presented at: 2008 International Conference on Emerging Infectious Diseases; March 16 to March 19, 2008; Atlanta, GA.

2007

Nevin RL, Carbonell IS, Miller SN, Thurmond VA, Tobler S. Device-specific rates of needlestick injury at Walter Reed Army Medical Center: Establishing baseline metrics for process improvement. Poster presented at: 10th Annual Force Health Protection Conference; August 7 to August 10, 2007; Louisville, KY.

Nevin RL, Means GE, Tobler S. Longer flight times as a risk factor for increased pain among deployed rotary-wing aviators. Poster presented at: 10th Annual Force Health Protection Conference; August 7 to August 10, 2007; Louisville, KY.

Nevin RL, Hu Z, Tobler S. Suspected pulmonary tuberculosis exposure at a remote U.S. Army camp in northeastern Afghanistan, 2007. Poster presented at: 10th Annual Force Health Protection Conference; August 7 to August 10, 2007; Louisville, KY.

Hsu LL, Martin CB, **Nevin RL**, Tobler S. Trends in overweight and obesity among 18-year-old applicants for U.S. military service, 1995-2006. Poster presented at: 10th Annual Force Health Protection Conference; August 7 to August 10, 2007; Louisville, KY.

Eick AA, Wang Z, Hu Z, **Nevin R**, Tobler SK. Serosurveillance for H5N1: Large-scale serological testing for H5N1 exposure among U.S. military service members deployed to Thailand, Indonesia, or Vietnam. Poster presented at: Options for the Control of Influenza VI Conference; June 17 to June 23, 2007; Toronto, Canada.

Knapik JJ, Jones SB, Darakjy S, **Nevin R**, Hauret KG, Canham-Chervak M, Jones BH. Musical athletes: Injuries and injury risk factors in the United States Army Band. Abstract in: *Med Sci Sports Exerc.* 2007;39(5 Supplement):S395. Poster presented at: 54th Annual Meeting of the American College of Sports Medicine; May 30 to June 2, 2007; New Orleans, LA.

Eick A, **Nevin RL**, Hu Z, Hughes H, Ford SM. Measles, mumps, and rubella immunity and concordance among U.S. military recruits, 2000-2004. Poster presented at: 46th Annual NEHC Occupational Health and Preventive Medicine Conference; March 17 to March 22, 2007; Norfolk, VA.

Hughes H, **Nevin RL**, Ford SM, Anderson RG. An economic analysis of the U.S. Army Accession Screening and Immunization Program (ASIP). [Poster 152]. Presented at: 41st National Immunization Conference (NIC); March 5 to March 8, 2007; Kansas City, MO.

Eick A, Wang Z, Hu Z, Tobler S, **Nevin R**, Rubertone M. Serosurveillance for avian and pandemic influenza: Utilizing the resources of the DoDSR and AMSA. Poster presented at: 2007 Seasonal and Pandemic Influenza Conference; February 1 to February 2, 2007; Crystal City, VA.

Nevin RL. First-time episodes of mental health specialty care resulting from Post-Deployment Health Reassessments (PDHRA): Analysis of health care utilization following screening and referral. Poster presented at: 2007 TRICARE Conference; January 29, 2007; Washington, DC.

Nevin RL, Hughes H, Rooks P, Pablo K. Demonstrating the feasibility and cost-effectiveness of serologic screening for recruit immunizations: The U.S. Army Accession Screening and Immunization Program General

Leonard Wood Army Community Hospital (GLWACH) pilot implementation. Poster presented at: 2007 TRICARE Conference; January 29, 2007; Washington, DC.

2006 **Nevin RL**, Hughes H, Ford SM, Anderson R, Eick A. Risk of mumps in foreign-born U.S. military recruits deferred MMR vaccination following serologic confirmation of measles and rubella immunity. [Poster 841]. Presented at: 44th International Meeting of the Infectious Diseases Society of America (IDSA); October 15, 2006; Toronto, Canada.

Nevin RL, Green DJ. Mental health specialty clinic referrals generated during the Post-Deployment Health Reassessment process: Numbers of referrals, referral completion rates, and resultant first-time use among active duty soldiers. Poster presented at: 9th Annual Force Health Protection Conference; August 5 to August 12, 2006; Albuquerque, NM.

Nevin RL, Agnew RP. Numbers of Post-Deployment Health Reassessment forms outstanding among deployed soldiers: Cost estimates and estimated credentialed health care provider time required for resolution. Poster presented at: 9th Annual Force Health Protection Conference; August 5 to August 12, 2006; Albuquerque, NM.

Nevin RL, Kong V, Taubman S, Ford SM. Rates of influenza-like illness among active duty servicemembers receiving live attenuated influenza virus vaccine-trivalent versus trivalent inactivated influenza vaccine during the 2005-2006 influenza season. Poster presented at: 9th Annual Force Health Protection Conference; August 5 to August 12, 2006; Albuquerque, NM.

Nevin RL, Gustave J, Ford SM. Mumps cases reported in the military healthcare system during the 2006 epidemic: Geospatial comparison of counts against historical baselines among active duty servicemembers and beneficiaries. Poster presented at: 9th Annual Force Health Protection Conference; August 5 to August 12, 2006; Albuquerque, NM.

Nevin RL. Economic analysis of Latent Tuberculosis (LTBI) screening in military recruits: QuantiFERON-TB Gold In-Tube (QFT-GIT) versus Tuberculin Skin Testing (TST). [Poster PIN4]. In: Contributed Poster Presentations. *Value in Health*. 2006;9(3):A154. Presented at: 11th International Meeting of the International Society for Pharmacoeconomics and Outcomes Research (ISPOR); May 21, 2006; Philadelphia, PA.

Rooks P, Pablo K, **Nevin R**. Demonstrating the feasibility and cost-effectiveness of serologic screening for recruit immunizations: The U.S. Army Accession Screening and Immunization Program General Leonard Wood Army Community Hospital pilot implementation. Poster presented at: 34th Annual Meeting of the Society of Armed Forces Medical Laboratory Scientists; March 26 to March 30, 2006; Reno, NV.

Nevin RL. An economic analysis of serologic screening prior to immunization of Navy enlisted accessions. Poster presented at: 45th Annual NEHC Occupational Health and Preventive Medicine Conference; March 18 to March 23, 2006; Norfolk, VA.

Nevin RL, Rubertone MV. Enabling improved DoD pandemic influenza preparedness: Capabilities of the proposed Armed Forces Health Surveillance Center (AFHSC). Presented at the 45th Annual NEHC

Occupational Health and Preventive Medicine Conference; March 18 to March 23, 2006; Norfolk, VA.

2005 **Nevin RL**, Niebuhr DW. Incremental cost-benefit of screening for Anti-HAV in mass screening and immunization programs: Results of a 2004 U.S. Army seroprevalence study. [Poster 176]. In: Abstracts. *Am J Trop Med Hygiene.* 2005;73(6 Supplement):59. Presented at: 54th Annual Meeting of the American Society of Tropical Medicine and Hygiene (ASTMH); December 13, 2005; Washington, DC.

Bennett JW, **Nevin RL**, Polhemus ME, Ogutu BR. Cost-effectiveness of empiric antimalarial treatment among febrile children aged 0-4 years in areas of high malaria endemicity. Poster presented at the DC Chapter of the American College of Physicians Meeting; November 4, 2005; Bethesda, MD.

Nevin RL, Niebuhr DW. Seroprevalence of hepatitis A antibodies among new enlisted accessions to the U.S. military in 2004. [Poster 1026]. Presented at: 43rd Annual Meeting of the Infectious Diseases Society of America (IDSA); October 8, 2005; San Francisco, CA.

Nevin RL, Niebuhr DW. Hepatitis A seroprevalence among young adults: Effects of ACIP immunization recommendations. [Poster #LB01]. In: Abstracts. *Annals of Epidemiology.* 2005;15(8):660. Accepted for presentation at: 2005 Meeting of the American College of Epidemiology (ACE); September 19, 2005; New Orleans, LA. (cancelled).

Nevin RL, Niebuhr DW, Frick KD. Mathematical modeling of occupational needlestick injury reduction in a U.S. Army mass immunization program through universal serologic screening for pre-existing immunity. [Poster 50443]. In: Poster Abstracts. *American Journal of Infection Control.* 2005;33(5):e139-140. Poster presented at: 32nd Annual Educational Conference and International Meeting of the Association for Professionals in Infection Control and Epidemiology (APIC); June 19, 2005; Baltimore, MD.

Nevin RL, Niebuhr DW, Frick KD. Cost-minimization analysis of serologic screening policy options for U.S. Army accession immunizations. [Poster PHP47]. In: Contributed Poster Presentations. *Value in Health*. 2005;8(3):436. Poster presented at: 10th International Meeting of the International Society for Pharmacoeconomics and Outcomes Research (ISPOR); May 16, 2005; Washington, DC.

1999 Norwich KH, **Nevin R**. The information of simple physical events. In: *Proceedings of the 25th Canadian Medical and Biological Engineering Conference.* London, Ontario, Canada; June 1999; p 72. Poster presented at: 25th Canadian Medical and Biological Engineering Conference; June 1999; London, Ontario, Canada.

Presentations

2015 **Nevin RL**, Ritchie EC. Mefloquine Intoxication In Clinical And Forensic Psychiatry. *Workshop 1763.* Presented at: 168th Annual Meeting of the American Psychiatric Association; May 20, 2015; Toronto, Canada.

2014 **Nevin RL***,* Ritchie EC. Mefloquine and the U.S. Military. Presented at: 2014 Annual Continuing Educational Meeting of the Association of

Military Surgeons of the United States; December 3, 2014; Washington, DC.

Nevin RL. Controversies Abound Around PTSD. *Workshop 5576*. Presented at: 167th Annual Meeting of the American Psychiatric Association; May 6, 2014; New York, NY.

Nevin RL. Anabolic Steroid and Supplement Use in the Military. *Workshop 5054*. Presented at: 167th Annual Meeting of the American Psychiatric Association; May 4, 2014; New York, NY.

Nevin RL. The Mefloquine Toxidrome in Clinical and Forensic Psychiatry. *Workshop 5072.* Presented at: 167th Annual Meeting of the American Psychiatric Association; May 3, 2014; New York, NY.

2013 **Nevin RL**. Mefloquine Neurotoxicity Plausibly Contributes to the Burden of PTSD, TBI, Suicide, and Violence within the U.S. Military. *Workshop 57*. Presented at: 166th Annual Meeting of the American Psychiatric Association; May 20, 2013; San Francisco, CA.

Nevin RL. Steroid Use and Consequences in the Military. *Workshop 83.* Presented at: 166th Annual Meeting of the American Psychiatric Association; May 20, 2013; San Francisco, CA.

Nevin RL. Controversies Around Posttraumatic Stress Disorder. *Workshop 73.* Presented at: 166th Annual Meeting of the American Psychiatric Association; May 20, 2013; San Francisco, CA.

Nevin RL. Violence and the American Soldier. *Workshop 40*. Presented at: 166th Annual Meeting of the American Psychiatric Association; May 19, 2013; San Francisco, CA.

2009 Jacobsmuhlen T, Gaydos C, Meyers M, Gaydos J, **Nevin R**, Foster A. Surveillance of chlamydia among female soldiers assigned to U.S. Forces Korea. Presented at: 2009 Force Health Protection Conference; August 18 to August 21, 2009; Albuquerque, NM.

Sutcliffe S, **Nevin RL**, Pakpahan P, Bruzek DJ, Cole SR, DeMarzo AM, Gaydos CA, Issaacs WB, Nelson WG, Sokoll LJ, Zenilman JM, Cersovsky SB, Platz EA. Prostate involvement during sexually transmitted infections as measured by prostate specific antigen concentration. In: *J.Urol* 2009;181 Apr (4 Supplement 1):64. Presented at: 2009 Annual Meeting of the American Urological Association; April 25 to April 30, 2009; Chicago, IL.

2008 **Nevin RL**, Shuping EE, Frick KD, Gaydos JC, Gaydos CA. Cost-effectiveness of chlamydia screening policies among male military recruits. Presented at: 2008 International Conference on Emerging Infectious Diseases; March 16 to March 19, 2008; Atlanta, GA.

2007 Eick A, Wang Z, Hu Z, **Nevin RL,** Tobler S. Seasonal and avian influenza: Seroprevalence among deployed servicemembers and new accessions. Presented at: 10th Annual Force Health Protection Conference; August 7 to August 10, 2007; Louisville, KY.

Nevin RL, Eick A, Tobler S. Biobanking and biosurveillance: The biologic foundation for the future of armed forces health surveillance. Presented at: 10th Annual Force Health Protection Conference; August 7 to August 10, 2007; Louisville, KY.

