Attachment 4

Repatriation Medical Authority

Investigation into
Chemically acquired brain injury caused by mefloquine, tafenoquine or primaquine

For the **Repatriation Medical Authority**
For the **August 2017** RMA Meeting

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Glossary/abbreviations

ADF	Australian Defence Force
AMI	Army Malaria Institute
BoP	balance of probabilities
CI	confidence interval
OR	odds ratio
PTSD	posttraumatic stress disorder
RH	reasonable hypothesis
RMA	Repatriation Medical Authority
RR	relative risk
SMSE	sound medical-scientific evidence
SoP	statement of principles
VEA	Veterans' Entitlements Act

Current Statements of Principles

There are no Statements of Principles (SoPs) for chemically acquired brain injury due to exposure to mefloquine, tafenoquine or primaquine.

Background

At its February 2017 meeting, the Repatriation Medical Authority (the Authority) considered a request dated 6 February 2017 received from the President of the Repatriation Commission and Chair of the Military Rehabilitation and Compensation Commission Mr Simon Lewis PSM, seeking an investigation of chemically-acquired brain injury caused by mefloquine, tafenoquine or primaquine to find out whether SOPs may be determined concerning such a condition.

As no SOPs have been determined this condition, the Authority agreed to notify an investigation under s196G(1) of the VEA to ascertain if SOPs concerning chemically-acquired brain injury caused by mefloquine, tafenoquine or primaquine could be determined. An investigation notice was placed in the Government Notices Gazette on 14 February 2017.

Submissions/correspondence

1. Email correspondence in respect of mefloquine exposure and mefloquine toxicity syndrome dated 4 January 2016 was received from Dr Jane Quinn. Attached to the email was a paper in which Dr Quinn requested that a SoP for mefloquine toxicity syndrome be developed by the RMA, together with information explaining the scientific basis for the request. The response to Dr Quinn explained that mefloquine was currently a causal factor in a number of SoPs, and at that time, the RMA was not undertaking an investigation into "mefloquine toxicity syndrome". Dr Quinn did not subsequently request that this information be considered a formal submission to the current investigation, but in any case the relevant sound medical-scientific evidence (SMSE) cited in the paper was taken into consideration.

2. An online submission was received from a veteran on 15 February 2017. The veteran explained that he had taken mefloquine for 6 months while on deployment in East Timor in 2001 and had subsequently been diagnosed with posttraumatic stress disorder. No SMSE was supplied with the submission.

3. A submission was received from Dr Geoffrey Dow on 10 May 2017, on the basis of having expertise relevant to the investigation. Dr Dow has a degree in biotechnology, with honours in veterinary biology and a PhD in veterinary biology and biomedical science (parasitology). He is the Chief Scientific Officer, Chief Executive Officer and Chairman of 60 Degrees Pharmaceuticals, the US Army’s licensee for tafenoquine for malaria prophylaxis. Dr Dow has been involved in research efforts to find a well-tolerated chemotherapeutic agent for malaria, firstly through investigating the utility of mefloquine analogues with lower brain penetration and subsequently through the completion of the development of tafenoquine. He states his belief that the scientific evidence does not suggest that primaquine of tafenoquine are neurotoxic. He points out a lack of prospective,

blinded studies which could show a causal link between mefloquine and adverse post-deployment outcomes, though there is evidence that it can cause neurological damage in animal studies. The submission included 14 peer-reviewed articles relating to mefloquine, primaquine or tafenoquine.

- Dow G, Brown T, Reid M, Smith B and Toovey S (2017) Tafenoquine is not neurotoxic following supertherapeutic doses in rats. Travel Medicine and Infectious Diseases.

- Dow GS, McCarthy WF, Reid M, Smith B, Tang D, Shanks GD. (2014) A retrospective analysis of the protective efficacy of tafenoquine and mefloquine as prophylactic anti-malarials in non-immune individuals during deployment to a malaria-endemic area. Malar J. Feb 6;13:49.

- Dow GS, Milner E, Bathurst I et al (2011).Central nervous system exposure of next generation quinoline methanols is reduced relative to mefloquine after intravenous dosing in mice. Malar J. Jun 6;10:150.

- Dow G, Bauman R, Caridha D, Cabezas M, Du F, Gomez-Lobo R, Park M, Smith K, Cannard K. (2006) Mefloquine induces dose-related neurological effects in a rat model. Antimicrob Agents Chemother. Mar;50(3):1045-53.

- Cullen KA, Arguin PM; Centers for Disease Control and Prevention. (2013) Malaria surveillance - United States, 2011. MMWR Surveill Summ. Nov 1;62(5):1-17.

- Cullen KA, Mace KE, Arguin PM; Centers for Disease Control and Prevention. (2016) Malaria Surveillance - United States, 2013. MMWR Surveill Summ. 2016 Mar 4;65(2):1-22.

- Clayman CB, Arnold J, Hockwald RS, Yount EH, Edgcomb JH, Alving AS. (1952) Toxicity of primaquine in Caucasians. J Am Med Assoc. Aug 23;149(17):1563-8.

- Eick-Cost AA, Hu Z, Rohrbeck P, Clark LL. (2017) Neuropsychiatric Outcomes After Mefloquine Exposure Among U.S. Military Service Members. Am J Trop Med Hyg. Jan 11;96(1):159-166.

- Hill DR, Baird JK, Parise ME, Lewis LS, Ryan ET, Magill AJ. (2006) Primaquine: report from CDC expert meeting on malaria chemoprophylaxis I. Am J Trop Med Hyg. Sep;75(3):402-15.

- Kitchener SJ, Auliff AM, Rieckmann KH. (2000) Malaria in the Australian Defence Force during and after participation in the International Force in East Timor (INTERFET). Med J Aust. Dec 4-18;173(11-12):583-5.

- Lee SJ, Ter Kuile FO, Price RN, Luxemburger C, Nosten F. Adverse effects of mefloquine for the treatment of uncomplicated malaria in Thailand: A pooled analysis of 19, 850 individual patients. PLoS One. 2017 Feb 13;12(2):e0168780.

- Novitt-Moreno A, Ransom J, Dow G, Smith B, Read LT, Toovey S (2017) Tafenoquine for malaria prophylaxis in adults: An integrated safety analysis, Travel Medicine and Infectious Disease.

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

- Nasveld PE, Edstein MD, Reid M, Brennan L, Harris IE, Kitchener SJ, Leggat PA, Pickford P, Kerr C, Ohrt C, Prescott W; Tafenoquine Study Team (2010) Randomised, double-blind study of the safety, tolerability, and efficacy of tafenoquine versus mefloquine for malaria prophylaxis in nonimmune subjects. Antimicrob Agents Chemother. Feb;54(2):792-8.

- Toovey S. (2009) Mefloquine neurotoxicity: a literature review. Travel Med Infect Dis. Jan;7(1):2-6.

- Waller M, Treloar SA, Sim MR et al (2012). Traumatic events, other operational stressors and physical and mental health reported by Australian Defence Force personnel following peacekeeping and war-like deployments. BMC Psychiatry, 12: 88.

Of these studies, one study was about military stressors (Waller et al 2012) and four studies were about malaria generally (Cullen et al 2013, Cullen et al 2016, Dow et al 2014 and Kitchener et al 2000) and did not directly relate to the issue of whether or not mefloquine, primaquine or tafenoquine can cause a brain injury with chronic effects.

4. A female veteran sent a submission on 10 May 2017, listing a number of symptoms she had experienced during and after taking mefloquine, which she believes has caused permanent changes to her brain.

   The symptoms experienced while taking mefloquine included muscle pain, muscle weakness, abdominal cramps/stomach pain, lethargy, disorientation, feeling of skin "crawling", diarrhoea, "eye lid aggravation", headache, sore throat, neck and shoulder ache, photophobia, decreased appetite, earache, increased agitation, increased anger, paranoia, panic/anxiety attacks, mood changes, increased anxiety, nightmares, ringing in the ears, memory lapses and out of character behaviour.

   The symptoms experienced after returning to Australia and ceasing mefloquine included ongoing anxiety, general feeling of being "unwell", tiredness, stomach/intestinal pain, nausea, worsening back pain (previous injury), thyroglossal cyst, lethargy, flushes/night sweats, chronic dysthymia (depressive mood), somatoform symptoms, problems adjusting

back into unit post deployment, mood swings, and vertigo/tinnitus (diagnosed with endolymphatic hydrops and hearing loss).

The submission included a number of personal medical records and a web page concerning PTSD as a "diagnosis of convenience". No SMSE was included with the submission.

5. A veteran sent an email on 16 May 2017 in order to register his interest in participating in any investigation that would lead to a determination in respect of chemically acquired brain injury or any other side effects caused by being prescribed mefloquine. He had served in East Timor during April to October 2001. On taking mefloquine during this deployment he experienced hallucinations, weird vivid dreams, broken sleep, "brain fog", anxiety and "stress attacks". Many of these symptoms, along with anger and depression, have continued up to the current time. No SMSE was supplied with the submission.

6. A submission was received from Dr Jane Quinn on 18 May 2017, on the basis of having expertise relevant to the investigation. Dr Quinn points out that, although there is no specific category for chemically acquired brain injury in DSM-5 or ICD-10, a relevant category would be "substance/medication-induced major or mild neurocognitive disorder". The following SMSE is cited in support of the argument that mefloquine in particular could cause medium to long term or permanent brain injury:

    - Adshead S. (2014) The adverse effects of mefloquine in deployed military personnel. J R Nav Med Serv. Vol 100(3):232-7.

    - Eick-Cost AA, Hu Z, Rohrbeck P, Clark LL. (2017) Neuropsychiatric Outcomes After Mefloquine Exposure Among U.S. Military Service Members. Am J Trop Med Hyg. Jan 11;96(1):159-166.

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

    - Nevin RL (2012) Limbic encephalopathy and central vestibulopathy caused by mefloquine: a case report. Travel Med Infect Dis. 2012 May;10(3):144-51.

    - Milatovic D, Jenkins JW, Hood JE, Yu Y, Rongzhu L, Aschner M. (2011) Mefloquine neurotoxicity is mediated by non-receptor tyrosine kinase. Neurotoxicology. Oct;32(5):578-85.

    - Maxwell NM, Nevin RL, Stahl S, Block J, Shugarts S, Wu AH, Dominy S, Solano-Blanco MA, Kappelman-Culver S, Lee-Messer C, Maldonado J, Maxwell AJ. (2015) Prolonged neuropsychiatric effects following management of chloroquine intoxication with psychotropic polypharmacy. Clin Case Rep. Jun;3(6):379-87.

- Nevin R, Ritchie E (2015) The Mefloquine Intoxication Syndrome: A Significant Potential Confounder in the Diagnosis and Management of PTSD and Other Chronic Deployment-Related Neuropsychiatric Disorders. In; Posttraumatic Stress Disorder and Related Diseases in Combat Veterans, pp 257-278. Available at http://link.springer.com/chapter/10.1007/978-3-319-22985-0_19.

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

- Ringqvist Å, Bech P, Glenthøj B, Petersen E. (2015) Acute and long-term psychiatric side effects of mefloquine: a follow-up on Danish adverse event reports. Travel Med Infect Dis. Jan-Feb;13(1):80-8.

- Yu D, Ding D, Jiang H, Stolzberg D, Salvi R. (2011) Mefloquine damage vestibular hair cells in organotypic cultures. Neurotox Res. Jul;20(1):51-8.