Nevin RL, Tobler S, Caci J, Johnson J. Hepatitis E outbreak in eastern Afghanistan, 2007: Risk of seroconversion among U.S. personnel and implications for vaccine development. Presented at: 10th Annual Force Health Protection Conference; August 7 to August 10, 2007; Louisville, KY.

Ford S, Hughes H, **Nevin RL**. Outcomes research for military vaccination policy: The U.S. Army Accession Screening and Immunization Program. Presented at: 12th International Meeting of the International Society for Pharmacoeconomics and Outcomes Research (ISPOR); May 21, 2007; Arlington, VA.

2006 **Nevin RL**, Shuping EE, Frick KD, Gaydos JC, Gaydos CA. Cost-effectiveness of chlamydia screening among male military recruits. In: *Chlamydial Infections: Proceedings of the Eleventh International Symposium on Human Chlamydial Infections.* International Chlamydia Symposium; San Francisco, CA; pp 477-480. Presented at: 11th International Symposium on Human Chlamydial Infections; June 18 to June 23, 2006; Niagara-on-the-Lake, Canada.

Nevin RL, Rubertone MV. Numbers and frequencies of specimens in the Department of Defense serum repository. Presented at: 2006 Annual Meeting of the International Society of Biologic and Environmental Repositories; May 1, 2006; Bethesda, MD.

Nevin RL. The U.S. Army Accession Screening and Immunization Program at Army training centers. Presented at: U.S. Army Training and Doctrine Command Initial Entry Training Soldier Care Conference; April 11, 2006; Hampton, VA.

Nevin RL. Improving the efficiency of accession medical processing: The MEPCOM role in screening. Presented at: 2nd Annual Joint Accessions Research & Best Practices Symposium; April 6, 2006; San Antonio, TX.

Nevin RL. An economic analysis of serologic screening prior to immunization of Navy enlisted accessions. Presented at: 45th Annual NEHC Occupational Health and Preventive Medicine Conference; 8th Operational Research Competition; March 18, 2006; Norfolk, VA.

2005 Bennett JW, **Nevin RL**, Polhemus ME. Cost-effectiveness of empiric antimalarial treatment among febrile children aged 0-4 years in areas of high malaria endemicity. Presented at: Army American College of Physicians Meeting; November 19, 2005; San Antonio, TX.

Nevin RL. The U.S. Army Accession Screening and Immunization Program: Implementation and directions for future research. Presented at: U.S. Army Accessions Command Accessions Research Consortium; October 20, 2005; Hampton, VA.

Nevin RL. Cost-effectiveness modeling of serologic screening policy options for U.S. Army accession immunizations: Implications for improving the efficiency of accession medical processing. Presented at: 1st Annual Accessions Training Research & Best Practices Symposium; August 25, 2005; Lincolnshire, IL.

Nevin RL, Niebuhr DW, Frick KD. Implementing cost-effective serologic screening for recruit immunizations: The U.S. Army Accession Screening and Immunization Program (ASIP) business plan. Presented at: 8th

Annual U.S. Army Center for Health Promotion and Preventive Medicine Force Health Protection Conference; August 12, 2005; Louisville, KY.

Nevin RL. Improving the efficiency of military accession immunization programs through centralized screening for pre-existing immunity among Department of Defense applicants at military entrance processing stations: Variable cost modeling of policy options. Presented at: 8th Annual U.S. Army Center for Health Promotion and Preventive Medicine Force Health Protection Conference; August 12, 2005; Louisville, KY.

Invited Talks

2014 **Nevin RL**. Central Nervous System Toxicity of Antiparasitic Quinolines. Presentation to the Johns Hopkins University School of Medicine, Department of Clinical Pharmacology; April 2, 2014: Baltimore, MD.

2013 **Nevin RL**. An Antimalarial Toxidrome? New Insights into the Psychiatric Adverse Effects of Mefloquine (Lariam®). Presentation to the Veterans Health Administration Northwest Mental Illness Research Education & Clinical Center; December 18, 2013. Online.

Nevin RL. Mefloquine and Special Forces: An Update. Presentation to the Green Beret Foundation Annual Board Meeting; November 9, 2013: Fayeteville, NC.

Nevin RL. Mefloquine limbic encephalopathy: a model of impulsive suicidality. Presentation to the James Kirk Bernard Foundation Science Planning Meeting; March 18, 2013: Denver, CO.

Nevin RL. Mefloquine neurotoxicity. Presentation to Food and Drug Administration, Office of the Commissioner/Office of Special Health Issues (OSHI); January 11, 2013: White Marsh, MD.

2011 **Nevin RL**. Neuropsychiatric adverse events associated with mefloquine. Presentation to the Special Operations Medical Association 2011 Annual Meeting; December 12, 2011; Tampa, FL.

Nevin RL. Neuropsychiatric adverse events associated with mefloquine. Presentation to the U.S. Army Special Operations Command Preventive Medicine Symposium; April 20, 2011. Fayetteville, NC.

2010 **Nevin RL**. Neuropsychiatric adverse events associated with mefloquine. Presentation to the Special Operations Medical Association 2010 Annual Meeting; December 16, 2010; Tampa, FL.

Nevin RL. The epidemiology of weaponized disease agent outbreaks. Presentation to the Uniformed Services Academy of Family Physicians 2010 Annual Meeting; February 24, 2010; New Orleans, LA.

2006 **Nevin RL**. Uses of the Department of Defense serum repository in support of vaccine-related studies: Case-control, cohort, and cross-sectional study designs. Presentation to the Johns Hopkins Bloomberg School of Public Health Department of International Health; October 5, 2006; Baltimore, MD.

Nevin RL. The U.S. Army Accession Screening and Immunization Program. Presentation to the Military Vaccine Agency (MILVAX) Annual Meeting; June 6, 2006; Arlington, VA.

Nevin RL. Advancing research in seroepidemiology: Visions for the future of the Department of Defense serum repository. Presentation to the National Institutes of Health Autoimmune Diseases Coordinating Committee, NIH; February 24, 2006; Rockville, MD.

2005 **Nevin RL**. The Department of Defense serum repository: Opportunities for seroepidemiolgic research utilizing the world's largest serum repository. Presentation to the Johns Hopkins Bloomberg School of Public Health Department of Epidemiology; October 31, 2005; Baltimore, MD.

Acknowledgements

2012 Wang Z, Chen F, Ward M, Bhattacharyya T. Compliance with Surgical Care Improvement Project Measures and Hospital-Associated Infections Following Hip Arthroplasty. *J Bone Joint Surg Am*. 2012;94(15):1359-1366.

2011 Hutfless S, Matos P, Talor MV, Caturegli P, Rose NR. Significance of Prediagnostic Thyroid Antibodies in Women with Autoimmune Disease. *J Clin Endocrin Metab*. 2011;96(9):e1466-71.

2009 Ollivier L, Romand O, Marimoutou C, Michel R, Pognant C, Todesco A, Migliani R, Baudon D, Boutin J. Use of short message service (SMS) to improve malaria chemoprophylaxis compliance after returning from a malaria endemic area. *Malar J*. 2009;8:236.

2007 Army Medical Surveillance Activity. Concordance of measles and rubella immunity with immunity to mumps; enlisted accessions, U.S. armed forces, 2000-2004. *MSMR*. 2007;13(2):10-12.

2006 Munger KL, Levin LI, Hollis BW, Howard NS, Ascherio A. Serum 25-hydroxyvitamin D levels and risk of multiple sclerosis. *JAMA*. 2006:296(23);2832-8.

Army Medical Surveillance Activity. Hepatitis A immunity among enlisted accessions to the U.S. Army, Fort Benning, GA, April-August 2006. *MSMR*. 2006;12(7):18-20.

Army Medical Surveillance Activity. Incidence of mumps in relation to universal MMR vaccination versus vaccination after serological screening of U.S. military recruits, 2000-2004. *MSMR*. 2006;12(7):21-23.

Army Medical Surveillance Activity. Hepatitis B immunity among U.S. Army basic trainees, Fort Leonard Wood, MO, July 2005-December 2005. *MSMR*. 2006;12(5):7-8.

Attachment 3

Chapter 19

MEFLOQUINE AND POSTTRAUMATIC STRESS DISORDER

REMINGTON L. NEVIN, MD, MPH*

**Doctoral Student, Johns Hopkins Bloomberg School of Public Health, Department of Mental Health, 624 North Broadway, Room 782, Baltimore, Maryland 21205; formerly Major, Medical Corps, US Army*

INTRODUCTION

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

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

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

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

THE DEVELOPMENT OF MEFLOQUINE

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

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

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

THE HISTORY OF MEFLOQUINE USE IN US MILITARY POPULATIONS

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

CLINICAL FEATURES OF MEFLOQUINE INTOXICATION

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

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

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

CHRONIC EFFECTS OF MEFLOQUINE TOXICITY

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

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

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

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

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

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

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

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

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

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

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

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

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

FORENSIC APPLICATIONS

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

SUMMARY

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

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

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

DISCLOSURES

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

REFERENCES

1. Toovey S. Mefloquine neurotoxicity: a literature review. *Travel Med Infect Dis*. 2009;7:2–6.
2. Thomas K. FDA strengthens warnings on Lariam, an anti-malaria drug. *New York Times*. July 29, 2013. http://www.nytimes.com/2013/07/30/business/fda-strengthens-warnings-on-lariam-anti-malaria-drug.html. Accessed May 20, 2014.
3. Ritchie EC, Block J, Nevin RL. Psychiatric side effects of mefloquine: applications to forensic psychiatry. *J Am Acad Psychiatry Law*. 2013;41:224–235.
4. Rendi-Wagner P, Noedl H, Wernsdorfer WH, Wiedermann G, Mikolasek A, Kollaritsch H. Unexpected frequency, duration and spectrum of adverse events after therapeutic dose of mefloquine in healthy adults. *Acta Trop*. 2002;81:167–173.
5. Andersson H, Askling HH, Falck B, Rombo L. Well-tolerated chemoprophylaxis uniformly prevented Swedish soldiers from Plasmodium falciparum malaria in Liberia, 2004–2006. *Mil Med*. 2008;173:1194–1198.
6. F Hoffmann-La Roche Ltd. Lariam Product Insert. Australia. January 2012.
7. F Hoffmann-La Roche Ltd. Lariam Product Insert. Ireland. July 2013.
8. F Hoffmann-La Roche Ltd. Lariam Guide to Healthcare Professionals. July 2013.
9. F Hoffmann-La Roche Ltd. Lariam Dear Healthcare Professional Letter. Ireland. July 2013. http://www.imb.ie/images/uploaded/documents/Lariam DHCP FINAL 01.07.13.pdf. Accessed May 20, 2014.
10. Magill A, Cersovsky S, DeFraites R. Special considerations for US military deployments. In: *Centers for Disease Control and Prevention Yellow Book - Travelers' Health*. Chapter 8. Atlanta, GA: Centers for Disease Control and Prevention; 2012.
11. Nevin RL. Mefloquine prescriptions in the presence of contraindications: prevalence among US military personnel deployed to Afghanistan, 2007. *Pharmacoepidemiol Drug Saf*. 2010;19:206–210.
12. Ohnmacht CJ, Patel AR, Lutz RE. Antimalarials. 7. Bis(trifluoromethyl)-(2-piperidyl)-4-quinolinemethanols. *J Med Chem*. 1971;14:926–928.
13. Ainley AD, King H. Antiplasmodial action and chemical constitution. Part II. Some simple synthetic analogues of quinine and cinchonine. *Proceedings of the Royal Society of London. Series B, Biological Sciences*. 1938;125:60–92.
14. Berliner RW, Blanchard KC, Butler TC, et al. Tables. In: Wiselogle FY, ed. *A Survey of Antimalarial Drugs, 1941–194*5. Vol 2, Part 2. Ann Arbor, MI: Edwards Brothers; 1946:988–1921.
15. Mosher HS. *Antimalarials: Natural and Synthetic. Confidential Report.* Ann Arbor, MI: Edwards Brothers; 1942.
16. Clark WM. History of the co-operative wartime program. In: Wiselogle FY, ed. *A Survey of Antimalarial Drugs, 1941–1945*. Vol 1. Ann Arbor, MI: Edwards Brothers; 1946:2–57.

17. Berliner RW, Butler TC. Summary of data on the drugs tested in man. In: Wiselogle FY, ed. *A Survey of Antimalarial Drugs, 1941–1945*. Vol 1. Ann Arbor, MI: Edwards Brothers; 1946:221–451.

18. Loken AC, Haymaker W. Pamaquine poisoning in man, with a clinicopathologic study of one case. *Am J Trop Med Hyg*. 1949;29:341–52.

19. Schmidt LH, Crosby R, Rasco J, Vaughan D. Antimalarial activities of various 4-quinolonemethanols with special attention to WR-142,490 (mefloquine). *Antimicrob Agents Chemother*. 1978;13:1011–1030.