Dr Quinn argues that since tafenoquine has a similar pharmacokinetic profile to mefloquine, it could also have the same effect. The following SMSE is cited in support of the argument that tafenoquine could cause medium to long term or permanent brain injury:

- Dow G, Brown T, Reid M, Smith B and Toovey S (2017) Tafenoquine is not neurotoxic following supertherapeutic doses in rats. Travel Medicine and Infectious Diseases.

- Ebstie YA, Abay SM, Tadesse WT, Ejigu DA. (2016) Tafenoquine and its potential in the treatment and relapse prevention of Plasmodium vivax malaria: the evidence to date. Drug Des Devel Ther. Jul 26;10:2387-99.

- Elmes NJ, Nasveld PE, Kitchener SJ, et al (2008). The efficacy and tolerability of three different regimens of tafenoquine versus primaquine for post-exposure prophylaxis of plasmodium vivax malaria in the southwest pacific. Trans R Soc Trop Med.

- Hale BR, Owusu-Agyei S, Fryauff DJ, et al (2003). A randomised, double-blind, placebo-controlled, dose-ranging trial of tafenoquine for weekly prophylaxis against plasmodium falciparum. Clin Infect Dis, 36(5): 541-9.

- Nasveld PE, Edstein MD, Reid M, Brennan L, Harris IE, Kitchener SJ, Leggat PA, Pickford P, Kerr C, Ohrt C, Prescott W; Tafenoquine Study Team (2010) Randomised, double-blind study of the safety, tolerability, and efficacy of tafenoquine versus mefloquine for malaria prophylaxis in nonimmune subjects. Antimicrob Agents Chemother. Feb;54(2):792-8.

- Novitt-Moreno A, Ransom J, Dow G, Smith B, Read LT, Toovey S (2017) Tafenoquine for malaria prophylaxis in adults: An integrated safety analysis, Travel Medicine and Infectious Disease.

7. A submission was received from Dr Remington Nevin on 17 May 2017, on the basis of having expertise relevant to the investigation. A number of his own and other published peer-reviewed articles were cited. Most of these had already been obtained, apart from the three studies below:

   - Loken A, Haymaker W. (1949) Pamaquine poisoning in man, with a clinicopathologic study of one case. Am J Trop Med Hyg. May;29(3):341-52.

   - Schmidt I, Schmidt L. (1948) Neurotoxicity of the 8-aminoquinolines; lesions in the central nervous system of the rhesus monkey induced by administration of plasmocid. J Neuropathol Exp Neurol. Oct;7(4):368-98.

   - Schmidt I, Schmidt L. (1949) Neurotoxicity of the 8-aminoquinolines; reactions of various experimental animals to plasmocid.J Comp Neurol. Dec;91(3):337-67.

   In addition to these articles, Dr Nevin included a poster obtained by freedom of information from the Walter Reed Army Institute of Research in December 2014. The undated poster appeared to have been written by a college student during a summer semester, under the supervision of institutional staff. The poster described an experiment in which 8 antimalarial drugs were tested in cell cultures of rat neuronal cells, kidney cells and macrophages. Tafenoquine exhibited the highest level of neurotoxicity followed by mefloquine. There does not appear to be any paper published in the peer-reviewed literature in relation to this work. Even if a paper reporting these findings had been published, it would be insufficient on its own to change the weight of evidence concerning causation of chronic brain injury in humans.

8. A further submission was received from Dr Geoffrey Dow on 3 July 2017. The submission explained the parameters for an upcoming clinical trial of tafenoquine, which will include assessment of ophthalmological safety, psychiatric disorders and sleep disorders. The submission included three published peer-reviewed articles.

   - Novitt-Moreno A, Ransom J, Dow G, Smith B, Read LT, Toovey S (2017) Tafenoquine for malaria prophylaxis in adults: An integrated safety analysis, Travel Medicine and Infectious Disease.

   - Elmes NJ, Nasveld PE, Kitchener SJ, et al (2008). The efficacy and tolerability of three different regimens of tafenoquine versus primaquine for post-exposure prophylaxis of plasmodium vivax malaria in the southwest pacific. Trans R Soc Trop Med.

   - Nasveld PE, Edstein MD, Reid M, Brennan L, Harris IE, Kitchener SJ, Leggat PA, Pickford P, Kerr C, Ohrt C, Prescott W; Tafenoquine Study Team (2010) Randomised, double-blind study of the safety, tolerability, and efficacy of tafenoquine versus mefloquine for malaria prophylaxis in nonimmune subjects. Antimicrob Agents Chemother. Feb;54(2):792-8.

Literature Search

Literature searches were conducted using the Ovid search engine from 1996 to March Week 5 2017, limited to English language. The search terms were:

- Mefloquine/ae, po, to [Adverse Effects, Poisoning, Toxicity];
- Mefloquine/ and Psychotic Disorders/ or neuropsychiatric.mp. or Mental Disorders/
- Tafenoquine.mp and adverse effects.mp;
- Primaquine/ae, po, to.
- Brain Injuries/ci, et [Chemically Induced, Etiology] AND drugs.mp. or Pharmaceutical Preparations/ or chemicals.mp. or Inorganic Chemicals/ or Organic Chemicals/.

Articles were selected based on relevance, study quality, reliability and journal authority. The above search was supplemented by PubMed searches using the terms "mefloquine or primaquine or tafenoquine toxicity" or "mefloquine or primaquine or tafenoquine and neuropsychiatric", internet searches, manual searches of reference lists and extracts from relevant sections of textbooks.

Definition

In relation to the performance of its investigative role following requests for investigation, the RMA's task includes the identification of what constitutes a disease or injury.

A legal opinion concerning the task of the RMA of defining disease, injury or death has been provided by Dermott Ryan SC (2013).[1] Relevant sections are quoted below:

> **What is a disease?**
> 26.4. It is necessarily implicit in the statutory scheme for veterans' compensation that the RMA's task includes, in relation to requests for investigation, the identification of what constitutes a disease for the performance of its investigative role.
>
> 26.5. The addition of the qualifier "particular" to the phrase is also important. The RMA must be able to identify, from a request, a particular disease that can be investigated.
>
> 26.6. The words of the statutory definition must be applied, but in doing so there remains room for the application of expert medico-scientific opinion of the kind held by the RMA.
>
> 30. it is my view that the RMA must make a decision anterior to the conduct of an investigation, that there is a particular kind of disease that is the subject matter of the request. If no such disease can be discerned after the RMA has applied the definition in the Act and its own expertise, then it has the power and duty to decline to conduct the investigation requested. The requisite subject matter of such an investigation would not be present.
>
> **A morbid condition**
> 34. One of the matters that have to be considered by the RMA in relation to a request is whether a "morbid condition", which is found in the definition of "disease" in the Act, is present.

[1] Ryan D, SC (2013) Memorandum. Available at http://www.rma.gov.au/foi/what.htm.

The question arises whether a "morbid condition" would include any claimed syndrome or "cluster of symptoms". An example is alcohol dependence, which is recognised as comorbid with accepted PTSD. However, in such a case there is an otherwise known "disease" accepted by scientific-medical opinion.

35. In my opinion this too is a question involving the expert opinion of the RMA. It is tasked with identifying the particular "morbid condition" (and thus "disease") the subject of the request. If a proper assessment of a "cluster of variable symptoms" said to be suffered by veterans is not sufficient to allow the RMA to identify the relevant "morbid condition", as against an inchoate and inherently variable group of complaints, then it can properly conclude that no morbid condition has been identified as the particular morbid condition, and thus disease, that the RMA is being asked to investigate.

Does the definition of SMSE compel the RMA to find that there is a 'disease'?
50. Accordingly, I do not think that a contention that, in effect, the assertion of a disease is sufficient to trigger the RMA's duty to investigate. Whether there is a particular disease remains a question for the RMA.

Definitions of disease, disorder, syndrome and ailment

The *Veterans' Entitlements Act 1987* (the VEA) provides the following definition of disease or injury in section 5D:

disease means:
(a) any physical or mental ailment, disorder, defect or morbid condition (whether of sudden onset or gradual development); or
(b) the recurrence of such an ailment, disorder, defect or morbid condition;
but does not include:
(c) the aggravation of such an ailment, disorder, defect or morbid condition; or
(d) a temporary departure from:
(i) the normal physiological state; or
(ii) the accepted ranges of physiological or biochemical measures;
that results from normal physiological stress (for example, the effect of exercise on blood pressure) or the temporary effect of extraneous agents (for example, alcohol on blood cholesterol levels).

Dorland's medical dictionary, 32nd edition

Disease - any deviation from or interruption of the normal structure or function of a part, organ, or system of the body as manifested by characteristic symptoms and signs; the etiology, pathology, and prognosis may be known or unknown.
Disorder- a derangement or abnormality of function: a morbid physical or mental state.
Syndrome- a set of symptoms that occur together; the sum of signs of any morbid state; a symptom complex.
Ailment- any disease or affection of the body, usually referring to slight or mild disorder

Oxford English Dictionary, 11th edition

Disease -a disorder of structure or function in a human, animal or plant, especially one that produces specific symptoms that affect a specific part.
Disorder - a disruption of normal physical or mental functions
Syndrome- 1. a group of symptoms which consistently occur together. 2. a characteristic combination of opinions, emotions, or behaviour

Ailment- a minor illness

In order to make SoPs for any given disease or injury, the condition must first be ascertained to be a disease or injury that is capable of being defined using recognised diagnostic criteria. In general, diseases may be classified or defined according to a range of criteria. For example, in ICD-10,[2] conditions are classified according to:

- aetiology (eg infectious disease, nutritional deficiency, pregnancy, injury, poisoning, chromosomal abnormalities),
- histology (eg cancer),
- anatomical systems or location in the body (eg gastrointestinal, musculoskeletal, peripheral nervous system),
- symptom pattern and type of symptom (eg psychiatric illness),
- pathological process (eg degenerative disease, endocrine disease, inflammation, demyelination),
- timing of occurrence (eg congenital, perinatal, developmental).

In order to determine whether brain injury can occur as a result of exposure to mefloquine, tafenoquine or primaquine it is necessary to consider whether there is sound medical-scientific evidence showing persistent neurocognitive deficits, supported by evidence of pathological damage to the brain in humans as well as animals. These deficits must be linked to taking the drug.

A method for linking drug reactions to a drug has been suggested by Naranjo et al (1981).[3] Other widely used criteria are the World Health Organization-Uppsala Monitoring Center (WHO-UMC) criteria.[4] The applicability of these criteria to long term persistent effects as opposed to short term events is unclear, especially when one of the criteria relates to reversibility and brain damage is permanent. However, the criteria do list consideration of alternative causes, and whether or not the reaction can be confirmed by objective evidence.

Naranjo criteria

1. Are there previous conclusive reports on this reaction? *Yes (+1) No (0) Do not know or not done (0)*
2. Did the adverse events appear after the suspected drug was given? *Yes (+2) No (-1) Do not know or not done (0)*
3. Did the adverse reaction improve when the drug was discontinued or a specific antagonist was given? *Yes (+1) No (0) Do not know or not done (0)*
4. Did the adverse reaction appear when the drug was readministered? *Yes (+2) No (-1) Do not know or not done (0)*

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[2] The International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Australian Modification, Eighth Edition (2013) World Health Organisation (2010), modified by the National Casemix and Classification Centre, Australian health Services Research Institute, University of Wollongong, Sydney.

[3] Naranjo CA, Busto U, Sellers EM, Sandor P, et al (1981). A method for estimating the probability of adverse drug reactions. Clinical Pharmacology - Therapeutics, 30(2) pp 239-245.