20. Coatney GR. Pitfalls in a discovery: the chronicle of chloroquine. *Am J Trop Med Hyg*. 1963;12:121–128.

21. Tigertt WD. The army malaria research program. *Ann Intern Med*. 1969;70:150–153.

22. Modell W. Malaria and victory in Vietnam: the first battle against drug-resistant malignant malaria is described. *Science*. 1968;162:1346–1352.

23. Rieckmann KH, Trenholme GM, Williams RL, Carson PE, Frischer H, Desjardins RE. Prophylactic activity of mefloquine hydrochloride (WR 142 490) in drug-resistant malaria. *Bull World Health Organ*. 1974;51:375–377.

24. Trenholme CM, Williams RL, Desjardins RE, et al. Mefloquine (WR 142,490) in the treatment of human malaria. *Science*. 1975;190:792–794.

25. Quintanilla J. Psychosis due to quinidine intoxication. *Am J Psychiatry*. 1957;113:1031–1032.

26. Krüger E, Grube M, Hartwich P. [Acute paranoid hallucinatory psychosis following mefloquine prophylaxis (Lariam)]. *Psychiatrische Praxis*. 1999;26:252–254.

27. Good MI, Shader RI. Behavioral toxicity and equivocal suicide associated with chloroquine and its derivatives. *Am J Psychiatry*. 1977;134:798–801.

28. Kiel FW. Chloroquine suicide. *JAMA*. 1964;190:398–400.

29. Maugh TH. Malaria drugs: new ones are available, but little used. *Science*. 1977;196:415.

30. Reba RC. Report Number 1. *Phase I Clinical Testing Antimalarial Drugs Annual Report*. ADA044243, contract DAMD-17-75-C-5036. College Park, MD: 1977.

31. Reba RC, Barry KG, Altstatt LB. *Army Drug Development Program Phase I Clinical Testing Annual and Final Report*. College Park, MD: 1983. Contract DAMD17-75-C-5036.

32. Canfield CJ, Rozman RS. Clinical testing of new antimalarial compounds. *Bull World Health Organ*. 1974;50:203–212.

33. Rieckmann KH, Powell RD, McNamara JV, et al. Effects of tetracycline against chloroquine-resistant and chloroquine-sensitive Plasmodium falciparum. *Am J Trop Med Hyg*. 1971;20:811–815.

34. F Hoffmann LaRoche Ltd. New Drug Application 19-591: Lariam. 1989.

35. Boudreau E, Schuster B, Sanchez J, et al. Tolerability of prophylactic Lariam regimens. *Trop Med Parasitol*. 1993;44:257–265.

36. Arthur JD, Shanks GD, Echeverria P. Mefloquine prophylaxis. *Lancet*. 1990;335:972.

37. Department of Defense. Armed Forces Epidemiological Board. *Recommendations on Mefloquine Chemoprophylaxis for Military Personnel*. Falls Church, VA: DoD; 1989.

38. Benjamin M, Olmsted D. VA alerts doctors to malaria-drug concerns. *United Press International*. 2004. http://www.upi.com/Business_News/Security-Industry/2004/06/24/VA-alerts-doctors-to-malaria-drug-concerns/UPI-38131088119375/. Accessed May 20, 2014.

39. Lobel HO, Bernard KW, Williams SL, Hightower AW, Patchen LC, Campbell CC. Effectiveness and tolerance of long-term malaria prophylaxis with mefloquine: need for a better dosing regimen. *JAMA*. 1991;265:361–364.

40. Food and Drug Administration Anti-Infective Drugs Advisory Committee. *Transcript of Anti-Infective Drugs Advisory Committee Meeting #41, October 31-November 1, 1991*. Rockville, MD: FDA; 1991.

41. Llewellyn CH. Command responsibilities in maintaining troop health (Fig 1-4). In: Kelley PW, ed. *Military Preventive Medicine: Mobilization and Deployment* (Volume 1). Washington, DC: Borden Institute; 2003:14–15.

42. Warsame M, Lebbad M, Ali S, Wernsdorfer WH, Björkman A. Susceptibility of Plasmodium falciparum to chloroquine and mefloquine in Somalia. *Trans R Soc Trop Med Hyg.* 1988;82:202–204.

43. Warsame M, Wernsdorfer WH, Willcox M, Kulane AA, Björkman A. The changing pattern of Plasmodium falciparum susceptibility to chloroquine but not to mefloquine in a mesoendemic area of Somalia. *Trans R Soc Trop Med Hyg.* 1991;85:200–203.

44. Wallace MR, Sharp TW, Smoak B, et al. Malaria among United States troops in Somalia. *Am J Med*. 1996;100:49–55.

45. Joellenbeck LM, Russell PK, Guze SB, Institute of Medicine. *Strategies to Protect the Health of Deployed US Forces: Medical Surveillance, Record Keeping, and Risk Reduction*. Washington, DC: The National Academies Press; 1999. http://www.nap.edu/catalog/9711.html. Accessed May 20, 2014.

46. Gullahorn GM, Bohman HR, Wallace MR. Anaesthesia emergence delirium after mefloquine prophylaxis. *Lancet.* 1993;341:632.

47. Smoak BL, Writer JV, Keep LW, Cowan J, Chantelois JL. The effects of inadvertent exposure of mefloquine chemoprophylaxis on pregnancy outcomes and infants of US Army servicewomen. *J Infect Dis*. 1997;176:831–833.

48. Magill AJ, Smoak BL. Failure of mefloquine chemoprophylaxis for malaria in Somalia. *NEJM*. 1993;329:1206.

49. Armed Forces Epidemiological Board. *Transcript of Winter Meeting, February 18, 2004*. Falls Church, VA: AFEB; 2004.

50. Sánchez JL, DeFraites RF, Sharp TW, Hanson RK. Mefloquine or doxycycline prophylaxis in US troops in Somalia. *Lancet.* 1993;341:1021–1022.

51. Recasens C, Zittoun C, Féline A. A psychotic episode in a patient coming home from Africa: the possible role of mefloquine. *Ann Psychiatry.* 1993;8:100–103.

52. Benjamin M, Olmsted D. Army Fort Bragg study faces scrutiny. *United Press International*. November 8, 2002.

53. Benjamin M, Olmsted D. UPI investigates: Lariam and suicide. *United Press International*. May 22, 2002.

54. Burke BM. Mefloquine. *Lancet.* 1993;341:1605–1606.

55. Jones R, Kunsman G, Levine B, Smith M, Stahl C. Mefloquine distribution in postmortem cases. *Forensic Sci Int*. 1994;68:29–32.

56. Benjamin M, Olmsted D. Army had 1996 Lariam warning. *United Press International*. August 22, 2002. http://www.upi.com/Top_News/2002/08/22/Army-had-1996-Lariam-warning/UPI-63031030060809/. Accessed May 20, 2014.

57. Kotwal RS, Wenzel RB, Sterling RA, Porter WD, Jordan NN, Petruccelli BP. An outbreak of malaria in US Army Rangers returning from Afghanistan. *JAMA*. 2005;293:212–216.

58. Benjamin M, Olmsted D. Malaria drug warning follows problems. *United Press International*. July 10, 2003. http://www.upi.com/Business_News/Security-Industry/2003/07/10/Malaria-drug-warning-follows-problems/UPI-84261057867715/. Accessed May 20, 2014.

59. Kranish M. Army studies medication link in killings. *Boston Globe*. August 31, 2002.

60. Another soldier charged in wife's death kills self. *Los Angeles Times*. March 24, 2013. http://articles.latimes.com/2003/mar/24/nation/na-briefs24.2/. Accessed May 20, 2014.

61. Kohn D. The dark side of Lariam. *60 Minutes II.* January 27, 2003. http://www.cbsnews.com/news/the-dark-side-of-lariam/. Accessed May 20, 2014.

62. Office of The Surgeon General. *Fort Bragg Epidemiological Consultation Report, October 18, 2002*. Falls Church, VA: US Army OTSG; 2002.

63. Fleet M, Mann J. Military's use of malaria drug in question. *CNN.com.* May 20, 2004. http://www.cnn.com/2004/HEALTH/05/19/lariam/. Accessed May 20, 2014.

64. Hettena S. Worry spreads over GI drug side effects. *Associated Press*. February 13, 2005.

65. Associated Press. Hallucinations linked to drug given to troops. *MSNBC.com.* February 14, 2005. http://www.nbcnews.com/id/6947472/ns/health-mental_health/t/hallucinations-linked-drug-given-troops/. Accessed May 20, 2014.

66. Responses to UPI-CNN Lariam investigation. *United Press International*. September 7, 2004. http://www.upi.com/Business_News/Security-Industry/2004/09/07/Responses-to-UPI-CNN-Lariam-investigation/UPI-13621094601600/. Accessed May 20, 2014.

67. Benjamin M. Army sent mentally ill troops to Iraq. *United Press International*. March 12, 2004. http://www.upi.com/Business_News/Security-Industry/2004/03/12/Army-sent-mentally-ill-troops-to-Iraq/UPI-97331079131967/. Accessed May 20, 2014.

68. Heath M. *Deployment Medication Use and Pharmacy Data*. Presentation to the Mefloquine Adverse Events Study Design Options Panel Armed Forces Epidemiological Board Select Subcommittee. April 12, 2004.

69. Benjamin M, Olmsted D. Exclusive: Army surrenders to "coward" GI. *United Press International*. July 16, 2004. http://www.upi.com/Business_News/Security-Industry/2004/07/16/Exclusive-Army-surrenders-to-coward-GI/UPI-51631089996907. Accessed May 20, 2014.

70. Brant M. War stories: drugging the troops. *Newsweek.* January 9, 2004.

71. Benjamin M, Olmsted D. Army gave Congress bad data on suicides. *United Press International*. September 7, 2004. http://www.upi.com/Business_News/Security-Industry/2004/09/07/Army-gave-Congress-bad-data-on-suicides/UPI-29821094601600/. Accessed May 20, 2014.

72. Williams M. *Pharmacy Prescription Data*. Presentation to the Mefloquine Adverse Events Study Design Options Panel Armed Forces Epidemiological Board Select Subcommittee. April 12, 2004.

73. 108th Congress. Hearing on National Defense Authorization Act for Fiscal Year 2005 - HR 4200. February 25, 2004. http://commdocs.house.gov/committees/security/has056270.000/has056270_0f.htm. Accessed May 20, 2014.

74. Office of The Surgeon General. *Updated Health Care Provider Information on Use of Mefloquine Hydrochloride for Malaria Prophylaxis*. Washington, DC: Department of the Army; 2002. Memorandum.

75. Overbosch D, Schilthuis H, Bienzle U, et al. Atovaquone-proguanil versus mefloquine for malaria prophylaxis in nonimmune travelers: results from a randomized, double-blind study. *Clin Infect Dis.* 2001;33:1015–1021.

76. Benjamin M, Olmsted D. Army won't review medication in suicides. *United Press International*. January 29, 2004. http://www.upi.com/Business_News/Security-Industry/2004/01/29/Army-wont-review-medication-in-suicides/UPI-57551075401578/. Accessed May 20, 2014.

77. Laskas JM. The coward. *Gentleman's Quarterly*. 2004;74:106.

78. Kime P. Medical journal rejected drug danger case study in '02. *Army Times*. May 14, 2012:12.

79. Peterson AL, Seegmiller RA, Schindler LS. Severe neuropsychiatric reaction in a deployed military member after prophylactic mefloquine. *Case Rep Psychiatry*. 2011;2011:350–417.

80. Benjamin M, Olmsted D. Exclusive: Green Beret's strange suicide. *United Press International*. May 11, 2004. http://www.upi.com/Business_News/Security-Industry/2004/05/11/Exclusive-Green-Berets-strange-suicide/UPI-71431084296160/. Accessed May 20, 2014.

81. Office of the Assistant Secretary of Defense (Health Affairs). *Letter to Chairman John McHugh and Report of the Interagency Working Group for Antimalarial Chemotherapy*. Washington, DC; OASDHA; 2002.

82. Whitman TJ, Coyne PE, Magill AJ, et al. An outbreak of Plasmodium falciparum malaria in US Marines deployed to Liberia. *Am J Trop Med Hyg*. 2010;83:258–265.

83. McNeil DG. Officials say malarial marines didn't take medication properly. *The New York Times*. December 3, 2003. http://www.nytimes.com/2003/12/05/us/officials-say-malarial-marines-didn-t-take-medication-properly.html. Accessed May 20, 2014.