[4] World Health Organisation. (2017) Safety Monitoring of Medicinal Products: Guidelines for Setting Up and Running a Pharmacovigilance Centre. Available at http://apps.who.int/medicinedocs/en/d/Jh2934e/15.html. Accessed 19-5-17.

5. Are there alternative causes that could have caused the reaction? *Yes (-1) No (+2) Do not know or not done (0)*
6. Did the reaction reappear when a placebo was given? *Yes (-1) No (+1) Do not know or not done (0)*
7. Was the drug detected in any body fluid in toxic concentrations? *Yes (+1) No (0) Do not know or not done (0)*
8. Was the reaction more severe when the dose was increased, or less severe when the dose was decreased? *Yes (+1) No (0) Do not know or not done (0)*
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure? *Yes (+1) No (0) Do not know or not done (0)*
10. Was the adverse event confirmed by any objective evidence? *Yes (+1) No (0) Do not know or not done (0)*

Scoring

≥ 9 = definite ADR
5-8 = probable ADR
1-4 = possible ADR
0 = doubtful ADR

WHO-Uppsala Monitoring Centre criteria

1. *Certain*: a clinical event, including laboratory test abnormality, occurring in a plausible time relationship to drug administration, and which cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge procedure if necessary.

2. *Probable/Likely*: a clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfil this definition.

3. *Possible*: a clinical event, including laboratory test abnormality, with a reasonable time sequence to administrations of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.

4. *Unlikely*: a clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations.

5. *Conditional/Unclassified*: a clinical event, including laboratory test abnormality, reported as an adverse reaction, about which more data is essential for a proper assessment, or the additional data is under examination.

6. *Unassessable/Unclassifiable*: a report suggesting an adverse reaction which cannot be judged because information is insufficient or contradictory, and which cannot be supplemented or verified.

Synonyms

Chronic mefloquine toxicity syndrome, mefloquine intoxication syndrome, chronic mefloquine-induced encephalopathy

ICD codes

There are no relevant ICD codes

Introduction

Quinoline derivatives include chloroquine, amodiaquine, quinine, quinidine, mefloquine, primaquine, lumefantrine, halofantrine and tafenoquine. Mefloquine is in the subclass of 4-methanolquinolines, which also includes quinine and quinidine. Primaquine and tafenoquine are in the subclass of 8-aminoquinolines, although primaquine is the only 8-aminoquinoline in clinical use.[5]

Acquired brain injury

The Australian Institute of Health and Welfare (2007)[6] defines acquired brain injury as

> multiple disabilities arising from damage to the brain acquired after birth. It results in deterioration in cognitive, physical, emotional or independent functioning. It can be as a result of accidents, stroke, brain tumours, infection, poisoning, lack of oxygen, degenerative neurological disease etc.

In other words, the brain can be injured or damaged after birth by various different pathological mechanisms. Substances, chemicals or drugs which can damage the brain with high doses or chronic heavy use include amphetamines,[7] solvents,[8] lead,[9] and chemotherapy for cancer,[10] [11]especially high dose and intrathecal methotrexate.[12]

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[5] Travassos M and Laufer M (2017) Antimalarial drugs: An overview. UpToDate. Available at www.uptodate.com. Accessed 22-5-17.

[6] Australian Institute of Health and Welfare (2007) Disability in Australia: acquired brain injury. Bulletin 55. Available at http://www.aihw.gov.au/WorkArea/DownloadAsset.aspx?id=6442453666%20. Accessed 6-3-17.

[7] Silva AP, Martins T, Baptista S, Goncalves J, Agasse F, Malva JO. (2010) Brain injury associated with widely abused amphetamines: neuroinflammation, neurogenesis and blood-brain barrier. Current Drug Abuse Reviews. 3(4):239-54, Dec.

[8] Beckley J, Woodward J (2013) Volatile Solvents as Drugs of Abuse: Focus on the Cortico-Mesolimbic Circuitry. Neuropsychopharmacology. Dec; 38(13): 2555–2567.

[9] de Souza A, Narvencar KP, Desai PK, D'Costa Z, Nilajkar G. (2013) Adult lead encephalopathy. Neurological Research. 35(1):54-8, Jan.

[10] Ricard D, Taillia H, Renard JL. (2009) Brain damage from anticancer treatments in adults. Current Opinion in Oncology. 21(6):559-65, Nov.

[11] Lee E (2017) Overview of neurologic complications of platinum-based chemotherapy. UpToDate. Available at https://www.uptodate.com/contents/overview-of-neurologic-complications-of-platinum-based-chemotherapy?source=search_result&search=solvent%20encephalopathy&selectedTitle=17~150#H25. Accessed 6-3-17

[12] Lee E (2017) Overview of neurologic complications of non-platinum cancer chemotherapy. UpToDate. Available at https://www.uptodate.com/contents/overview-of-neurologic-complications-of-non-platinum-cancer-chemotherapy/print?source=search_result&search=solvent%20encephalopathy&selectedTitle=16~150. Accessed 6-03-17.

Chronic abusers of solvents show impairments in short-term memory, attention, response inhibition, and problem solving.[13] These impairments are associated with loss of white matter volume throughout the brain with a particularly high level of white matter abnormalities found in the frontal and temporal lobes.

De Souza et al (2013) discuss lead encephalopathy in adults.[14] Acute encephalopathy is often seen with levels of 150 µg/dl but chronic brain dysfunction may be present with levels of 70 µg/dl or less. Lead levels of 70 µg/dl may be associated with clinical features of encephalopathy and macroscopic brain lesions visible on CT and MRI. Cumulative lead exposure has been reported to be associated with an increase in the prevalence and severity of white matter disease.

In these examples of chemically induced brain damage, subjects demonstrate symptoms and signs of neurocognitive impairment, with evidence of lesions on CT of MRI. DSM-5 provides a definition of neurocognitive disorder, which may be classified as major or mild, and may be induced by a substance or medication.[15]

> Major neurocognitive disorder
> A. Evidence of significant cognitive decline from a previous level of performance in one or more cognitive domains (complex attention, executive function, learning and memory, language, perceptual-motor, or social cognition) based on:
>
> 1. Concern of the individual, a knowledgeable informant, or the clinician that there has been a significant decline in cognitive function; and
> 2. A substantial impairment in cognitive performance, preferably documented by standardized neuropsychological testing or, in its absence, another quantified clinical assessment.
>
> B. The cognitive deficits interfere with independence in everyday activities (i.e., at a minimum, requiring assistance with complex instrumental activities of daily living such as paying bills or managing medications).
> C. The cognitive deficits do not occur exclusively in the context of a delirium.
> D. The cognitive deficits are not better explained by another mental disorder (e.g., major depressive disorder, schizophrenia).
>
> Mild neurocognitive disorder
> A. Evidence of modest cognitive decline from a previous level of performance in one or more cognitive domains (complex attention, executive function, learning and memory, language, perceptual-motor, or social cognition) based on:
>
> 1. Concern of the individual, a knowledgeable informant, or the clinician that there has been a mild decline in cognitive function; and
> 2. A modest impairment in cognitive performance, preferably documented by standardized neuropsychological testing or, in its absence, another quantified clinical assessment.

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[13] Beckley J, Woodward J (2013) Volatile Solvents as Drugs of Abuse: Focus on the Cortico-Mesolimbic Circuitry. Neuropsychopharmacology. Dec; 38(13): 2555–2567.
[14] de Souza A, Narvencar KP, Desai PK, D'Costa Z, Nilajkar G. (2013) Adult lead encephalopathy. Neurological Research. 35(1):54-8, Jan.
[15] American Psychiatric Association (2013) Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. Arlington VA, pp.591-643.

B. The cognitive deficits do not interfere with capacity for independence in everyday activities (i.e., complex instrumental activities of daily living such as paying bills or managing medications are preserved, but greater effort, compensatory strategies, or accommodation may be required).
C. The cognitive deficits do not occur exclusively in the context of a delirium.
D. The cognitive deficits are not better explained by another mental disorder (e.g., major depressive disorder, schizophrenia).

Substance/Medication-Induced Major or Mild Neurocognitive Disorder
A. The criteria are met for major or mild neurocognitive disorder.
B. The neurocognitive impairments do not occur exclusively during the course of a delirium and persist beyond the usual duration of intoxication and acute withdrawal.
C. The involved substance or medication and duration and extent of use are capable of producing the neurocognitive impairment.
D. The temporal course of the neurocognitive deficits is consistent with the timing of substance or medication use and abstinence (e.g., the deficits remain stable or improve after a period of abstinence).
E. The neurocognitive disorder is not attributable to another medical condition or is not better explained by another mental disorder.

Diagnostic features
Substance/medication-induced major or mild NCD is characterized by neurocognitive impairments that persist beyond the usual duration of intoxication and acute withdrawal (Criterion B). Initially, these manifestations can reflect slow recovery of brain functions from a period of prolonged substance use, and improvements in neurocognitive as well as brain imaging indicators may be seen over many months(Grant et al. 1987; Monnig et al. 2012; Rourke and Grant 2009). If the disorder continues for an extended period, persistent should be specified. The given substance and its use must be known to be capable of causing the observed impairments (Criterion C). While nonspecific decrements in a range of cognitive abilities can occur with nearly any substance of abuse and a variety of medications, some patterns occur more frequently with selected drug classes. For example, NCD due to sedative, hypnotic, or anxiolytic drugs (e.g., benzodiazepines, barbiturates) may show greater disturbances in memory than in other cognitive functions. NCD induced by alcohol frequently manifests with a combination of impairments in executive-function and memory and learning domains. The temporal course of the substance-induced NCD must be consistent with that of use of the given substance (Criterion D). In alcohol-induced amnestic confabulatory (Korsakoff's) NCD, the features include prominent amnesia (severe difficulty learning new information with rapid forgetting) and a tendency to confabulate. These manifestations may co-occur with signs of thiamine encephalopathy (Wernicke's encephalopathy) with associated features such as nystagmus and ataxia. Ophthalmoplegia of Wernicke's encephalopathy is typically characterized by a lateral gaze paralysis.

In addition to or independent of the more common neurocognitive symptoms related to methamphetamine use (e.g., difficulties with learning and memory; executive function), methamphetamine use can also be associated with evidence of vascular injury (e.g., focal weakness, unilateral incoordination, asymmetrical reflexes). The most common neurocognitive profile approximates that seen in vascular NCD.

Mefloquine

Mefloquine has been available for malaria chemoprophylaxis since 1985 in Europe, since 1990 in the USA and has been used by more than 35 million travellers for this indication.[16] Mefloquine is well tolerated in most users, though it is known for its association with acute neuropsychiatric reactions, and therefore contraindicated in those with a history of psychiatric disorders (Australian Medicines Handbook 2017).[17] Such reactions include acute anxiety, depression, psychosis, restlessness, confusion, dizziness, vertigo and nightmares (Larium product information[18], Castelli et al 2010[19], Adshead 2014[20]). The frequency of adverse events is considerably lower when the drug is used at prophylactic doses (250 mg/week) than when it is used for treatment.[21]

Some individuals appear to be particularly susceptible to these acute reactions, including those with a history of psychiatric disorders, females, younger persons and those with a genetic predisposition (Castelli et al 2010[22], Nevin 2012[23], Ringqvist et al 2015[24], van Riemsdijk et al 2005[25]).

Mefloquine is on the World Health Organisation's List of Essential Medicines.[26] Essential medicines are those that satisfy the priority health care needs of the population. They are selected with due regard to disease prevalence and public health relevance, evidence of clinical efficacy and safety, and comparative costs and cost-effectiveness.[27] Use of mefloquine for pregnant women in the second and third trimester is sanctioned by the World

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[16] Schlagenhauf P, Adamcova M, Regep L, Schaerer MT, Rhein HG. (2010) The position of mefloquine as a 21st century malaria chemoprophylaxis. Malar J. Dec 9;9:357.
[17] Australian Medicines Handbook (2017) Mefloquine. Available at https://amhonline.amh.net.au/chapters/chap-05/antiprotozoals/antimalarials/mefloquine. Accessed 6-3-17.
[18] MIMS (2015) Larium. Full product information. Available at https://www.mimsonline.com.au.
[19] Castelli F, Odolini S, Autino B et al (2010) Malaria Prophylaxis: A Comprehensive Review. Pharmaceuticals (Basel) October; 3(10): 3212–3239.
[20] Adshead S. (2014) The adverse effects of mefloquine in deployed military personnel. J R Nav Med Serv. Vol 100(3):232-7.
[21] Gonzalez R, Hellgren U, Greenwood B, et al (2014). Mefloquine safety and tolerability in pregnancy: a systematic literature review. Malar J, 13: 75.
[22] Castelli F, Odolini S, Autino B et al (2010) Malaria Prophylaxis: A Comprehensive Review. Pharmaceuticals (Basel) October; 3(10): 3212–3239.
[23] Nevin RL (2012). [Comment] Mefloquine Blockade of Connexin 36 and Connexin 43 Gap Junctions and Risk of Suicide. Biol Psychiatry, 71: e1-e2.
[24] Ringqvist Å, Bech P, Glenthøj B, Petersen E. (2015) Acute and long-term psychiatric side effects of mefloquine: a follow-up on Danish adverse event reports. Travel Med Infect Dis. Jan-Feb;13(1):80-8.
[25] van Riemsdijk MM, Sturkenboom MC, Pepplinkhuizen L, Stricker BH (2005). Mefloquine increases the risk of serious psychiatric events during travel abroad: a nationwide case-control study in The Netherlands. J Clin Psychiatry 66: 199–204.
[26] WHO Model List of Essential Medicines, 19th list (2015). Available at http://www.who.int/medicines/publications/essentialmedicines/EML_2015_FINAL_amended_NOV2015.pdf?ua=1. Accessed 6-3-17.
[27] WHO (2017) Essential Medicines. Available at http://www.who.int/medicines/services/essmedicines_def/en/. Accessed 6-3-17.

Health Organisation, and the Centers for Disease Control allow the use of mefloquine even in the first trimester.[28]

The **Australian Medicines Handbook (2017)**[29] states the following in relation to the neuropsychiatric effects of mefloquine:

> As well as the CNS effects listed above, disorders such as anxiety, panic attacks, agitation, aggression, acute psychosis, depression, forgetfulness, encephalopathy, can occur and may be prolonged. About 40% occur after the first dose and about 75% by the third dose.
>
> Risk of serious CNS effects is around 1:10 000 of those taking prophylaxis (comparable to chloroquine); they are 10 times more likely during treatment.
>
> Risk factors include history of CNS events, mefloquine dose, severity of malaria, mefloquine within the previous 2 months; women appear to be more at risk than men.

The **Product Information**[30] for mefloquine (Larium) states that:

> *Neuropsychiatric effects*
> LARIAM may cause psychiatric symptoms in a number of patients, ranging from anxiety, paranoia, and depression to hallucinations and psychotic behaviour. On occasions, these symptoms have been reported to continue long after LARIAM has been stopped. LARIAM should not be prescribed in patients with a history of psychiatric symptoms and should be used with caution in patients with a previous history of depression.
>
> In chemoprophylaxis the safety profile of mefloquine is characterised by a predominance of neuropsychiatric adverse reactions. During prophylactic use, if signs of unexplained acute anxiety, depression, restlessness or confusion are noticed, these may be considered prodromal to a more serious event. In these cases, the drug must be discontinued. Because of the long half-life of mefloquine, adverse reactions to Lariam may occur or persist after discontinuation of the drug. In a small number of patients it has been reported that some neuropsychiatric events (including depression, dizziness or vertigo and loss of balance) may continue for months or longer after discontinuation of the drug. Therapy should be initiated one week before travel commences, as acute psychiatric effects are more likely to manifest at the start of treatment.

This information is similar to that stated in a 2013 **US Food and Drug Administration**[31] (FDA) drug safety communication.

> The mefloquine drug label already states that mefloquine should not be prescribed to prevent malaria in patients with major psychiatric disorders or with a history of seizures. The changes to

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[28] Schlagenhauf P, Adamcova M, Regep L, Schaerer MT, Rhein HG. (2010) The position of mefloquine as a 21st century malaria chemoprophylaxis. Malar J. Dec 9;9:357.
[29] Australian Medicines Handbook (2017) Mefloquine. Available at https://amhonline.amh.net.au/chapters/chap-05/antiprotozoals/antimalarials/mefloquine. Accessed 6-3-17.
[30] MIMS (2015) Larium. Full product information. Available at https://www.mimsonline.com.au.
[31] FDA Drug Safety Communication: FDA approves label changes for antimalarial drug mefloquine hydrochloride due to risk of serious psychiatric and nerve side effects. (2013). Available at: http://www.fda.gov/Drugs/DrugSafety/ucm362227.htm.

> the mefloquine drug label better describe the possibility of persistent neurologic (vestibular) adverse effects after mefloquine is discontinued and the possibility of permanent vestibular damage.
>
> In conducting its assessment of vestibular adverse reactions associated with mefloquine use, FDA reviewed adverse event reports from the FDA Adverse Event Reporting System (FAERS) and the published literature, identifying patients that reported one or more vestibular symptoms such as dizziness, loss of balance, tinnitus, and vertigo. Patients who reported vestibular adverse reactions were healthy with no known major medical problems prior to taking mefloquine for malaria prophylaxis. Some patients did not suspect their symptoms were due to mefloquine and continued to take the drug after the symptoms started.
>
> In many cases, these symptoms developed early in the course of treatment, sometimes after one or two doses of mefloquine. Dizziness, loss of balance, tinnitus, or vertigo persisted for months to years after mefloquine was discontinued, and permanent vestibular damage was diagnosed in some cases. These symptoms interfered with patients' daily activities and ability to work. Some cases described abnormal vestibular function tests and a diagnosis of vestibular damage. In some cases, the vestibular damage was thought to be caused by mefloquine use. Some patients reported recurrence of psychiatric and vestibular symptoms when they took mefloquine for the second time. Patients who experienced vestibular symptoms usually had concomitant psychiatric symptoms such as anxiety, confusion, paranoia, and depression. Some of the psychiatric symptoms persisted for months to years after mefloquine was discontinued.

A discussion about the boxed warning in "Psychiatric News" included a comment from the FDA's media spokesperson, who stated that: "in our decision to add a boxed warning about vestibular neurologic adverse effects, it made sense to also highlight the existing warning about psychiatric adverse effects".[32]

Tafenoquine

Tafenoquine is an 8-aminoquinoline drug that has not been approved for use in Australia. Its use is limited to clinical trials. Tafenoquine is active against all stages of the malaria parasite, but there is specific interest in it as an alternative to primaquine for eliminating the hypnozoites of *Plasmodium vivax* and preventing relapse.[33] It has a long half-life (2–3 weeks) and recent clinical studies indicate a single dose of 300 mg as the optimal clinical dose for radical cure.[34] The much shorter dosing regimen is an advantage compared with a 14 day course of the related 8-aminoquinoline primaquine.

The most common known adverse effects of tafenoquine are gastrointestinal problems, reversible asymptomatic methaemoglobinemia, reversible vortex keratopathy and haemolytic anaemia in individuals with G6PD deficiency.[35]

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[32] Levin A (2013). FDA warning highlights mefloquine's mental health risks. Psychiatr News, 48(18): 1.
[33] Rajapakse S, Rodrigo C, Fernando SD. (2015) Tafenoquine for preventing relapse in people with Plasmodium vivax malaria. Cochrane Database Syst Rev. Apr 29;4:CD010458.
[34] Green JA, Patel AK, Patel BR, et al (2014).Tafenoquine at therapeutic concentrations does not prolong fridericia-corrected QT interval in healthy subjects. J Clin Pharmacol, 54(9): 995-1005
[35] Dow GS, Liu J, Lin G, Hetzell B, Thieling S, McCarthy WF, Tang D, Smith B. (2015) Summary of anti-malarial prophylactic efficacy of tafenoquine from three placebo-controlled studies of residents of malaria-endemic countries. Malar J. Nov 26;14(1):473.

Primaquine

Primaquine was developed in the 1940s and it has been the standard treatment for radical cure of vivax and ovale malaria for more than 60 years. Primaquine has also been used in addition to the standard treatment of falciparum malaria in areas of low transmission to reduce transmissibility of the treated infection. It has sometimes been used as chemoprophylaxis and in mass treatment campaigns.[36]

Ashley et al (2014)[37] describe the risks and benefits of primaquine in a recent review. Primaquine is an 8-aminoquinoline, a descendant of the first generally available synthetic anti-malarial plasmoquine (plasmochin, pamaquine). The 8-aminoquinolines have unique anti-malarial properties. The 8-aminoquinolines kill mature gametocytes of *Plasmodium falciparum*, developing parasites of all species in the liver (causal prophylactic activity), the dormant hypnozoites of *Plasmodium vivax* and *Plasmodium ovale* (radical curative activity), and they have weak asexual stage activity (very weak for *P. falciparum*).

The principal biological activity of 8-aminoquinolines is thought to be due to highly reactive metabolites such as the 5-methoxy metabolite, which are short-lived *in vivo*. It has not been possible to dissociate the antimalarial properties of these drugs from their oxidant toxicity, which suggests that they have a common mechanism.[38]

The hypnozoitocidal activity of primaquine is predominantly a function of total dose administered; 3.5 mg base/kg (adult dose,15 mg/day for 14 days) prevents >90% of long latency *P. vivax* relapses, whereas twice the dose (total 7 mg base/kg; adult dose 30 mg/day for 14 days) is required for short latency frequently relapsing infections in east Asia and Oceania.[39]

After oral administration, primaquine is absorbed quickly, reaching peak plasma concentrations within approximately 2 hours. It has a large volume of distribution. In studies with healthy volunteers, the terminal elimination half-life was estimated at 4–6 hours.[40]

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[36] Recht J, Ashley EA, White NJ (2014) Safety of 8-Aminoquinoline Antimalarial Medicines. Geneva: World Health Organization;. Downloadable at: http://www.who.int/malaria/publications/atoz/9789241506977/en/.

[37] Ashley et al. (2014) Primaquine: the risks and the benefits. Malaria Journal, 13:418. Available at http://www.malariajournal.com/content/13/1/418. Accessed 13-2-17.

[38] Recht J, Ashley EA, White NJ (2014) Safety of 8-Aminoquinoline Antimalarial Medicines. Geneva: World Health Organization;. Downloadable at: http://www.who.int/malaria/publications/atoz/9789241506977/en/.

[39] Ashley et al. (2014) Primaquine: the risks and the benefits. Malaria Journal, 13:418. Available at http://www.malariajournal.com/content/13/1/418. Accessed 13-2-17.

[40] Recht J, Ashley EA, White NJ (2014) Safety of 8-Aminoquinoline Antimalarial Medicines. Geneva: World Health Organization;. Downloadable at: http://www.who.int/malaria/publications/atoz/9789241506977/en/.