84. Armed Forces Epidemiological Board. *Armed Forces Epidemiological Board (AFEB) Select Subcommittee to Develop Mefloquine Study Options*. The Surgeon General, US Department of the Army; The Surgeon General, US Department of the Navy; The Surgeon General, Department of the Air Force, Memorandum to the Assistant Secretary of Defense (Health Affairs), May 21, 2004. http://www.pdhealth.mil/AFEBMemorandum.pdf. Accessed May 20, 2014.

85. Benjamin M, Olmsted D. Feinstein to Rumsfeld: review malaria drug. *United Press International*. November 5, 2003.

86. Combined Joint Task Force Seven. *CJTF-7 Policy on Malaria Prevention*. Memorandum to Distribution, February 12, 2004. http://www.pdhealth.mil/downloads/CJTF-7_Policy_Malaria_Prevention_.pdf. Accessed May 20, 2014.

87. Multinational Corps-Iraq. *MNC-I Policy on Malaria Prevention*. Memorandum, December 28, 2004. http://www.pdhealth.mil/downloads/malaria_policy_fy2005.pdf. Accessed May 20, 2014.

88. Lydersen K. Family blames soldier's suicide on anti-malaria drug. *The Washington Post*. October 12, 2008. http://articles.washingtonpost.com/2008-10-12/news/36784724_1_side-effects-suicides-lariam-action-usa. Accessed May 20, 2014.

89. Third United States Army United States Army Forces Central Command. *Third US Army/USARCENT/CFLCC Policy Memorandum SUR-01*. Washington, DC: US CENTCOM; 2006.

90. Armed Forces Health Surveillance Center. Update: Malaria, US Armed Forces, 2008. *Medical Surveillance Monthly Report*. 2009;16:8–11.

91. Wooltorton E. Mefloquine: contraindicated in patients with mood, psychotic or seizure disorders. *CMAJ*. 2002;167:1147.

92. Triggs M. Army study to dispel Lariam suicide myths. *Fort Sam Houston News Leader*. March 4, 2004. http://www.samhouston.army.mil/pao/2004pdf/03_04_04.pdf. Accessed May 20, 2014.

93. US Army Office of The Surgeon General. *Updated Guidance on Use of Mefloquine (Lariam) for Malaria Prophylaxis*. Washington, DC: OTSG; 2009. Memorandum to Distribution. http://www.pdhealth.mil/downloads/DASG_Memorandum.pdf. Accessed May 20, 2014.

94. Office of the Assistant Secretary of Defense (Health Affairs). *Policy Memorandum on the Use of Mefloquine (Lariam) in Malaria Prophylaxis*. Washington, DC: OASDHA; 2009. HA Policy 09-017.

95. Associated Press. Army curbs prescriptions of anti-malaria drug. *USA Today*. November 19, 2011. http://www.usatoday.com/news/military/story/2011-11-19/military-malaria-drug/51311040/1. Accessed May 20, 2014.

96. Nevin RL. Falling rates of malaria among US military service members in Afghanistan substantiate findings of high compliance with daily chemoprophylaxis. *Am J Trop Med Hyg*. 2012;87:957–958.

97. Solano TL. *Doxy daily maintains APS-11 Marines' unit effectiveness*. United States Africa Command, April 28, 2011. http://www.africom.mil/Newsroom/Article/8259/doxy-daily-maintains-aps-11-marines-unit-effective. Accessed May 20, 2014.

98. Montgomery N. Navy looks for answers after Seabee dies from malaria. *Stars and Stripes*. April 19, 2010. http://www.stripes.com/news/navy-looks-for-answers-after-seabee-dies-from-malaria-1.101030. Accessed May 20, 2014.

99. Nevin RL. Limbic encephalopathy and central vestibulopathy caused by mefloquine: a case report. *Travel Med Infect Dis*. 2012;10:144–151.

100. Kime P. New concerns rising over antimalaria drug. *Army Times*. April 11, 2012. http://www.armytimes.com/news/2012/04/military-new-concerns-antimalaria-doxycycline-mefloquine-041112w/. Accessed May 20, 2012.

101. Department of Defense. *Prevention, Policies and Priorities to Reduce the Impact of Malaria on US Forces*: *Department of Defense Malaria Stakeholders Meeting*. Silver Spring, MD: Armed Forces Health Surveillance Center; 2011:46. http://afhsc.mil/viewDocument?file=Training/2011_DOD_malaria_MeetingSynopsis.pdf. Accessed May 6, 2014.

102. United States Africa Command. United States Africa Command Notice. Change 2 to ACM 4200.03, Force Health Protection Procedures for Deployment and Travel, September 20, 2011.

103. Office of the Assistant Secretary of Defense for Health Affairs. *Service Review of Mefloquine Prescribing Practices*. Memorandum to the 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, January 17, 2012. Washington, DC: OASDHA; 2012. https://truth-out.org/files/Mefloquine-QA-Memo-JAN-2012-(Signed).pdf. Accessed May 20, 2014.

104. Editorial. Safer antimalaria meds. *Army Times*. April 16, 2012.

105. Pellerin C. DoD mefloquine policy mirrors FDA update on malaria drug. *American Forces Press Service*. September 23, 2013. http://health.mil/News_And_Multimedia/News/detail/13-09-26/DOD_Mefloquine_Policy_Mirrors_FDA_Update_on_Malaria_Drug.aspx. Accessed May 20, 2014.

106. Woodson J. *Guidance on Medications for Prophylaxis of Malaria*. Washington, DC: DoD; 2013. HA Policy Memorandum 13-02. http://www.health.mil/Policies/2013/04/15/Guidance-on-Medications-for-Prophylaxis-of-Malaria. Accessed May 20, 2014.

107. Croft AM. A lesson learnt: the rise and fall of Lariam and Halfan. *J R Soc Med*. 2007;100:170–174.

108. Croft AM. Developing safe antimalaria drugs: key lessons from mefloquine and halofantrine. *Int J Risk & Safety in Med*. 2007;19:153–161.

109. Kersgard CM, Hickey PW. Adult malaria chemoprophylaxis prescribing patterns in the military health system from 2007–2011. *Am J Trop Med Hyg*. 2013;89:317–325.

110. Baudry S, Pham YT, Baune B, et al. Stereoselective passage of mefloquine through the blood-brain barrier in the rat. *J Pharm Pharmacol*. 1997;49:1086–1090.

111. Dow GS, Milner E, Bathurst I, et al. Central nervous system exposure of next generation quinoline methanols is reduced relative to mefloquine after intravenous dosing in mice. *Malar J*. 2011;10:150.

112. Chung L, Moore SD. Neuropeptides modulate compound postsynaptic potentials in basolateral amygdala. *Neuroscience*. 2009;164:1389–1397.

113. Behrens CJ, Ul Haq R, Liotta A, Anderson ML, Heinemann U. Nonspecific effects of the gap junction blocker mefloquine on fast hippocampal network oscillations in the adult rat in vitro. *Neuroscience*. 2011;192:11–19.

114. Gee CE, Benquet P, Demont-Guignard S, Wendling F, Gerber U. Energy deprivation transiently enhances rhythmic inhibitory events in the CA3 hippocampal network in vitro. *Neuroscience*. 2010;168:605–12.

115. Bissiere S, Zelikowsky M, Ponnusamy R, Jacobs NS, Blair HT, Fanselow MS. Electrical synapses control hippocampal contributions to fear learning and memory. *Science.* 2011;331:87–91.

116. Prochnow N, Abdulazim A, Kurtenbach S, et al. Pannexin1 stabilizes synaptic plasticity and is needed for learning. *PloS One*. 2012;7:e51767.

117. Allison DW, Ohran AJ, Stobbs SH, et al. Connexin-36 gap junctions mediate electrical coupling between ventral tegmental area GABA neurons. *Synapse*. 2006;60:20–31.

118. Lassen MB, Brown JE, Stobbs SH, et al. Brain stimulation reward is integrated by a network of electrically coupled GABA neurons. *Brain Res*. 2007;1156:46–58.

119. Steffensen SC, Bradley KD, Hansen DM, et al. The role of connexin-36 gap junctions in alcohol intoxication and consumption. *Synapse*. 2011;65:695–707.

120. Allison DW, Wilcox RS, Ellefsen KL, et al. Mefloquine effects on ventral tegmental area dopamine and GABA neuron inhibition: a physiologic role for connexin-36 GAP junctions. *Synapse*. 2011;65:804–813.

121. Lall VK, Dutschmann M, Deuchars J, Deuchars SA. The anti-malarial drug mefloquine disrupts central autonomic and respiratory control in the working heart brainstem preparation of the rat. *J Biomed Sci.* 2012;19:103.

122. Garcia-Rill E, Heister DS, Ye M, Charlesworth A, Hayar A. Electrical coupling: novel mechanism for sleep-wake control. *Sleep*. 2007;30:1405–1414.

123. Beck P, Odle A, Wallace-Huitt T, Skinner RD, Garcia-Rill E. Modafinil increases arousal determined by P13 potential amplitude: an effect blocked by gap junction antagonists. *Sleep.* 2008;31:1647–1654.

124. Cummings DM, Yamazaki I, Cepeda C, Paul DL, Levine MS. Neuronal coupling via connexin36 contributes to spontaneous synaptic currents of striatal medium-sized spiny neurons. *J Neurosci Res*. 2008;86:2147–2158.

125. Ozden I, Sullivan MR, Lee HM, Wang SS-H. Reliable coding emerges from co-activation of climbing fibers in microbands of cerebellar Purkinje neurons. *J Neurosci*. 2009;29:10463–10473.

126. Urbano FJ, Leznik E, Llinás RR. Modafinil enhances thalamocortical activity by increasing neuronal electrotonic coupling. *Proceedings of the National Academy of Sciences of the United States of America.* 2007;104:12554–12559.

127. Fuller SJ, Naraqi S, Gilessi G. Paranoid psychosis related to mefloquine antimalarial prophylaxis. *P N G Med J*. 2002;45:219–221.

128. Gascón J, Almeda J, Corominas N, Corachán M. [Severe neuropsychiatric reaction following mefloquine use]. *Med Clin (Barc)*. 1993;101:515–516.

129. Potasman I, Seligmann H. A unique case of mefloquine-induced psoriasis. *J Travel Med*. 1998;5:156.

130. Tran TM, Browning J, Dell ML. Psychosis with paranoid delusions after a therapeutic dose of mefloquine: a case report. *Malar J*. 2006;5:74.

131. Clattenburg RN, Donnelly CL. Case study: neuropsychiatric symptoms associated with the antimalarial agent mefloquine. *J Am Acad Child Adolesc Psychiatry*. 1997;36:1606–1608.

132. Colebunders R. Cured of fear of flying. *Travel Med Infect Dis*. 2011;9:82.

133. Javorsky DJ, Tremont G, Keitner GI, Parmentier AH. Cognitive and neuropsychiatric side effects of mefloquine. *J Neuropsychiatry Clin Neurosci.* 2001;13:302.

134. Tor PC, Lee HY, Tan CH. Mefloquine-induced mania in a 22-year-old Chinese man. *Singapore Med J*. 2006;47:549–550.

135. De Gennes C, Colas C, Nollet D, et al. [Panic attack after therapeutic administration of mefloquine]. *Ann Med Interne (Paris)*. 1991;142:631.

136. Stuiver PC, Ligthelm RJ, Goud TJ. Acute psychosis after mefloquine. *Lancet*. 1989;2:282.

137. Nosten F, Imvithaya S, Vincenti M, et al. Malaria on the Thai-Burmese border: treatment of 5192 patients with mefloquine-sulfadoxine-pyrimethamine. *Bull World Health Organ*. 1987;65:891–896.

138. Piening RB, Young SA. Mefloquine-induced psychosis. *Ann Emerg Med*. 1996;27:792–793.

139. Meszaros K, Kasper S. [Psychopathological phenomena in long-term follow-up of acute psychosis after preventive mefloquinine (Lariam) administration]. *Nervenarzt*. 1996;67:404–406.

140. Barrett PJ, Emmins PD, Clarke PD, Bradley DJ. Comparison of adverse events associated with use of mefloquine and combination of chloroquine and proguanil as antimalarial prophylaxis: postal and telephone survey of travellers. *BMJ*. 1996;313:525–528.

141. Hollweg M, Soyka M, Greil W. [Mefloquine-induced psychoses–problems in etiologic classification based on 2 case reports]. *Psychiatr Prax*. 1995;22:33–36.

142. Folkerts H, Kuhs H. [Psychotic episode caused by prevention of malaria with mefloquine. A case report]. *Nervenarzt*. 1992;63:300–302.

143. Borruat FX, Nater B, Robyn L, Genton B. Prolonged visual illusions induced by mefloquine (Lariam): a case report. *J Travel Med*. 2001;8:148–149.

144. Lapras J, Vighetto A, Trillet M, Garin JP. [Transient disorders of memory after a malaria attack. Caused by mefloquine?]. *Presse Méd*. 1989;18:776.

145. Marsepoil T, Petithory J, Faucher JM, Ho P, Viriot E, Benaiche F. [Encephalopathy and memory disorders during treatments with mefloquine]. *Rev Med Interne*. 1993;14:788–791.

146. Caillon E, Schmitt L, Moron P. Acute depressive symptoms after mefloquine treatment. *Am J Psychiatry*. 1992;149:712.

147. Hennequin C, Bourée P, Bazin N, Bisaro F, Feline A. Severe psychiatric side effects observed during prophylaxis and treatment with mefloquine. *Arch Int Med*. 1994;154:2360–2362.

148. Lebain P, Juliard C, Davy JP, Dollfus S. [Neuropsychiatric symptoms in preventive antimalarial treatment with mefloquine: apropos of 2 cases]. *Encéphale*. 2000;26:67–70.

149. Jousset N, Rougé-Maillart C, Turcant A, Guilleux M, Le Bouil A, Tracqui A. Suicide by skull stab wounds: a case of drug-induced psychosis. *Am J Forensic Med Pathol*. 2010;31:378–381.

150. Moore TJ, Glenmullen J, Furberg CD. Prescription drugs associated with reports of violence towards others. *PloS One*. 2010;5:e15337.

151. Rønn AM, Bygbjerg IC. [Acute brain syndrome after mefloquine treatment]. *Ugeskr Laeger*. 1994;156:6044–6045.

152. Bernard J, Le Camus J, Sarrouy J, et al. Toxic encephalopathy induced by mefloquine: 3 case reports. *Médecine et Armées*. 1989;17:209–211.

153. Ries S. [Cerebral spasm during malaria prophylaxis with mefloquine]. *Deutsche medizinische Wochenschrift (1946)*. 1993;118:1911–1912.

154. Meyer P, Combes N, Corne P, Jonquet O. [Convulsions and shock during antimalarial chemoprophylaxis with mefloquine]. *Presse Méd*. 2003;32:408.

155. Singh K, Shanks GD, Wilde H. Seizures after mefloquine. *Ann Int Med*. 1991;114:994.

156. Jallon P. Use of mefloquine in epileptic patients. *J Neurol Neurosurg Psychiatry*. 1988;51:732.

157. Olson PE, Kennedy CA, Morte PD. Paresthesias and mefloquine prophylaxis. *Ann Int Med*. 1992;117:1058–1059.

158. Chester AC, Sandroni P. Case report: peripheral polyneuropathy and mefloquine prophylaxis. *Am J Trop Med Hyg*. 2011;85:1008–1009.

159. Mefloquine. First report of parkinsonism: case report. *Reactions*. 2007:20.

160. Grupp D, Rauber A, Fröscher W. Neuropsychiatric disturbances after malaria prophylaxis with mefloquine. *Akt Neurol*. 1994;21:134–136.

161. Bhanji A, Atkins C, Karim M. Postural orthostatic tachycardia syndrome: a case report of palpitations and dizziness following prophylactic mefloquine use. *Int J Clin Pharmacol Ther*. 2010;48:577–581.

162. Bourgeade A, Tonin V, Keudjian F, Levy PY, Faugere B. [Accidental mefloquine poisoning]. *Presse Méd*. 1990;19:1903.

163. Lobel HO, Coyne PE, Rosenthal PJ. Drug overdoses with antimalarial agents: prescribing and dispensing errors. *JAMA*. 1998;280:1483.

164. Lysack JT, Lysack CL, Kvern BL. A severe adverse reaction to mefloquine and chloroquine prophylaxis. *Aust Fam Physician*. 1998;27:1119–1120.

165. Perlin JB. Under Secretary for Health's Information Letter IL 10-2004-007. *Possible Long Term Health Effects from the Malarial Proprophylaxis Mefloquine (Lariam)*. Washington, DC: DVA; 2004.

166. Chevli R, Fitch CD. The antimalarial drug mefloquine binds to membrane phospholipids. *Antimicrob Agents Chemother*. 1982;21:581–586.

167. Nevin RL. Neuropharmacokinetic heterogeneity of mefloquine in the treatment of progressive multifocal leukoencephalopathy. *Intern Med*. 2012;51:2257.

168. Patchen LC, Campbell CC, Williams SB. Neurologic reactions after a therapeutic dose of mefloquine. *NEJM*. 1989;321:1415–1416.

169. Schwartz E, Potasman I, Rotenberg M, Almog S, Sadetzki S. Serious adverse events of mefloquine in relation to blood level and gender. *Am J Trop Med Hyg*. 2001;65:189–192.

170. Nevin RL. Pharmacokinetic considerations in the repositioning of mefloquine for treatment of progressive multifocal leukoencephalopathy. *Clin Neurol Neurosurg*. 2012;114:1204–1205.

171. Zaigraykina N, Potasman I. [Polymorphism at the MDR1 locus as a cause of mefloquine-induced psychosis]. *Harefuah*. 2010;149:583–584, 620, 619.

172. Aarnoudse AL, van Schaik RH, Dieleman J, et al. MDR1 gene polymorphisms are associated with neuropsychiatric adverse effects of mefloquine. *Clin Pharmacol Ther*. 2006;80:367–374.

173. Barraud de Lagerie S, Comets E, Gautrand C, et al. Cerebral uptake of mefloquine enantiomers with and without the P-gp inhibitor elacridar (GF1210918) in mice. *Br J Pharmacol*. 2004;141:1214–1222.

174. Riffkin CD, Chung R, Wall DM, et al. Modulation of the function of human MDR1 P-glycoprotein by the antimalarial drug mefloquine. *Biochem Pharmacol*. 1996;52:1545–1552.

175. Lee HS, Go ML. Effects of mefloquine on Ca2+ uptake and release by dog brain microsomes. *Arch Int Pharmacodyn Thér*. 1996;331:221–231.

176. Dow GS, Hudson TH, Vahey M, Koenig ML. The acute neurotoxicity of mefloquine may be mediated through a disruption of calcium homeostasis and ER function in vitro. *Malar J*. 2003;2:14.

177. Phillips-Howard PA, Bjorkman AB. Ascertainment of risk of serious adverse reactions associated with chemoprophylactic antimalarial drugs. *Bull World Health Organ.* 1990;68:493–504.

178. Wells TS, Smith TC, Smith B, et al. Mefloquine use and hospitalizations among US service members, 2002–2004. *Am J Trop Med Hyg.* 2006;74:744–749.

179. Coster T. *Mefloquine Use and Antidepressants*. Presentation to the Army Office of the Surgeon General, December 1, 2008.

180. Hoge CW, Auchterlonie JL, Milliken CS. Mental health problems, use of mental health services, and attrition from military service after returning from deployment to Iraq or Afghanistan. *JAMA*. 2006;295:1023–1032.

181. Meier CR, Wilcock K, Jick SS. The risk of severe depression, psychosis or panic attacks with prophylactic antimalarials. *Drug Saf.* 2004;27:203–213.

182. Rønn AM, Rønne-Rasmussen J, Gøtzsche PC, Bygbjerg IC. Neuropsychiatric manifestations after mefloquine therapy for Plasmodium falciparum malaria: comparing a retrospective and a prospective study. *Trop Med Int Health*. 1998;3:83–88.

183. Andreasen NC. Posttraumatic stress disorder: a history and a critique. *Ann N Y Acad Sci.* 2010;1208:67–71.

184. Crocq MA, Crocq L. From shell shock and war neurosis to posttraumatic stress disorder: a history of psychotraumatology. *Dialogues Clin Neurosci.* 2000;2:47–55.

Attachment 4

Hindawi Publishing Corporation
Journal of Parasitology Research
Volume 2015, Article ID 260106, 8 pages
http://dx.doi.org/10.1155/2015/260106

Review Article

Rational Risk-Benefit Decision-Making in the Setting of Military Mefloquine Policy

Remington L. Nevin

Department of Mental Health, Johns Hopkins Bloomberg School of Public Health, 624 N. Broadway, Room 782, Baltimore, MD 21205, USA

Correspondence should be addressed to Remington L. Nevin; rnevin@jhu.edu

Received 24 July 2015; Accepted 7 October 2015

Academic Editor: Boyko B. Georgiev

Mefloquine is an antimalarial drug that has been commonly used in military settings since its development by the US military in the late 1980s. Owing to the drug's neuropsychiatric contraindications and its high rate of inducing neuropsychiatric symptoms, which are contraindications to the drug's continued use, the routine prescribing of mefloquine in military settings may be problematic. Due to these considerations and to recent concerns of chronic and potentially permanent psychiatric and neurological sequelae arising from drug toxicity, military prescribing of mefloquine has recently decreased. In settings where mefloquine remains available, policies governing prescribing should reflect risk-benefit decision-making informed by the drug's perceived benefits and by consideration both of the risks identified in the drug's labeling and of specific military risks associated with its use. In this review, these risks are identified and recommendations are made for the rational prescribing of the drug in light of current evidence.

1. Introduction

The antimalarial drug mefloquine (commonly marketed as Lariam) had until recently enjoyed a long history of preferred use in certain military settings in the prophylaxis of chloroquine-resistant *P. falciparum* malaria. Originally developed by the US military in a Vietnam War-era drug development program and subsequently licensed for prophylactic use in the US in 1989 [1], mefloquine has, in the over quarter century since, been widely used by the US military and by various international militaries during deployments in malaria-endemic areas, including the Horn of Africa [2–4], sub-Saharan Africa [5], Australasia [6, 7], Southeast Asia [8], and the Middle East—particularly during recent large-scale operations in Iraq and Afghanistan [8, 9].

Mefloquine is a 4-quinolinemethanol closely related to quinine, and the drug shares a common structural core with related quinoline antimalarial and antiparasitic compounds that exhibit clinically significant but idiosyncratic neurotoxicity [10]. Recently, mefloquine was itself recognized as an idiosyncratic neurotoxicant that may cause permanent injury to the central nervous system (CNS) [10]. Mefloquine readily crosses the blood brain barrier (BBB), where it may adversely affect the function of neurons particularly in the limbic system and brainstem [10, 11]. In susceptible individuals, likely owing to idiosyncratic genetic and environmentally mediated variability in neuropharmacokinetics that may serve to limit its enzyme-mediated efflux back across the BBB [12], the drug may accumulate to intoxicating and even neurotoxic concentrations in the CNS during prophylactic use [10].

At prophylactic doses of 250 mg weekly, a sizeable minority of mefloquine users may experience one or more neuropsychiatric symptoms attributable to the drug [13]. Recent mefloquine drug labels describe "very common" side effects including insomnia and abnormal dreaming affecting greater than 10% of prophylactic users and "common" side effects including anxiety and depression affecting between 1 and 10% of prophylactic users [14]. Other side effects described as "uncommon" but reported in between 1 and 10 prophylactic users per 1,000 include agitation, aggression, restlessness, panic attacks, mood swings, and confusion [15].

Rather than representing isolated "side effects," various mefloquine drug labels have emphasized that certain of these must be considered as "prodromal" symptoms [14, 16]—potentially indicating a personal idiosyncratic susceptibility to more serious CNS drug toxicity. For example, the current US drug label warns that "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" [17]. Among susceptible individuals, such prodromal symptoms may progress to a potentially life-threatening condition [11] that early drug labeling euphemistically referred to as "a more serious event" [16] but which may represent the effects of a progressive limbic encephalopathy caused by drug intoxication [18]. Such encephalopathy commonly manifests as a paranoid, manic, confusional, or dissociative psychosis and may be associated in severe cases with a risk of permanent neurological sequelae including neurotoxic brainstem injury [10, 18] and permanent psychiatric sequelae including homicidal violence and suicide [8, 11, 19, 20]. Among those reporting adverse events from the drug—and as would be expected from a postencephalopathy syndrome [11]—some continue to experience neurological and psychiatric sequelae, including vertigo, dizziness, disequilibrium [21], nightmare disorder, and cognitive impairment [22] years after acute intoxication. Such chronic neurological and psychiatric sequelae may plausibly confound the diagnosis and management of other conditions associated with military service, including traumatic brain injury and posttraumatic stress disorder [8, 23, 24].

Although drug label warnings dating back to the US introduction of mefloquine in 1989 noted the drug "must be discontinued" at the onset of certain listed prodromal symptoms [16], recently these warnings have been widely updated to more explicitly define under what conditions continued use of the drug should be contraindicated. In 2013, US drug regulators mandated the inclusion of a boxed warning on generic versions of the drug clarifying that "if psychiatric or neurologic symptoms occur" during prophylactic use—a warning cautiously encompassing all possible neuropsychiatric symptoms of the intoxication prodrome—the drug "should be discontinued" [17]. That same year, European regulators issued guidance to physicians that should those taking mefloquine experience "a neuropsychiatric reaction," including "changes to their mental state," "they should stop taking mefloquine immediately and seek urgent medical advice" [25]. Similarly, at least one "Dear Doctor" letter has explicitly counseled healthcare providers to advise their patients to "seek immediate medical advice" for any "psychological changes" including "sleep disorders" or "abnormal dreaming" that occur while taking the drug [26].