Dosing of primaquine is limited by abdominal discomfort at doses over 1 mg/kg. In general, primaquine is well tolerated at individual doses ≤0.5 mg base/kg if given together with food. Some methaemoglobinaemia is common, but is very seldom dangerous.[41]

The main adverse effect of primaquine is oxidant haemolysis. Although some red cell loss may occur in normal subjects, patients who are G6PD deficient are particularly vulnerable. There are over 180 different genetic G6PD variants (gene frequency typically 3-30% in malaria endemic areas). Nearly all variants confer an unstable enzyme, which degrades more rapidly than the normal variant thereby rendering older red cells vulnerable to oxidant damage. The extent of haemolysis depends on the degree of G6PD deficiency and the dose and duration of exposure to primaquine.[42]

In six decades of primaquine use in approximately 200 million people, 14 deaths have been reported, of which 12 were from severe haemolysis, one was due to hepatic necrosis, and the cause the other was not stated. In 12 mass administration programmes for radical cure, 27 serious adverse events were reported, the majority of which were haemolysis. This gave an estimated incidence of 1.8 episodes of severe haemolysis per million people receiving mass administration.[43]

[41] Ashley et al. (2014) Primaquine: the risks and the benefits. Malaria Journal, 13:418. Available at http://www.malariajournal.com/content/13/1/418. Accessed 13-2-17.
[42] Ashley et al. (2014) Primaquine: the risks and the benefits. Malaria Journal, 13:418. Available at http://www.malariajournal.com/content/13/1/418. Accessed 13-2-17.
[43] Ashley et al. (2014) Primaquine: the risks and the benefits. Malaria Journal, 13:418. Available at http://www.malariajournal.com/content/13/1/418. Accessed 13-2-17.

Findings

Mefloquine

Reviews

Nevin and Ritchie (2016)[44] discuss the problem of diagnosing acute mefloquine intoxication, given that its symptoms may readily mimic those of acute stress reaction or other disorders attributable to deployment stressors. They suggest that in some people these symptoms are a "prodrome" for more chronic psychiatric effects as well as additional neurological effects likely due to central nervous system injury.

The authors state that no biomarkers or genotypes correlate with risk of mefloquine toxicity, nor has there been any imaging modality that can reliably diagnose mefloquine toxicity. Types of testing suggested as being potentially useful are functional MRI, neuropsychological testing and EEG.

Apart from the FDA warning and commentaries referencing this warning (Prescrire International 2014[45], Levin 2013), epidemiological papers cited in support of long term effects of mefloquine included the article based on adverse event reports by Ringqvist et al (2015), a case report of acute psychosis with persistent vertigo (Nevin 2012), a case report persistent neuropsychiatric effects after 3 months of mefloquine overdosage (Lobel et al 1998) and a case report in German of acute psychosis after mefloquine prophylaxis (Meszaros et al 1996). Animal studies and case reports of pathological effects of other quinolines are suggested as providing evidence of possible similar effects of mefloquine on the central nervous system.

Nevin and Croft (2016)[46] review the history of psychiatric effects attributed to malaria and discuss the potentially confounding role of the adverse effects of anti-malarial drugs, including mefloquine, in the attribution of certain psychiatric effects to malaria. They suggest that some psychiatric effects previously attributed to malaria may have been due in whole or in part to the effects of quinoline anti-malarials.

McCarthy (2015)[47] reviewed a number of aspects of mefloquine use in relation to the Australian Defence Force. The paper discusses a wide range of issues directly and indirectly related to chronic effects, including other toxic encephalopathies, neurotoxicology, historical aspects of mefloquine development and use, acute neuropsychiatric effects of mefloquine,

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[44] Nevin and Ritchie (2016) The mefloquine toxicity syndrome: A significant potential confounder in the diagnosis and management of PTSD and other chronic deployment-related neuropsychiatric disorders. In Post-Traumatic Stress Disorder and Related Diseases in Combat veterans (In Press). Springer International: Switzerland.

[45] Prescrire International (2014). Mefloquine: persistent vestibular disorders. Prescrire International, 23(150): 157.

[46] Nevin RL, Croft AM. (2016) Psychiatric effects of malaria and anti-malarial drugs: historical and modern perspectives. Malar J. 2016 Jun 22;15:332.

[47] McCarthy S (2015). Malaria prevention, mefloquine neurotoxicity, neuropsychiatric illness, and risk-benefit analysis in the Australian Defence Force. Journal of Parasitology Research, available at https://www.hindawi.com/journals/jpr/2015/287651/. Accessed 20-4-17.

barriers to reporting of symptoms in the military, and the possibility of misdiagnosis and mistreatment of cases.

There appeared to be only three articles which have been relied upon as direct evidence in support of a chronic mefloquine CNS toxicity syndrome: Ritchie et al (2013), Nevin (2014) and Ringqvist et al (2015). These papers are described below.

Gogtay and Ferner (2015)[48] advocate that mefloquine be reserved for third line use in the military, after doxycycline and atovaquone-proguanil, because its side-effect profile make it less suitable for use by combat troops. They were particular concerned about possible impairment of fine motor skills and coordination and acute psychosis, agitation or depression.

Nevin (2015)[49] wrote a section on chronic effects of mefloquine toxicity for a book chapter. He cites a case in which psychiatric symptoms lasted 12 months (Lysack et al 1998). He also refers to the FDA product warning. He suggests these effects as "reflecting central nervous system toxicity resulting from the drug's heterogeneous accumulation in the brain," which has been demonstrated in a study of rats (Dow et al 2003).

Quinn (2015)[50] has published a review of the pharmacology, cellular neurobiology, and membrane channel kinetics of mefloquine. The author states that

> Significant evidence now exists for a primary role for membrane channel blockade in the presentation and severity of adverse neuropsychiatric reactions in patients exposed to mefloquine at normal prophylactic or treatment levels. How these complex cellular interactions manifest as neuroelectrophysiological and neurochemical changes, synaptic dysfunction, or neuronal cell death is still not clear but it seems likely that the delicate balance between excitation and inhibition caused by mefloquine exposure, both intra- and intercellularly, is likely to play a central role with connexins and K_{ATP} channels both implicated in this process.
>
> Further studies, including functional and structural imaging of deep brain regions in patients suffering from mefloquine toxicity and examination of electrophysiological changes in cells of the substantia with mutation or variation in both K_{ATP} and connexin channels on exposure to mefloquine, could begin to elucidate the delicate interplay between excitation and inhibition in cases of mefloquine toxicoses.

Nevin (2014)[51] cites the European and U.S. product labeling for mefloquine warning of a risk of permanent and irreversible neurological sequelae including vertigo, loss of balance and symptoms of polyneuropathy as evidence in support of the permanent nature of certain

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[48] Gogtay NJ, Ferner RE. (2015) Mefloquine for malarial prophylaxis in military personnel. BMJ. Nov 3;351:h5797.
[49] Nevin (2015) Mefloquine and Posttraumatic Stress Disorder. In Textbook of Military Medicine. Forensic and ethical issues in military behavioural health. EC Ritchie (ed). Borden Institute. Washington DC. Pp. 277-296.
[50] Quinn J (2015) Complex Membrane Channel Blockade: A Unifying Hypothesis for the Prodromal and Acute Neuropsychiatric Sequelae Resulting from Exposure to the Antimalarial Drug Mefloquine. Journal of Parasitology Research. Article ID 368064, http://dx.doi.org/10.1155/2015/368064.
[51] Nevin RL (2014). Idiosyncratic quinoline central nervous system toxicity: historical insights into the chronic neurological sequelae of mefloquine. Int J Parasitol Drugs Drug Resist, 4: 118-25.

neurological effects of mefloquine. He proposes that many of the reported lasting adverse neurological effects of mefloquine are consistent with the chronic sequelae of a well characterized but idiosyncratic central nervous system (CNS) toxicity syndrome common to certain historical antimalarial and antiparasitic quinolines (pamaquine, plasmocid and clioquinol). These drugs were reported to have caused damage to brainstem nuclei in animal studies, as well as one report in an autopsy case of an overdose and persisting symptoms in a series of human cases.

Ritchie et al (2013)[52] acknowledge that long-term follow up of mefloquine intoxication is only rarely documented in the literature, although vertigo lasting as long as 18 months has been reported. Animal studies have shown a pattern of multifocal microscopic lesions of the brain and brainstem on histopathology with related antimalarial compounds. Rats given high doses of mefloquine had neuronal degeneration in brainstem nuclei.

Mefloquine has been implicated in many cases of aggressive violence or suicide. These behaviours may be due to mefloquine psychosis, which frequently involves vivid visual or auditory hallucinations, along with symptoms of derealisation, depersonalisation, compulsions toward dangerous objects, and morbid curiosity about death. The authors suggest that these symptoms may reflect an underlying limbic encephalopathy, sometimes with additional involvement of the prefrontal cortex, basal ganglia and brainstem.

Mawson (2013)[53] hypothesises that the therapeutic effectiveness of mefloquine and its adverse effects could be related to the ability of the 8-aminoquinolines to alter the metabolism of retinoids (vitamin A and its congeners) in the liver, resulting in an endogenous form of hypervitaminosis A. He proposes that through a process of mefloquine-induced dehydrogenase inhibition there follows the accumulation of retinoids in the liver, retinoid-induced hepatocellular damage, the spillage of stored retinoids into the circulation, and the transport of these compounds to the gut and brain in toxic concentrations.

Early Arctic explorers experienced hypervitaminosis A by consuming vitamin A-rich polar bear or seal liver. Reported symptoms included drowsiness, irritability, severe headaches, nausea, and various forms of impulsive and irrational behaviour. In addition to causing neuropsychiatric symptoms such as depression, psychosis, and violence, synthetic retinoids in particular have also been linked to a wide range of adverse and often severe gastrointestinal effects.

The retinoid hypothesis could be tested clinically by comparing cases of mefloquine toxicity and untreated controls in terms of retinoid profiles (retinol, retinyl esters, percent retinyl esters, and retinoic acid). Cases would be expected to have a significantly increased percentage of plasma retinyl esters as a fraction of total vitamin A, as well as increased retinoic acid concentrations.

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[52] Ritchie EC, Block J, Nevin RL. (2013) Psychiatric side effects of mefloquine: applications to forensic psychiatry. J Am Acad Psychiatry Law.;41(2):224-35.
[53] Mawson A. (2013) Mefloquine use, psychosis, and violence: a retinoid toxicity hypothesis. Medical Science Monitor. 19:579-83, Jul 15.

Shin et al (2012)[54] investigated the effect of mefloquine on autophagy in neuroblastoma cells, in order to study the mechanism associated with the adverse neurological effects of mefloquine. In this study, they identified mefloquine as a potent autophagy inducer. Suppression of autophagy significantly intensified mefloquine-mediated cytotoxicity.

Several other mechanisms have been proposed to explain mefloquine-associated neurotoxicity, including inhibition of acetylcholinesterase and butylcholinesterase, regulation of the adenosine receptor, suppression of p-glycoprotein and interference with neuronal calcium homeostasis, or oxidative stress. The role played by mefloquine mediated autophagy requires further elucidation.

Nevin (2012)[55] suggests that the neuropsychiatric adverse effects of mefloquine may be due altered gap junction communication. Heterogeneity in response to mefloquine, despite similar brain and serum concentrations, may be related to genetic polymorphisms in the MDR1 gene.

Castelli et al (2010)[56] reviewed all forms of malaria prophylaxis. The mechanism of action of mefloquine is not completely understood, though is probably similar to that of quinine but with a slower action. After oral administration, blood peak concentration is reached after 2-12 hours. Mean half-life of mefloquine is 14-27 days, therefore it can be administered weekly. Neuropsychiatric adverse events may occur during mefloquine chemoprophylaxis, from nightmares to psychosis. Usually, neuropsychiatric adverse effects occur after 2-3 doses, mostly in subjects with history of neuropsychiatric disturbances.