Prior to the these changes, the writings of numerous influential authors may have served to undermine earlier recommendations by the drug's manufacturer to immediately discontinue mefloquine at the onset of certain of these symptoms [27], by claiming, for example, that the drug could be continued even following the development of certain listed prodromal symptoms such as anxiety [28] or by suggesting that assumed prodromal symptoms of CNS toxicity might instead be due to causes other than mefloquine, such as recreational substance use, preexisting mental illness, the stresses of travel [28, 29], or stressful military environments [30]—failing to emphasize the recommendation to nonetheless immediately discontinue the drug despite this uncertainty.

Additionally, widespread confusion that only those with a history of certain mental health disorders were susceptible to the adverse psychiatric effects of mefloquine—a confusion which appears to have increased when such a history was added to the drug label as a formal contraindication [31]—may have contributed, at least in certain cases [32], to prodromal symptoms of CNS toxicity being erroneously misattributed to such a presumed history and not to the drug. In military settings, widespread belief among senior leaders that such prodromal symptoms occurred only rarely [33–35] and far less commonly than had been previously demonstrated [32] may have further contributed to the drug not being discontinued as often as drug label guidance recommended—for example, as rarely as in 1 in 334 users in one early example of US military use [4].

With recent strengthened warnings and with understanding that prodromal symptoms may occur quite commonly even in perfectly healthy individuals, efforts to better comply with drug label guidance now make the "very common" incidence of prodromal symptoms induced by mefloquine incompatible with the drug's widespread convenient and safe use in prophylaxis. In randomized blinded trials, at least 29% [36, 37] of prophylactic mefloquine users reported one or more neuropsychiatric symptoms consistent with the prodrome of intoxication, thus contraindicating continued use of the drug in accordance with current drug label guidance.

In military settings where the background incidence of such symptoms may already be increased owing to common stressors associated with deployment or to preexisting mental health conditions which may be prevalent in 10% or more of deploying military personnel [38], the recognition and correct attribution of prodromal symptoms to drug intoxication may be particularly confounded [23]. Such confounding increases the risk of potentially life-threatening or permanent sequelae of severe intoxication if the cause of such symptoms is erroneously misattributed and the drug is consequently not immediately discontinued.

As awareness has increased both of these considerations and of the potentially permanent effects of the drug's CNS toxicity [39–41], use of the drug has decreased [42, 43] and has been formally deprioritized by policy in certain military settings, in favor of the more widespread use of safer and better tolerated alternatives [44–46].

Although even the innovator license holder has conceded that mefloquine is no longer the most effective available antimalarial for the prevention of malaria [47], use of mefloquine in certain military settings has been claimed as potentially advantageous for a number of other reasons, including the drug's convenient weekly dosing (which may facilitate directly observed therapy) [48, 49], its somewhat lower cost relative to certain alternatives [50, 51], and its indication for long term use in the absence of contraindications [52].

Owing to slight international differences in such costs and indications, as well as to differences in risk-benefit decision-making, international military antimalarial policies have varied, even between deployments posing similar risks to military forces. For example, for military deployments to Djibouti (a nation located in the Horn of Africa) French military forces discontinued the widespread use of mefloquine in 2002 in favor of preferred use of the broad-spectrum antibiotic and

antimalarial doxycycline [2]. In contrast, US forces, which had been prescribing mefloquine to its personnel there at a dose of 250 mg weekly, delayed preferred use of doxycycline until 2009 [2], before next substituting the combination drug atovaquone/proguanil (commonly marketed as Malarone) in 2011 [46]. In contrast, German forces have always preferentially used atovaquone/proguanil for the duration of their deployments there [2].

Military policies that retain the widespread use of mefloquine for its perceived advantages or for use in rare cases where preferred alternative antimalarials cannot be taken should reflect rational risk-benefit decision-making informed not only by awareness of the drug's presumed benefits and of the risks identified in the drug's labeling, but also by changing awareness, recognition, and acknowledgement of the risks associated with any use of the drug in military settings. In this review, specific risks associated with military use of mefloquine are identified, and recommendations for the rational use of the drug in military settings are then made in light of current evidence.

2. Military Specific Risks

Years prior to the original licensing of mefloquine, concerns were raised at certain risks associated with use of the drug in military settings. For example, one study, published in 1982, noted "legitimate concern for mefloquine's safe use in aircrewmen" [53]. Such initial concerns were motivated mostly by consideration of the drug's quinine-like neurological effects, which subsequently contributed to initial recommendations [54], later formalized, to prohibit all use of the drug among aviation personnel.

Although the initial US drug label had advised that owing to concerns of "neuropsychiatric reactions" "caution should be exercised" while "piloting airplanes," "driving," and "operating machines" [16], in contrast to concerns over its use in aviation personnel, with limited exceptions [55], these warnings did not contribute to particular recommendations against use of the drug in other military occupational settings—for example, among drivers or machine operators. Although early research would demonstrate that dizziness and "lightheadedness" were not infrequently reported [32], other research suggested, somewhat counterintuitively, that mefloquine either had no significant effect on [56] or could even improve psychomotor performance, including performance on certain driving tests [57]. Similarly, a study suggesting subjective "ability to work" was not affected by mefloquine may reflect the effects of selection bias owing to the study's very high nonresponse rate [58]. With recent understanding of the adverse neurological effects of mefloquine on structures in the brainstem, including the inferior olive [59], research has emerged demonstrating that mefloquine may impair motor learning during certain complex tasks, such as those comparable to marksmanship, with "clinical implications for mefloquine users" [60].

Similarly, although mefloquine was noted during early testing to adversely alter patterns of dreaming and significantly reduce overall sleep duration [32] and despite broad military acknowledgement of the importance of sleep hygiene [61], such concerns have not, until recently, significantly informed military use of the drug. Early warnings by the drug manufacturer for users of the drug to report "sleep disorders including abnormal dreaming" [26] to their physician were similarly not widely communicated. Only in recent years, as awareness has grown that symptoms of disturbed sleep, including insomnia and abnormal dreaming, are "very common" with prophylactic use of mefloquine [14] and that vivid nightmares described occasionally as having "technicolor clarity" [32] are not benign and should be considered contraindications to the drug's further use, have the potentially negative impact of these effects on military performance and military operations been more broadly considered in military settings.

Likewise, reports of symptoms such as panic attacks and confusion, which while being described as "uncommon" may nonetheless affect between 1 and 10 prophylactic users per 1,000 [15] and thus may not be infrequent during large military deployments, may be problematic in military settings. Disturbing case reports of deployed service members experiencing episodes of panic resulting in abnormal behavior [8] or of being confused and found "wandering aimlessly" [62] raise legitimate concerns for their likely occurrence in deployed environments. Of potentially similar concern are the drug's noted subclinical effects among military personnel particularly on measures of "tension" and "anger" [32], which may serve to measurably shift patterns of behavior in large populations exposed to the drug.

Although not unique to military settings, concern of suicide associated with use of the drug has also been a pervasive concern, particularly in the US military, dating at least back to the first large-scale deployment of troops to Iraq in 2003 during which use of mefloquine was widespread [8] and an increased risk of suicide was observed [63]. Although the US drug label had by this time acknowledged reports of suicide and suicidal ideation with the drug [64], military officials initially testified they did not believe that mefloquine "represents the big causal factor in our suicide rates" [33]. Yet subsequently, at least one military suicide was considered consistent on psychological autopsy with the effects of mefloquine intoxication [65]. A later media-affiliated study among Irish service members suggested that risk of suicide could have been increased up to fivefold among deployed cohorts exposed to mefloquine [66]. With mefloquine known to increase the risk of mental disorders [67] and with mental disorders known to increase risk of suicide [68], such results are plausible and qualitatively consistent with known suicide epidemiology. Unfortunately, despite independent recommendations [69] to more formally study the epidemiology of mefloquine suicide—and although such studies initially described as seeking "to dispel… [mefloquine] suicide myths" [70] had been previously claimed by senior military officials to be either planned or in progress [71, 72]—the results of these studies remain unpublished in the peer-reviewed literature. Recent large-scale military-sponsored studies of suicide have similarly failed to consider exposure to mefloquine in their risk factor analysis [73, 74], potentially confounding the observed association of suicide

with deployments [73] where use of the drug may have been widespread [8, 75].

In addition to concerns of self-directed violence, mefloquine is strongly associated in postmarketing studies with risk of violence towards others, including homicide [20, 76], magnifying concerns of these consequences with the drug's use among military personnel who are likely to be heavily armed during use of the drug. Owing to the known association of the drug with agitation and aggression, which may affect between 1 and 10 in 1000 users [15], and to the drug's known association with symptoms of more acute intoxication including dissociative and paranoid psychosis, there has been reasonable speculation by military and government officials that mefloquine intoxication may have contributed to cases of homicidal violence overseas [77] and among returned service members [78].

Similar concerns arose recently following receipt by the US Food and Drug Administration (FDA) of a drug adverse event report of uncertain provenance [79] describing a US service member who "developed homicidal behavior" which "led to [h]omicide killing 17 Afghanis [sic]." Although this report alludes clearly to a well-known case of a soldier found guilty of a similar crime who had been issued with mefloquine during a prior deployment [80], US military officials have neither confirmed nor denied his use of mefloquine during his most recent deployment [81], making any causal association of this incident with acute intoxication speculative.

Intriguingly, although public records reveal the soldier had been prescribed doxycycline, at the time of his arrest, this bottle of medication was found sealed and unopened [82]. At the time of the incident, the soldier was assigned to a special forces unit affiliated with US Army Special Operations Command (USASOC) and was known to have been given multiple prescription drugs without documentation by special forces personnel [82, 83]. Within a year and a half of the massacre, USASOC issued a formal order prohibiting the use of mefloquine among its personnel, acknowledging that "consideration must be made for the impact of this medication on our population" [44].

3. Discussion

In the over quarter century of international military use of mefloquine, many of the drug's unique risks in military settings have become more widely appreciated and now more routinely inform policies for the use of the drug. Similarly, over this period, many of the drug's perceived advantages have been disproved both by formal evidence and by experience.

For example, and in contrast to original expectations, certain studies have found equal or higher compliance with daily as compared with weekly prophylaxis [84, 85], and recent military deployments where daily antimalarial drugs have been prioritized for use have been ecologically associated with significantly lower rates of malaria than comparable deployments where mefloquine had previously been the drug of choice [5, 86, 87]. A number of these daily antimalarial drugs have also obtained formal indications for use in many jurisdictions independent of duration of therapy [88, 89], removing one of the remaining perceived advantages of mefloquine [58] relative to these safer and better tolerated medications.

Likewise, the findings of prior economic analyses which have found cost advantages with use of mefloquine [50, 52, 90] are typically not generalizable to military settings, in that these analyses fail to consider the high potential costs of risks unique to these contexts. As experience and this review have demonstrated, these costs, which include both direct and indirect economic costs, may be significant.

As described elsewhere [13], even independent of these considerations—and although mefloquine clearly remains indicated for prophylaxis in every jurisdiction in which it was originally licensed—owing to the high rate of preexisting contraindications to its use and to the high rate of induced contraindications with use of the drug, convenient and safe use of mefloquine on a widespread basis as a "drug of choice" is now prohibitive in most military settings. While such considerations alone should preclude the mass prescribing of mefloquine as a first-line agent, use of the drug may still be considered by some militaries as a second- or third-line agent [55], in spite of the broader concerns identified in this review, on an individualized basis among those with contraindications or intolerance to preferred alternative antimalarials.

Unlike the case with mefloquine, true contraindications to alternative drugs for prophylaxis of chloroquine-resistant *P. falciparum* are very rare: of the alternative drugs commonly available internationally for this indication, although intolerance to doxycycline is not at all uncommon [91], atovaquone/proguanil is, in contrast, exceptionally well tolerated [85, 88], with blinded trials reporting a rate of discontinuation due to adverse events of only 1% to 2% during prophylactic use [36, 37]. Military policies that deprioritize use of mefloquine to a second- or third-line drug, for use only in those with contraindications or intolerance to these alternatives, should therefore expect to see fewer than 1-2% prescribed mefloquine, and any greater rate of prescribing should prompt a careful review of prescribing practices [75] to identify the causes of deviation from such policy. Additionally, certain recommendations, first described elsewhere [13] and outlined more fully below, should be considered in the setting of military policies that permit continued use of the drug.