Neuropsychiatric disturbances after mefloquine intake are more frequent in women and in people under 34 years of age. Mefloquine-associated disturbances are due to personal hypersensitivity and travellers who do not report side effects during their first mefloquine use will probably not do so even during subsequent use.

When mefloquine is well tolerated after the first weeks of administration, it is generally well tolerated also for a longer period. The authors cite reports of mefloquine usage in different cohorts. In prospective study performed on 5120 Italian soldiers deployed in Somalia and Mozambique in 1992-94, mefloquine was well tolerated for as long as six months (Peragallo et al 1999); the same was observed in Peace Corps Volunteers up to 2.5 years (Lobell et al 1993). Significant side effects were reported in only 0.3% of German sailors who took mefloquine for six months (Chen et al 2006).

Toovey (2009)[57] reviewed studies concerning the neurotoxicity of mefloquine. Adverse events described in association with mefloquine use include nausea, dizziness, sleep disturbances,

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[54] Shin JH, Park SJ, Jo YK et al (2012) Suppression of autophagy exacerbates Mefloquine-mediated cell death. Neuroscience Letters. 515(2):162-7, May 02.
[55] Nevin RL (2012). [Comment] Mefloquine Blockade of Connexin 36 and Connexin 43 Gap Junctions and Risk of Suicide. Biol Psychiatry, 71: e1-e2.
[56] Castelli F, Odolini S, Autino B et al (2010) Malaria Prophylaxis: A Comprehensive Review. Pharmaceuticals (Basel) October; 3(10): 3212–3239.
[57] Toovey S. (2009) Mefloquine neurotoxicity: a literature review. Travel Med Infect Dis. Jan;7(1):2-6.

anxiety, and frank psychosis and hearing loss. The incidence of "disabling" neuropsychiatric events has varied from 0.1% to 14%, with a higher rate reported for treatment than prophylaxis.

Nevin (2009)[58] raises the novel hypothesis, "based solely on biological plausibility" that people who are heterozygous for the EPM1 gene may be more susceptible to epilepsy when taking mefloquine. People with this mutation have impairments in the normal spectrum of neuronal physiologic safeguards, with resulting neuronal hyperexcitability and hastening of neuronal cell death. He proposes post-marketing genetic studies in mefloquine users who have suffered seizures to test this hypothesis, as well as post-mortem studies of military personnel who had been taking mefloquine.

Systematic reviews

González et al (2014)[59] systematically reviewed published studies which evaluated the use of mefloquine for malaria prevention or treatment in pregnant women and which reported data on drug tolerability and/or pregnancy outcomes. 18 articles fitted the inclusion criteria, only one study was double-blind and placebo controlled. 8 reported safety data of mefloquine when used for malaria treatment and ten evaluated mefloquine in pregnant women for malaria prevention. Studies were conducted in Asia and Africa, where malaria is prevalent.

Mefloquine is considered appropriate for chemoprophylaxis for pregnant women travellers of all gestational ages to high risk areas by various expert agencies such as the United States Centers for Disease Control and Prevention and the French Reference Centre on Teratogenic Agents. Mefloquine was recently reclassified as pregnancy category B (though initially rated as C) by the US- Food and Drug Administration.

No differences were found in the risk of adverse pregnancy outcomes in women exposed to mefloquine compared to those exposed to other anti-malarials or to the general population. No trials reported any serious adverse effects, when mefloquine was used for either treatment or prevention. Common side effects were dizziness and gastrointestinal symptoms. Mefloquine combined with artesunate seems to be better tolerated than standard quinine therapy for non-severe falciparum malaria but a mefloquine loading (10 mg/kg) dose was associated with more dizziness compared with placebo.

Neuro-psychiatric adverse events (such as anxiety, depression, behavioural changes, etc.) are difficult to assess and monitor, especially in resource- constrained settings where malaria is endemic. Thus it is possible that such adverse events were underreported.

The evidence provided by one previous large but not randomised or blinded study suggests that the tolerability to mefloquine when used as prophylaxis in pregnant women is similar to that of chloroquine, although the risk of dizziness might be higher with mefloquine (Steketee et

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[58] Nevin RL (2009). Epileptogenic potential of mefloquine chemoprophylaxis- a pathogenic hypothesis. Malaria Journal, 8- 188

[59] González R, Hellgren U, Greenwood B, Menéndez C. (2014) Mefloquine safety and tolerability in pregnancy: a systematic literature review. Malar J. Feb 28;13:75.

al 1996). The only randomized, controlled, double-blind trial which compared mefloquine tolerability to placebo did not find differences in the rates of reported adverse effects between study arms in those not given a mefloquine loading dose (Nosten et al 1994).

The authors highlight the need for more randomised and blinded trials. When study participants are aware of the possibility of specific adverse events either through the consent form or through general knowledge of the drug, reporting rates of those adverse events typically increase. Such knowledge is also likely to affect the evaluation of relatedness to the drug treatment by the investigator. In the trial by Brian et al 2009, it was observed that the frequency of related adverse events decreased with increasing number of doses, as in other studies of chemoprophylaxis with mefloquine in pregnancy, but also in reports from travellers, indicating that a true tolerance effect might play a role. However, the incidence of adverse events reporting also decreases with time in the placebo group in absence of drug treatment.

Mefloquine combined with artesunate seems to be better tolerated than standard quinine therapy for treatment of non-severe falciparum malaria, but a mefloquine loading dose (10 mg/kg) was associated with more dizziness compared with placebo. When used for intermittent preventive treatment, mefloquine (15 mg/kg) may have more side effects than sulphadoxine- pyrimethamine.

In a Cochrane review of randomised trials, **Jacquerioz and Croft (2009)**[60] compared the effects of currently used antimalarial drugs when given as prophylaxis to non-immune adult and child travellers who are travelling to regions with *Plasmodium falciparum* resistance to chloroquine. Eight trials met the inclusion criteria. The term “neuropsychiatric adverse effects” was not defined.

Limited evidence showed that mefloquine users have worse total mood disturbance scores and experience more neuropsychiatric adverse outcomes (events and effects) than users of atovaquone-proguanil or doxycycline. This review was withdrawn in October 2015 due to errors in a subsidiary analysis of observational studies.[61]

Randomised controlled trials

González et al (2014)[62] evaluated the safety and efficacy of mefloquine for intermittent preventive treatment in pregnancy compared to sulfadoxine-pyrimethamine (SP) in 4,749 HIV-negative women in an open-label randomised clinical trial conducted in Benin, Gabon, Mozambique, and Tanzania. The study arms were: (1) SP, (2) single dose mefloquine (15 mg/kg), and (3) split-dose mefloquine in the context of long lasting insecticide treated nets.

Serious adverse events (SAEs) were defined as an AE that met any of the following criteria: (1) results in death, (2) is life-threatening, (3) requires hospitalisation (or prolongation of

[60] Jacquerioz FA, Croft AM. Drugs for preventing malaria in travellers. Cochrane Database Syst Rev. 2009 Oct 7;(4):CD006491.

[61]

[62] González et al (2014) Intermittent preventive treatment of malaria in pregnancy with mefloquine in HIV-negative women: a multicentre randomized controlled trial. PLoS Med. 2014 Sep 23;11(9):e1001733.

existing hospitalisation), (4) results in disability/incapacity, (5) is a congenital anomaly, or (6) any event of special interest (including miscarriage and stillbirths of women not admitted to hospital).

Mefloquine recipients had less clinical malaria than SP recipients, and the pregnancy outcomes and safety profile were similar. Tolerability was poorer in the two mefloquine groups compared to SP. The most frequently reported related adverse events were dizziness (ranging from 33.9 -35.5% after dose 1; and 16.0 - 20.8% after dose 2) and vomiting (30.2 - 31.7%, after dose 1 and 15.3 - 17.4% after dose 2) with similar proportions in the full and split mefloquine arms.

The number of women who had SAEs considered as drug-related by the site investigator was higher in the mefloquine groups: one in the SP group (0.1%; a miscarriage), 11 in the mefloquine full-dose group (0.7%; one urinary tract infection, one generalized urticaria, one stillbirth, one premature delivery, two miscarriages, and five vomiting episodes), and ten in the mefloquine split-dose group (0.6%; two miscarriages, two stillbirths, three preterm delivery, one malaria, and three vomiting episodes). No psychiatric events were reported in the mefloquine arm. No serious neurological adverse events were reported among study participants.

A limitation of this study is that only two doses of drug were administered, so effects after longer term use could not be evaluated.

Nasveld et al (2010)[63] conducted a randomised, double-blinded phase III trial of the safety, tolerability, and effectiveness of tafenoquine compared with mefloquine for malaria prophylaxis in a group of Australian soldiers deployed for 6 months. Subjects received weekly malaria prophylaxis with 200 mg tafenoquine (492 subjects) or 250 mg mefloquine (162 subjects) for 6 months on a peacekeeping deployment to East Timor. After returning to Australia, tafenoquine-receiving subjects received a placebo and mefloquine-receiving subjects received 30 mg primaquine daily for 14 days.

There were no clinically significant differences between haematological and biochemical parameters of the treatment groups. Treatment-related adverse events for the two groups were similar (tafenoquine, 13.4%; mefloquine, 11.7%). Three subjects on tafenoquine (0.6%) and none on mefloquine discontinued prophylaxis because of possible drug-related adverse events. The adverse events in those taking tafenoquine were abdominal pain (severe), depression (moderate) and hyperesthesia (moderate).

In total, 64 (13.0%) tafenoquine subjects and 23 (14.2%) mefloquine subjects reported neuropsychiatric adverse events, the most common being vertigo, dizziness and various sleep disorders. There was no significant difference between the treatment groups in the incidence

[63] Nasveld PE, Edstein MD, Reid M, Brennan L, Harris IE, Kitchener SJ, Leggat PA, Pickford P, Kerr C, Ohrt C, Prescott W; Tafenoquine Study Team (2010) Randomised, double-blind study of the safety, tolerability, and efficacy of tafenoquine versus mefloquine for malaria prophylaxis in nonimmune subjects. Antimicrob Agents Chemother. Feb;54(2):792-8.

and type of neuropsychiatric events. All events were reported as mild or moderate, and none as severe.

In a subset of subjects recruited for detailed safety assessments, treatment-related mild vortex keratopathy was detected in 93% (69 of 74) of tafenoquine subjects but none of the 21 mefloquine subjects. The vortex keratopathy was not associated with any effect on visual acuity and was fully resolved in all subjects by 1 year.

TABLE 1 NEUROPYCHIATRIC EVENTS IN SUBJECTS ON TAFENOQUINE OR MEFLOQUINE (PROPHYLACTIC PHASE)

Adverse event	No. (%) of subjects by AE severity and treatment group					
	Mild		Moderate		Total	
	Tafenoquine	Mefloquine	Tafenoquine	Mefloquine	Tafenoquine	Mefloquine
Vertigo	22 (5)	7 (4)	0	1 (<1)	22 (5)	8 (5)
Somnolence	12 (2)	6 (4)	0	0	12 (2)	6 (4)
Abnormal dreams	7 (1)	2 (1)	0	0	7 (1)	2 (1)
Dizziness	5 (1)	2 (1)	0	0	5 (1)	2 (1)
Insomnia	4 (<1)	3 (2)	1 (<1)	0	5 (1)	3 (2)
Abnormal coordination	2 (<1)	1 (<1)	0	0	2 (<1)	1 (<1)
Anxiety	2 (<1)	0	0	0	2 (<1)	0
Agitation	2 (<1)	0	0	0	2 (<1)	0
Euphoria	2 (<1)	0	0	0	2 (<1)	0
Tremor	2 (<1)	0	0	0	2 (<1)	0
Depression	0	0	1 (<1)	1 (<1)	1 (<1)	1 (<1)
Paroniria	1 (<1)	0	0	0	1 (<1)	0
Amnesia	1 (<1)	0	0	0	1 (<1)	0

[a] In total, there were 492 tafenoquine subjects and 162 mefloquine subjects. There were no severe adverse events (AEs) of this type.