4. Recommendations

Military policies that permit continued use of mefloquine as a second- or third-line antimalarial drug should ensure the implementation of a number of precautions to properly comply with recent labeling guidance and to reduce the risk of more severe intoxication and its potentially chronic, permanent, or life-threatening sequelae.

First, in accordance with international labeling guidance, such policies must ensure that service members that prescribed mefloquine are informed that any neuropsychiatric symptoms that may develop while taking the drug may be evidence of a personal susceptibility to drug intoxication that should mandate its immediate discontinuation. Although

prior to recent labeling changes such symptoms were poorly appreciated as evidence of CNS toxicity and commonly attributed to other causes, current drug label guidance has clarified that even relatively common symptoms, including insomnia or other sleep disturbances, vivid dreams or nightmares, mild anxiety or depressive symptoms, and other even potentially subtle changes in "mental state" such as irritability or personality change, should be considered as cause to seek medical attention and immediately discontinue the drug [13].

Similarly, counseling at the time of prescribing and dispensing should extend beyond the mere issuance of a printed warning (or "wallet card") and be complemented by a documented test of knowledge of its contents, as well as by educational efforts extended throughout the service member's chain of command, particularly to ensure that others are aware of the typically subtle signs and symptoms of mefloquine intoxication. In prior military settings, absent widespread awareness of the symptoms of intoxication, these have been both occasionally overlooked or unrecognized by the service member [18, 62] or even when recognized they were erroneously attributed both by medical personnel and to the chain of command to causes other than the drug [8, 13].

Second, particularly in military settings where strong disincentives may exist against the reporting of mental health symptoms, including those resulting from fears of stigma, even with adequate education, certain intoxicated patients may fail to heed drug label guidance to report such symptoms and may therefore risk continuing taking the drug. To minimize these risks, where directly observed therapy is implemented, this should be conducted in private by medical personnel and not through the chain of command so as to minimize barriers to reporting of potentially stigmatizing prodromal symptoms. Similarly, where directly observed therapy is not implemented, medical personnel should nonetheless conduct routine evaluations of those on the drug to rule out prodromal symptoms of intoxication—such as paranoia or confusion—which may limit such reporting [13, 80, 92].

Third, as many cases of mild intoxication—though not all—may be identified during the first few weeks of drug use [27], to further reduce the risk of more severe intoxication with continued dosing, military policies should strongly consider limiting initial prescribing of the drug to a small number of tablets to be taken prior to deployment, with the service member evaluated regularly and carefully by medical personnel during this period to assess the development of prodromal symptoms. If none are detected, policy could then permit prescribing the remaining tablets for deployment [13].

Similarly, as it can take as many as 7–10 weekly doses of mefloquine for the drug to achieve steady state and protective concentrations in serum, where deployment dates are known this far in advance, a prolonged period of use prior to deployment should be considered both to improve the drug's antimalarial effectiveness and to further minimize the risk of unrecognized intoxication that might occur during deployment. This consideration is particularly relevant during remote deployments, where the patient may be far from medical care and where certain of the preceding recommendations requiring medical evaluation may not be feasible [13].

Finally, and in this respect, the military clinician and the chain of command should be prepared for the consequences of the need for service members to immediately discontinue the medication while in a malaria-endemic area and when far from medical care. In those cases where the drug is prescribed as a second-line drug, policy should require the coprescribing of a few weeks' supply of an alternative third-line antimalarial, to be used on discontinuation of mefloquine until medical evaluation can be arranged. Similarly, in those rare cases where the drug is prescribed as a "drug of last resort"—as such use implies that no other prophylactic medications are available to switch to—in areas where malaria is highly endemic and where mosquito-avoidance measures alone may be insufficient, this may mandate the service member's early evacuation to minimize risks when mefloquine is discontinued. Although under such conditions it may appear reasonable for the chain of command or the military clinician to recommend continuing the use of mefloquine until evacuation can be arranged, the risks associated with such continued dosing could outweigh even the risk of sequelae from a treatable episode of malaria that could develop during the period, making such a recommendation decidedly unwise [13].

Faithful implementation of these recommendations may serve to minimize the risks associated with use of mefloquine. However, given that severe intoxication and permanent effects have been reported after as little as a single 250 mg tablet [93], these recommendations may serve to minimize but will not fully eliminate the unique military risks considered in this review that are associated with continued use of mefloquine, even rarely as a second- or third-line drug.

5. Conclusions

Military policies that permit the continued use of mefloquine expose militaries to certain unique risks not encountered with most civilian use of the drug. These risks, when fully recognized and acknowledged, exceed the drug's benefits in many military settings. While international drug regulators may consider a more limited set of risks when addressing issues in drug safety regulation, militaries must consider these additional risks in formulating policies for the rational use of this medication. Consideration of the issues in this review may aid militaries in formulating rational policies for the safer use of the drug. Depending on these militaries' risk tolerance, such consideration may serve to motivate further prohibitions on the use of mefloquine in line with those already in place in a growing number of military settings.

Conflict of Interests

Remington L. Nevin has been retained as consultant and expert witness in legal cases involving claims of antimalarial drug toxicity.

Authors' Contribution

Remington L. Nevin conceived the review and wrote the paper.

References

[1] A. M. Croft, "A lesson learnt: the rise and fall of Lariam and Halfan," *Journal of the Royal Society of Medicine*, vol. 100, no. 4, pp. 170–174, 2007.

[2] L. Ollivier, R. L. Nevin, H. Y. Darar et al., "Malaria in the republic of Djibouti, 1998–2009," *The American Journal of Tropical Medicine and Hygiene*, vol. 85, no. 3, pp. 554–559, 2011.

[3] M. S. Peragallo, G. Sabatinelli, G. Majori, G. Calí, and G. Sarnicola, "Prevention of malaria among Italian troops in Somalia and Mozambique (1993-1994)," *Transactions of the Royal Society of Tropical Medicine and Hygiene*, vol. 89, no. 3, article 302, 1995.

[4] J. L. Sánchez, R. F. DeFraites, T. W. Sharp, and R. K. Hanson, "Mefloquine or doxycycline prophylaxis in US troops in Somalia," *The Lancet*, vol. 341, no. 8851, pp. 1021–1022, 1993.

[5] T. J. Whitman, P. E. Coyne, A. J. Magill et al., "An outbreak of plasmodium falciparum malaria in U.S. Marines deployed to liberia," *The American Journal of Tropical Medicine and Hygiene*, vol. 83, no. 2, pp. 258–265, 2010.

[6] S. J. Kitchener, P. E. Nasveld, R. M. Gregory, and M. D. Edstein, "Mefloquine and doxycycline malaria prophylaxis in Australian soldiers in East Timor," *The Medical Journal of Australia*, vol. 182, no. 4, pp. 168–171, 2005.

[7] M. S. Peragallo, A. M. Croft, and S. J. Kitchener, "Malaria during a multinational military deployment: the comparative experience of the Italian, British and Australian Armed Forces in East Timor," *Transactions of the Royal Society of Tropical Medicine and Hygiene*, vol. 96, no. 5, pp. 481–482, 2002.

[8] R. L. Nevin, "Mefloquine and posttraumatic stress disorder," in *Textbook of Military Medicine. Forensic and Ethical Issues in Military Behavioral Health*, E. C. Ritchie, Ed., pp. 277–296, Borden Institute, Washington, DC, USA, 2015.

[9] A. M. Croft, A. H. Darbyshire, C. J. Jackson, and P. P. van Thiel, "Malaria prevention measures in coalition troops in Afghanistan," *The Journal of the American Medical Association*, vol. 297, no. 20, pp. 2197–2200, 2007.

[10] R. L. Nevin, "Idiosyncratic quinoline central nervous system toxicity: historical insights into the chronic neurological sequelae of mefloquine," *International Journal for Parasitology: Drugs and Drug Resistance*, vol. 4, no. 2, pp. 118–125, 2014.

[11] E. C. Ritchie, J. Block, and R. L. Nevin, "Psychiatric side effects of mefloquine: applications to forensic psychiatry," *Journal of the American Academy of Psychiatry and the Law*, vol. 41, no. 2, pp. 224–235, 2013.

[12] R. L. Nevin, "Neuropharmacokinetic heterogeneity of mefloquine in the treatment of progressive multifocal leukoencephalopathy," *Internal Medicine*, vol. 51, no. 16, p. 2257, 2012.

[13] R. L. Nevin, "Issues in the prevention of malaria among women at war," in *Women at War*, E. C. Ritchie and A. L. Naclerio, Eds., pp. 93–119, Oxford University Press, London, UK, 2015.

[14] F. Hoffman-La Roche, *Lariam Product Insert*, F. Hoffmann-LaRoche Ltd, Clarecastle, Ireland, 2014.

[15] F. Hoffmann-La Roche, *Lariam Product Insert*, F. Hoffmann-La Roche, Sydney, Australia, 2014.

[16] F. Hoffman-La Roche, *Lariam Product Insert*, F. Hoffman-La Roche, New York, NY, USA, 1989.

[17] Roxanne Laboratories, *Mefloquine Hydrochloride. United States Product Insert. June, 2013*, Roxanne Laboratories, 2013.

[18] R. L. Nevin, "Limbic encephalopathy and central vestibulopathy caused by mefloquine: a case report," *Travel Medicine and Infectious Disease*, vol. 10, no. 3, pp. 144–151, 2012.

[19] F. Gebhart, "Some psychoactive prescription drugs associated with violence," *Drug Topics*, p. 37, 2011.

[20] T. J. Moore, J. Glenmullen, and C. D. Furberg, "Prescription drugs associated with reports of violence towards others," *PLoS ONE*, vol. 5, no. 12, Article ID e15337, 2010.

[21] 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*, U.S. Food and Drug Administration, 2013, http://www.fda.gov/downloads/Drugs/DrugSafety/UCM362232.pdf.

[22] Å. Ringqvist, P. Bech, B. Glenthøj, and E. Petersen, "Acute and long-term psychiatric side effects of mefloquine: a follow-up on Danish adverse event reports," *Travel Medicine and Infectious Disease*, vol. 13, no. 1, pp. 80–88, 2015.

[23] A. J. Magill, M. A. Forgione, J. D. Maguire, and M. M. Fukuda, "Special Considerations for US Military Deployments," 2014, http://wwwnc.cdc.gov/travel/yellowbook/2014/chapter-8-advising-travelers-with-specific-needs/special-considerations-for-us-military-deployments.

[24] A. Levin, "FDA warning highlights Mefloquine's mental health risks," *Psychiatric News*, vol. 48, no. 18, p. 1, 2013.

[25] F. Hoffman-La Roche, *Lariam Dear Doctor Letter*, F. Hoffman-La Roche, Dublin, Ireland, 2013.

[26] F. Hoffman-La Roche, *Lariam Dear Doctor Letter*, F. Hoffman-La Roche, Dublin, Ireland, 1996.

[27] D. Stürchler, J. Handschin, D. Kaiser et al., "Neuropsychiatric side effects of mefloquine," *The New England Journal of Medicine*, vol. 322, no. 24, pp. 1752–1753, 1990.

[28] H. O. Lobel, "Adverse health events and malaria prophylaxis," *Healthwise: A Newsletter for Peace Corps Medical Officers Worldwide*, vol. 5, no. 2, pp. 1–4, 1996.

[29] P. Schlagenhauf and R. Steffen, "Neuropsychiatric events and travel: do antimalarials play a role?" *Journal of Travel Medicine*, vol. 7, no. 5, pp. 225–226, 2000.

[30] J. S. McCarthy, "Malaria chemoprophylaxis: in war and peace," *The Medical Journal of Australia*, vol. 182, no. 4, pp. 148–149, 2005.

[31] E. Wooltorton, "Mefloquine: contraindicated in patients with mood, psychotic or seizure disorders," *Canadian Medical Association Journal*, vol. 167, no. 10, p. 1147, 2002.

[32] E. Boudreau, B. Schuster, J. Sanchez et al., "Tolerability of prophylactic Lariam regimens," *Tropical Medicine and Parasitology*, vol. 44, no. 3, pp. 257–265, 1993.

[33] 108th United States Congress, "Hearing on NDAA for FY 2005—H.R. 4200," 2004, http://commdocs.house.gov/committees/security/has056270.000/has056270_0f.htm.

[34] U.S. Army Office of the Surgeon General, *Updated Health Care Provider Information on Use of Mefloquine Hydrochloride for Malaria Prophylaxis*, Memorandum, U.S. Army Office of the Surgeon General, Washington, DC, USA, 2002.

[35] U.S. Army Office of the Surgeon General, *Memorandum. Subject: Updated Guidance on the Use of Mefloquine for Malaria Prophylaxis*, U.S. Army Office of the Surgeon General, 2009.

[36] D. Overbosch, H. Schilthuis, U. Bienzle et al., "Atovaquone-proguanil versus mefloquine for malaria prophylaxis in nonimmune travelers: results from a randomized, double-blind study," *Clinical Infectious Diseases*, vol. 33, no. 7, pp. 1015–1021, 2001.

[37] P. Schlagenhauf, A. Tschopp, R. Johnson et al., "Tolerability of malaria chemoprophylaxis in non-immune travellers to sub-Saharan Africa: multicentre, randomised, double blind, four

arm study," *British Medical Journal*, vol. 327, no. 7423, pp. 1078–1081, 2003.

[38] R. L. Nevin, P. P. Pietrusiak, and J. B. Caci, "Prevalence of contraindications to mefloquine use among USA military personnel deployed to Afghanistan," *Malaria Journal*, vol. 7, article 30, 2008.

[39] Arznei-Telegramm, "New warnings and contraindications for Lariam," *Arznei-Telegramm*, vol. 44, no. 9, p. 84, 2013.

[40] Arznei-Telegramm, "CNS-toxic mefloquine (Lariam) still justified as a malaria medication?" *Arznei-Telegramm*, vol. 44, no. 8, p. 72, 2013.

[41] Arznei-Telegramm, "Mefloquine (Lariam): eye disorders and other lasting damages," *Arznei-Telegramm*, vol. 45, no. 2, p. 24, 2014.

[42] C. M. Kersgard and P. W. Hickey, "Adult malaria chemoprophylaxis prescribing patterns in the military health system from 2007–2011," *American Journal of Tropical Medicine and Hygiene*, vol. 89, no. 2, pp. 317–325, 2013.

[43] L. Bull-Otterson, *U.S. Army Pharmacovigilance Center Safety Communication No. 11: Mefloquine Use as a Second-Line Malaria Chemoprophlaxis*, 2014.

[44] US Army Special Operations Command, *Ceasing Use of Mefloquine in US Army Special Operations Command Units*, US Army Special Operations Command, 2013.

[45] Office of the Assistant Secretary of Defense (Health Affairs), *Memorandum. Subject: Notification for Healthcare Providers of Mefloquine Box Warning*, Office of the Assistant Secretary of Defense (Health Affairs), 2013.

[46] Armed Forces Health Surveilance Center, "Prevention, policies and priorities to reduce the impact of malaria on US forces," in *Proceedings of the DoD Malaria Stakeholders Meeting*, Silver Spring, Md, USA, August 2011.

[47] F. Hoffman-La Roche, *Protocol, 89th Annual General Meeting*, Shareholders of Roche, Basel, Switzerland, 2007.

[48] Armed Forces Epidemiological Board, "Transcript," in *Proceedings of the Winter Meeting*, Vienna, Austria, February 2004.

[49] A. J. Magill, *DoD Experience with Malaria and Antimalarials. Presentation to the Mefloquine Adverse Events Study Design Options Panel*, Armed Forces Epidemiological Board Select Subcommittee, 2004.

[50] J. P. Bryan, "Cost considerations of malaria chemoprophylaxis including use of primaquine for primary or terminal chemoprophylaxis," *American Journal of Tropical Medicine and Hygiene*, vol. 75, no. 3, pp. 416–420, 2006.

[51] J. A. Cockrill, A. M. Von Thun, and M. Fukuda, "Optimizing preventive strategies and malaria diagnostics to reduce the impact of malaria on US Military Forces," in *Proceedings of the DOD Malaria Stakeholder Meeting*, Bethesda, Md, USA, May 2012.

[52] P. Schlagenhauf, M. Adamcova, L. Regep, M. T. Schaerer, and H.-G. Rhein, "The position of mefloquine as a 21st century malaria chemoprophylaxis," *Malaria Journal*, vol. 9, article 357, 2010.

[53] J. R. Stockwell, "Aeromedical considerations of malaria prophylaxis with mefloquine hydrochloride," *Aviation, Space, and Environmental Medicine*, vol. 53, no. 10, pp. 1011–1013, 1982.

[54] Armed Forces Epidemiological Board, *Recommendations on Mefloquine Chemoprophylaxis for Military Personnel*, 1989.

[55] S. McCarthy, "Malaria prevention, mefloquine neurotoxicity, neuropsychiatric illness and risk-benefit analysis in the australian defence force," *Journal of Parasitology Research*, In press.

[56] P. Schlagenhauf, H. Lobel, R. Steffen et al., "Tolerance of mefloquine by Swissair trainee pilots," *The American Journal of Tropical Medicine and Hygiene*, vol. 56, no. 2, pp. 235–240, 1997.

[57] E. F. P. M. Vuurman, N. D. Muntjewerff, M. M. C. Uiterwijk et al., "Effects of mefloquine alone and with alcohol on psychomotor and driving performance," *European Journal of Clinical Pharmacology*, vol. 50, no. 6, pp. 475–482, 1996.

[58] A. G. Terrell, M. E. Forde, R. Firth, and D. A. Ross, "Malaria chemoprophylaxis and self-reported impact on ability to work: mefloquine versus doxycycline," *Journal of Travel Medicine*, 2015.

[59] R. S. Van Der Giessen, S. K. Koekkoek, S. van Dorp et al., "Role of olivary electrical coupling in cerebellar motor learning," *Neuron*, vol. 58, no. 4, pp. 599–612, 2008.

[60] T. A. van Essen, R. S. van der Giessen, S. K. E. Koekkoek et al., "Anti-malaria drug mefloquine induces motor learning deficits in humans," *Frontiers in Neuroscience*, vol. 4, article 191, 2010.

[61] C. V. Lentino, D. L. Purvis, K. J. Murphy, and P. A. Deuster, "Sleep as a component of the performance triad: the importance of sleep in a military population," *U.S. Army Medical Department Journal*, pp. 98–108, 2013.

[62] A. L. Peterson, R. A. Seegmiller, and L. S. Schindler, "Severe neuropsychiatric reaction in a deployed military member after prophylactic mefloquine," *Case Reports in Psychiatry*, vol. 2011, Article ID 350417, 4 pages, 2011.

[63] D. Miles, "2003 Suicide Rates Elevated Among Iraqi Freedom Troops; 2004 Rates Dip," 2004, http://www.defense.gov/news/newsarticle.aspx?id=27000.

[64] A. Manning, "Suicide link now listed on label of anti-malaria drug," 2002, http://usatoday30.usatoday.com/news/science/2002-09-04-malaria_x.htm.

[65] K. Lydersen, "Family Blames soldier's suicide on anti-malaria drug," *The Washington Post*, 2008, http://articles.washingtonpost.com/2008-10-12/news/36784724_1_side-effects-suicides-lariam-action-usa.

[66] R. O'Reilly, "Risk Factor," 2013, http://www.rte.ie/news/primetime/2013/0523/452211-risk-factor-rte-investigations-unit.

[67] C. R. Meier, K. Wilcock, and S. S. Jick, "The risk of severe depression, psychosis or panic attacks with prophylactic antimalarials," *Drug Safety*, vol. 27, no. 3, pp. 203–213, 2004.

[68] E. K. Mościcki, "Epidemiology of completed and attempted suicide: toward a framework for prevention," *Clinical Neuroscience Research*, vol. 1, no. 5, pp. 310–323, 2001.

[69] Armed Forces Epidemiological Board, *Memorandum. Subject: Armed Forces Epidemiological Board (AFEB) Select Subcommittee to Develop Mefloquine Study Options*, 2004.

[70] M. Triggs, "Army study to dispel Lariam suicide myths," *Fort Sam Houston News Leader*, vol. 37, no. 4, pp. 1–4, 2004.

[71] United Press International, *Responses to UPI-CNN Lariam Investigation*, 2004, http://www.upi.com/Business_News/Security-Industry/2004/09/07/Responses-to-UPI-CNN-Lariam-investigation/UPI-13621094601600.

[72] M. Benjamin and D. Olmsted, "Pentagon eyes malaria drug in suicides," 2004, http://www.upi.com/Business_News/Security-Industry/2004/02/25/Pentagon-eyes-malaria-drug-in-suicides/68081077755804.

[73] M. Schoenbaum, R. C. Kessler, S. E. Gilman et al., "Predictors of suicide and accident death in the Army Study to Assess Risk and Resilience in Servicemembers (Army STARRS): results from the Army Study to Assess Risk and Resilience in Servicemembers (Army STARRS)," *JAMA Psychiatry*, vol. 71, no. 5, pp. 493–503, 2014.

[74] R. C. Kessler, C. H. Warner, C. Ivany et al., "Predicting suicides after psychiatric hospitalization in US army soldiers: the Army Study to Assess Risk and Resilience in Servicemembers (Army STARRS)," *JAMA Psychiatry*, vol. 72, no. 1, pp. 49–57, 2015.

[75] Office of the Assistant Secretary of Defense (Health Affairs), *Service Review of Mefloquine Prescribing Practices*, Memorandum, Office of the Assistant Secretary of Defense (Health Affairs), 2012.

[76] "Medication-induced violence towards others," *Prescrire International*, vol. 23, no. 150, pp. 153–155, 2014.

[77] Somalia Commission of Inquiry, *Report of the Somalia Commission of Inquiry: Executive Summary*, Canadian Government Publishing, Ottawa, Canada, 1997.

[78] U.S. Army Office of the Surgeon General, *Fort Bragg Epidemiological Consultation Report*, U.S. Army Office of the Surgeon General, 2002.

[79] U.S. Food and Drug Administration, *FDA Advere Event Reporting System (FAERS) FOIA Case Report Information*, Case ID: 8504150, U.S. Food and Drug Administration, 2012.

[80] D. S. MacLean, *Crazy Pills*, 2013, http://www.nytimes.com/2013/08/08/opinion/crazy-pills.html.

[81] K. Thomas, "F.D.A. Strengthens Warnings on Anti-Malaria Drug," 2013, http://www.nytimes.com/2013/07/30/business/fda-strengthens-warnings-on-lariam-anti-malaria-drug.html.

[82] A. Ashton, "Army: Robert Bales' medical records to remain classified," 2014, http://www.thenewstribune.com/2014/09/02/3358411/army-robert-bales-medical-records.html.

[83] A. Ashton, "Army kicked out Green Beret who gave steroids to Robert Bales weeks before massacre," 2014, http://www.thenewstribune.com/news/local/military/article25871329.html.

[84] M. Brisson and P. Brisson, "Compliance with antimalaria chemoprophylaxis in a combat zone," *The American Journal of Tropical Medicine and Hygiene*, vol. 86, no. 4, pp. 587–590, 2012.

[85] H. Andersson, H. H. Askling, B. Falck, and L. Rombo, "Well-tolerated chemoprophylaxis uniformly prevented Swedish soldiers from *Plasmodium falciparum* malaria in Liberia, 2004–2006," *Military Medicine*, vol. 173, no. 12, pp. 1194–1198, 2008.

[86] R. L. Nevin, "Falling rates of malaria among U.S. Military Service Members in Afghanistan substantiate findings of high compliance with daily chemoprophylaxis," *The American Journal of Tropical Medicine and Hygiene*, vol. 87, no. 5, pp. 957–958, 2012.

[87] P. Kime, "Troops get malaria during Ebola deployment," 2015, http://www.militarytimes.com/story/military/benefits/health-care/2015/04/23/us-military-ebola-deployment-malaria/26236769.

[88] A. K. Boggild, M. E. Parise, L. S. Lewis, and K. C. Kain, "Atovaquone-proguanil: report from the CDC expert meeting on malaria chemoprophylaxis (II)," *The American Journal of Tropical Medicine and Hygiene*, vol. 76, no. 2, pp. 208–223, 2007.

[89] Pfizer, *Vibramycin-D Product Insert*, Pfizer, Tadworth, UK, 2009.

[90] L. L. Widmer, P. R. Blank, K. Van Herck, C. Hatz, and P. Schlagenhauf, "Cost-effectiveness analysis of malaria chemoprophylaxis for travellers to West-Africa," *BMC Infectious Diseases*, vol. 10, article 279, 2010.

[91] K. R. Tan, A. J. Magill, M. E. Parise, and P. M. Arguin, "Doxycycline for malaria chemoprophylaxis and treatment: report from the CDC expert meeting on malaria chemoprophylaxis," *The American Journal of Tropical Medicine and Hygiene*, vol. 84, no. 4, pp. 517–531, 2011.

[92] R. L. Nevin, "A memoir of mefloquine amnesia: a review of the answer to the riddle is me by David Stuart MacLean," *AJOB Neuroscience*, vol. 5, no. 4, pp. 88–91, 2014.

[93] D. Grupp, A. Rauber, and W. Froscher, "Neuropsychiatric disturbances after malaria prophylaxis with mefloquine," *Aktuelle Neurologie*, vol. 21, no. 4, pp. 134–136, 1994.