Schlagenhauf et al (2003)[64] compared the tolerability of malaria chemoprophylaxis regimens in non-immune travellers in a randomised, double blind, study set in travel clinics in Switzerland, Germany, and Israel. 623 non-immune travellers to sub-Saharan Africa: 153 each received either doxycycline, mefloquine, or the fixed combination chloroquine and proguanil, and 164 received the fixed combination atovaquone and proguanil.

Tolerability was assessed with three questionnaires. Participants completed these during recruitment and at follow up 13-11 days before departure, 6-4 days before departure, and 7-14 days after return.

A high proportion of patients reported adverse events, even in the initial placebo group. No events were serious (ie required hospitalisation).The mefloquine arm had the highest proportion of moderate to severe neuropsychological adverse events, particularly in women (8 graded as severe). Symptoms of neuropsychiatric events included headache, strange or vivid dreams, dizziness, anxiety, depression, sleeplessness, and visual disturbance. There was a significant excess of moderate neuropsychological problems with mefloquine compared with doxycycline and combined atovaquone and proguanil but not with combined chloroquine and proguanil.

In this trial Pfizer, GlaxoSmithKline, Roche, and Zeneca provided the drugs free of charge. GlaxoSmith Kline and Roche provided research grants. The guarantors accepted full

[64] Schlagenhauf P, Tschopp A, Johnson R, Nothdurft HD, Beck B, Schwartz E, Herold M, Krebs B, Veit O, Allwinn R, Steffen R. (2003) Tolerability of malaria chemoprophylaxis in non-immune travellers to sub-Saharan Africa: multicentre, randomised, double blind, four arm study. BMJ. Nov 8;327(7423):1078.

responsibility for the conduct of the study, had access to the data, and controlled the decision to publish. Competing interests were declared by three of the authors.

TABLE 2 ADVERSE EVENTS BY DRUG, TYPE AND SEVERITY

Table 2 Proportion of participants in each antimalarial prophylaxis arm reporting adverse events, by type and severity, Values are numbers (percentages, 95% confidence intervals) unless stated otherwise

Type of adverse event	Mefloquine group (n=153)	Chloroquine and proguanil group (n=153)	Doxycycline group (n=153)	Atovaquone and proguanil group (n=164)	P value
Neuropsychological*:					
Severe	8 (5, 2 to 9)	6 (4, 1 to 7)	1 (1, 0 to 2)	5 (3, 0 to 6)	0.139
Moderate	56 (37, 29 to 44)	46 (30, 23 to 37)	36 (24, 17 to 30)	32 (20, 13 to 26)	0.003
All events	118 (77, 70 to 84)	107 (70, 63 to 77)	105 (69, 61 to 76)	109 (67, 60 to 74)	0.187
Gastrointestinal†:					
Severe	6 (4, 1 to 7)	9 (6, 2 to 10)	3 (2, 0 to 4)	5 (3, 0 to 6)	0.312
Moderate	24 (16, 10 to 22)	31 (20, 14 to 27)	14 (9, 5 to 14)	26 (16, 10 to 22)	0.058
All events	89 (58, 50 to 66)	93 (61, 53 to 69)	81 (53, 45 to 61)	88 (54, 46 to 61)	0.451
Skin‡:					
Severe	1 (1, 0 to 2)	2 (1, 0 to 3)	3 (2, 0 to 4)	1 (1, 0 to 2)	0.635
Moderate	2 (1, 0 to 3)	12 (8, 4 to 12)	5 (3, 1 to 6)	4 (2, 0 to 5)	0.013
All events	36 (24, 17 to 30)	40 (26, 19 to 33)	36 (24, 17 to 30)	34 (21, 15 to 27)	0.730
Skin and vaginal§:					
Severe	2 (1, 0 to 3)	2 (1, 0 to 3)	4 (3, 0 to 5)	1 (1, 0 to 2)	0.509
Moderate	5 (3, 1 to 6)	13 (9, 4 to 13)	9 (6, 2 to 10)	4 (2, 0 to 5)	0.058
All events	45 (29, 22 to 37)	45 (29, 22 to 37)	42 (28, 20 to 35)	40 (24, 18 to 31)	0.717
Other:					
Severe	3 (2, 0 to 4)	5 (3, 0 to 6)	4 (3, 0 to 5)	2 (1, 0 to 3)	0.644
Moderate	12 (8, 4 to 12)	16 (11, 6 to 15)	12 (8, 4 to 12)	12 (7, 3 to 11)	0.748
All events	46 (30, 23 to 37)	47 (31, 23 to 38)	48 (31, 24 to 39)	36 (22, 16 to 28)	0.201

*Symptoms include headache, strange or vivid dreams, dizziness, anxiety, depression, sleeplessness, and visual disturbance.
†Nausea, diarrhoea, mouth ulcers.
‡Itching, abnormal reddening of skin.
§Itching, abnormal discharge.

van Riemsdijk et al (2002)[65] conducted a randomised double-blind, placebo-controlled trial to compare the occurrence of neuropsychiatric adverse events and concentration impairment during prophylactic use of either mefloquine (250 mg) or atovaquone plus chloroguanide (proguanil). The 119 subjects (mean age 35 years) were drawn from a population of persons attending a travel clinic in Rotterdam. Each subject was followed up from a baseline screening visit up to the index date, a scheduled visit 7 days after he or she left the malaria-endemic area.

They measured the interindividual and intraindividual changes in mood disturbance by means of the Dutch shortened Profile of Mood States and 3 domains of the Neurobehavioral Evaluation System, which included sustained attention, coding speed, and visuomotor accuracy between baseline and follow-up visit.

A total of 140 subjects enrolled in the cohort, 119 (85%) of whom completed the follow-up. Of the 21 who did not complete the study, 14 (67%) were taking mefloquine and 7 (33%) atovaquone plus chloroguanide. The reasons that subjects did not complete the study were as follows: cessation of use of the study medication because of adverse events (4 while taking atovaquone plus chloroguanide and 9 while taking mefloquine), withdrawal of informed

[65] van Riemsdijk MM, Sturkenboom MC, Ditters JM, Ligthelm RJ, Overbosch D, Stricker BH (2002). Atovaquone plus chloroguanide versus mefloquine for malaria prophylaxis: a focus on neuropsychiatric adverse events. Clin Pharmacol Ther 72: 294–301.

consent (n = 4), cancellation of the trip (n = 1), and staying abroad (n = 1). A further 2 subjects were excluded because they were suspected to have switched study drugs.

A significant deterioration in depression, anger, fatigue, vigour, and total mood disturbance domains occurred during use of mefloquine but not during use of atovaquone plus chloroguanide. This effect occurred during early use only (under 23 days) and occurred primarily in women.

Measures of concentration impairment showed no significant difference in change between subjects taking atovaquone plus chloroguanide and those taking mefloquine. In both treatment groups, sustained attention deteriorated after travel, especially with increased duration of stay, suggesting that the change might be related to travel rather than chemoprophylaxis.

A limitation of this study was a failure to analyse the data on an intention to treat basis, especially as 13 subjects did not complete the study due to undescribed adverse events.

TABLE 3 CHANGES IN SCORES ON PROFILE OF MOOD STATES

	Score		*Mean difference**		*P value between treatment arms†*
Domain	t_0	t_1	t_1–t_0	*95% CI*	
Atovaquone plus chloroguanide					
Tension	1.70	1.18	–0.52	–1.20 to 0.16	.451
Depression	0.49	0.46	–0.03	–0.54 to 0.48	**.006**
Anger	1.07	1.39	0.32	–0.36 to 1.02	.246
Fatigue	2.49	2.75	0.26	–0.78 to 1.30	**.005**
Vigor	11.82	11.54	–0.28	–1.52 to 0.96	**.026**
TMD	–6.07	–5.75	0.32	–2.50 to 3.13	**.005**
Mefloquine					
Tension	1.76	1.66	–0.10	–0.99 to 0.79	.451
Depression	0.29	1.86	**1.57**	**0.52 to 2.62**	**.006**
Anger	1.16	2.16	**1.00**	**0.07 to 1.93**	.246
Fatigue	2.10	4.90	**2.80**	**1.33 to 4.26**	**.005**
Vigor	12.62	10.36	**–2.26**	**−3.50 to −1.01**	**.026**
TMD	–7.31	0.21	**7.52**	**3.32 to 11.71**	**.005**

t_0, Baseline; t_1, follow-up visit; CI, confidence interval; TMD, tension plus depression plus anger plus fatigue minus vigor. Statistically significant differences are printed in bold.
*Mean difference in score between baseline measurement and after returning from travel (t_1–t_0) plus 95% CI.
†Comparison of mean difference per score between atovaquone plus chloroguanide and mefloquine.

Boudreau et al (1993)[66] report the findings of a randomised double-blind clinical trial involving 359 US Marines to assess tolerance of two prophylactic mefloquine regimens [250 mg weekly (n = 157) or 250 mg daily for 3 days followed by 250 mg weekly (n = 46)] compared with 300 mg weekly chloroquine (n = 156) over a 12-week period. The study participants were seen daily for four days, then weekly for 11 weeks. On each visit, the subject answered two computerized questionnaires (a review of body systems and an evaluation of mood states), participated in a physician interview, and was administered medications under supervision.

A random sample of each group was assigned to either pharmacokinetic sampling or two wear a wrist watch size computerised sleep monitor (actigraph). The frequencies of intercurrent illness and other concomitant medications were tabulated. End study mefloquine plasma levels were obtained on all study participants.

[66] Boudreau E, Schuster B, Sanchez J, et al (1993). Tolerability of prophylactic lariam regimens. Tropical medicine and parasitology, 44(3): 257-265.

The results obtained showed no compromise in function due to dizziness or incoordination in the mefloquine groups. Overall, both weekly mefloquine and loading dose mefloquine were well tolerated. Sleep disturbance and increased dream activity were detected in the mefloquine groups. Depressive feelings were noted in two to three times more individuals in the mefloquine groups than in the chloroquine group early in the course of the study (relative risks and confidence intervals not calculated). There was variability of symptoms over time, with evidence of a decline in depression as tolerance developed in the loading mefloquine group. Two individuals receiving mefloquine were hospitalised for depression during the course of the study, with both having had prior psychiatric problems.

TABLE 4 MOOD SYMPTOMS

	Weekly Mefloquine	Loading Mefloquine	Chloro-quine
Initial week (day 4)			
Depressed	10.3 %	17.8 %	5.2 %
Dizzy	10.3 %	6.7 %	3.3 %
Coordination off	3.2 %	8.9 %	0.7 %
Eyes irritated	5.1 %	0 %	11.7 %
Mid-study (week 6)			
Depressed	16.9 %	7.5 %	6.3 %
Irritable	14.3 %	12.5 %	5.6 %
Hands shaking	7.8 %	2.5 %	2.1 %
Nauseous	9.1 %	0 %	4.2 %

These symptoms demonstrate significant differences between groups.
% = # of individuals with symptoms/# in group × 100

TABLE 5 ACTIGRAPH DATA SLEEP PARAMETERS

	Weekly Mefloquine	Loading Mefloquine	Chloro-quine
Total sleep time (minutes per night)	340 (73)	341 (99)	362 (71)
Percent sleep	76 % (11)	77 % (12)	81 % (9)
Average activity	11.5 (5.7)	10.7 (4.9)	9.5 (4.2)
Sleep quality index	39.7 (10.4)	43.5 (11.3)	39.2 (6.4)

Uncontrolled cohort studies and clinical trials

Lee et al (2017)[67] presented the side effect profile of mefloquine for the treatment of uncomplicated malaria on the Thai-Myanmar/Cambodia borders. In total 19,850 patients received seven different regimens containing either 15 or 24-25 mg/kg of mefloquine, the latter given either as a single dose, or split over two or three days. Mefloquine was given alone or in combination with artesunate, artemether or sulfadoxine-pyrimethamine, The analysis focused on (predominantly) gastrointestinal and neuropsychiatric events as compared to the new fixed dose combination of mefloquine plus artesunate given as equal doses of 8 mg/kg MQ per day over three days.

[67] Lee SJ, Ter Kuile FO, Price RN, Luxemburger C, Nosten F. Adverse effects of mefloquine for the treatment of uncomplicated malaria in Thailand: A pooled analysis of 19, 850 individual patients. PLoS One. 2017 Feb 13;12(2):e0168780.

Serious neurological or psychiatric complications were defined as any event involving the Central Nervous System and requiring medical attention. These included acute psychosis, delusions, hallucinations, anxiety neuroses, major disorders of affect, disturbed consciousness, and seizures.

Serious neuropsychiatric side effects associated with mefloquine use were rare, with a total of 15 cases identified. Two of the four patients with serious psychiatric reactions had a history of psychiatric disorders. For a single 25 mg/kg dose the rate if serious reactions was 11.9 per 10,000 treatments (95% CI 4-285) vs. 7.8 (95% CI 3-15) for the 15 mg/kg dose. The risk with 25 mg/kg was much higher when it was given as repeat dosing in patients who had failed treatment with 15 mg/kg MQ in the preceding month; (RR 6.57, 95% CI 1.33 - 32.4). MQ was best tolerated as 15 mg/kg or as 24 mg/kg when given over three days in combination with artesunate.

Terrell et al (2015)[68] compared the effects of mefloquine and doxycycline on the ability to work as measured by self-reported severity of adverse effects via a questionnaire. Participants were UK soldiers selected from 10 consecutive units training in Kenya during 2012 and 2013.

Completion rates were consistently poor throughout the study period with only 150 to 250 questionnaires returned per tranche of around 1,000 troops. Questionnaires were available from 938 mefloquine users and 752 doxycycline users, with 891 of 938 (95.0%) mefloquine users and 695 of 752 (92.4%) doxycycline users reporting that they had taken their drugs as prescribed.

Of the 867 mefloquine users who reported on the impact of adverse effects, 109 (12.6%) reported that one or more adverse effects had impacted upon their ability to do their job, compared to 152 (22.2%) of the 685 doxycycline users who had reported on the impact of any adverse effects ($p < 0.0001$).

The authors did not report on the particular symptoms experienced by these soldiers. A literature review identified a higher proportion of gastrointestinal and dermatological symptoms in travellers taking doxycycline, whereas mefloquine users had a higher proportion of neuropsychiatric symptoms.

[68] Terrell AG, Forde ME, Firth R, Ross DA. (2015) Malaria Chemoprophylaxis and Self-Reported Impact on Ability to Work: Mefloquine Versus Doxycycline. J Travel Med. Nov-Dec;22(6):383-8.

TABLE 6 ADVERSE EVENTS IN TRAVELLERS

Adverse effect	Mefloquine	Doxycycline
Strange dreams	325/4220 (7.7%)	10/2185 (0.5%)
Sleep disturbance	396/4220 (9.4%)	109/2185 (5.0%)
Dizziness/vertigo	255/4220 (6.0%)	67/2185 (3.1%)
Headache	253/4220 (6.0%)	140/2185 (6.4%)
Fatigue/tiredness	125/4220 (3.0%)	96/2185 (4.4%)
Visual difficulty	72/4220 (1.7%)	—
Nausea	369/4020 (9.2%)	243/2185 (11.1%)
Diarrhea	273/4020 (7.3%)	347/2185 (15.9%)
Abdominal pain	104/4020 (2.6%)	125/2185 (5.7%)
Dyspepsia	5/4020 (0.1%)	61/2185 (2.8%)
Vomiting	33/4020 (0.8%)	22/2185 (1.0%)
Rash	38/1620 (2.3%)	19/558 (3.4%)
Itching	41/1620 (2.5%)	16/558 (2.9%)
Erythema	—	31/558 (5.6%)

In a critique of this study, **Nevin (2016)**[69] notes the poor response rates, which may introduce bias if non-responders are systematically different to responders. He also points out that the study did not specifically identify reports of anxiety and depression, although the purpose of the study was to assess the impact of symptoms on the ability of soldiers to work, rather than assess the symptoms themselves.

Saunders et al (2015)[70] conducted a survey of troops returning to Fort Drum, NY following a 12-month deployment to Operation Enduring Freedom, Afghanistan from 2006 to 2007. Of the 2,351 respondents, 95% reported taking at least one form of prophylaxis during their deployment, and 90% were deployed for > 10 months.

Compliance with daily doxycycline was poor (60%) compared with 80% with weekly mefloquine (MQ), although 26% did not report their compliance. Adverse events (AEs) were reported by approximately 30% with both MQ and doxycycline, with 10% discontinuing doxycycline compared with 4% of MQ users.

There were 596 subjects who took MQ prophylaxis during deployment. The two most common side effects reported were vivid dreams (23%) and dyspepsia (9.6%). The particular side-effects which led to discontinuation of MQ were not stated. It was also not stated whether or not there were any serious adverse events requiring hospitalisation or evacuation.

Adshead (2014)[71] conducted an uncontrolled prospective questionnaire-based cohort study of 150 deployed military personnel prescribed mefloquine as anti-malaria chemoprophylaxis.

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[69] Nevin RL. (2016) Bias in military studies of mefloquine. Journal of Travel Medicine. 23(2):tav028, Feb.
[70] Saunders DL; Garges E; Manning JE; Bennett K; Schaffer S; Kosmowski AJ; Magill AJ. (2015) Safety, Tolerability, and Compliance with Long-Term Antimalarial Chemoprophylaxis in American Soldiers in Afghanistan. American Journal of Tropical Medicine & Hygiene. 93(3):584-90, Sep.
[71] Adshead S. (2014) The adverse effects of mefloquine in deployed military personnel. J R Nav Med Serv. Vol 100(3):232-7.

Among 111 respondents taking mefloquine, 54% reported at least one adverse effect and 13% required a change in prescription to a second-line anti-malarial, due to significant side-effects. All females prescribed mefloquine reported at least one adverse reaction.

The two most common adverse effects were vivid dreams (39%) and sleep disturbance (38%). Less common adverse events included nightmares, anxiety, headache, nausea, vomiting and diarrhoea. There were two cases of clinically significant adverse reactions. Both case presented with palpitations and tachycardia shortly after taking mefloquine, but the symptoms resolved within hours. There were no consultations regarding adverse effects after day 17 of commencing mefloquine.

Carrara et al (2008)[72] assessed the effects on auditory function of a standard 3-day oral dose of artesunate (4 mg/kg/day) combined with mefloquine (25 mg/kg) in patients with acute uncomplicated falciparum malaria treated at the Shoklo Malaria Research Unit, on the Thai-Burmese border. Animal studies of artemisinin derivatives show neurotoxicity targeting mainly the auditory and vestibular pathways in the brainstem and cerebellum.

A complete auditory evaluation with tympanometry, audiometry and auditory brainstem responses (ABR) was performed before the first dose and seven days after initiation of the antimalarial treatment. Patients who had a positive rapid diagnosis test were eligible for the study provided that they gave fully informed consent.

Complete auditory tests at day 0 (D0) and day 7 (D7) were obtained for 93 patients. Hearing loss (threshold > 25 dB) on admission was common (57%) and associated with age only. Three patients had a small but measurable reduction in hearing threshold (5 dB for 2 patients and 10 dB for the last one); however none complained of a hearing loss. The authors thought it unlikely to be due to an ototoxic drug effect (asymmetric hearing loss, at the highest frequency only). No patient had a threshold change exceeding 10 dB between D0 and D7 at any tested frequency. No patient showed a shift in Wave III peak latency of more than 0.30 msec between baseline and D7.

The authors conclude that neither audiometric or the ABR tests showed clinical evidence of auditory toxicity seven days after receiving oral artesunate and mefloquine.

Fujii et al (2007)[73] investigated adverse events from mefloquine prophylaxis in Japanese service personnel deployed for a peacekeeping operation in East Timor. A total of 1,876 members were deployed between April 2002 and September 2003, for periods of 6 months. . All were put on mefloquine prophylaxis, starting one week before departure. Adverse events (AEs) were studied via questionnaires completed after the members returned home.

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[72] Carrara VI, Phyo AP, Nwee P et al (2008) Auditory assessment of patients with acute uncomplicated Plasmodium falciparum malaria treated with three-day mefloquine-artesunate on the north-western border of Thailand. Malaria Journal. 7:233.

[73] Fujii T, Kaku K, Jelinek T, Kimura M (2007). Malaria and mefloquine prophylaxis use among Japan Ground Self- Defense Force personnel deployed in east Timor. J Travel Med 14: 226–232.

Four members were evacuated: one each with optic neuritis, lung cancer with brain metastasis, IgA nephropathy, and psychotic reactions. It is likely that the first three cases were coincidental rather than causal – there are no other reports of optic neuritis or IgA nephropathy associated with mefloquine. The latter case was a 41-year-old man, who presented with hallucinations, psychomotor excitement, paranoia, and confusion approximately 1 month after starting mefloquine prophylaxis. Mefloquine prophylaxis was discontinued immediately after the onset of symptoms. On return to Japan, he was diagnosed as catatonic schizophrenia and was hospitalized for 2 months until the main symptoms subsided. The authors do not state whether or not this case had past history of family history of pscyhosis before taking mefloquine.

About 24% of questionnaire respondents reported AEs; however, none of the AEs was severe. Among the 447 members with AEs, 265 (59.3%) could identify the date on which the AEs first appeared. In nearly 45% of subjects, the AEs appeared within a day of the first dose. Cumulatively, AEs first appeared within 1 week, 1 month, 2 months, and 3 months in 49, 78, 86, and 94%, respectively. All AEs disappeared in due course despite continuing chemoprophylaxis in almost all individuals.

The cause of these AEs may have been multifactorial, with other contributing factors possibly including stress from international travel, tropical climates and an arduous mission, as well as other medications or intercurrent illnesses. Without a comparison group, it is unclear whether the incidence of AE was higher than expected. It is also noteworthy that the data on AEs was collected retrospectively, raising the possibility of recall bias.

TABLE 7 REPORTED ADVERSE EVENTS DUE TO MEFLOQUINE PROPHYLAXIS

Incidence ≥2.0%		2.0% > incidence ≥ 1.0%		1.0% > incidence ≥ 0.3%	
Symptom	No. (%)	Symptom	No. (%)	Symptom	No. (%)
Dizziness/vertigo	130 (7.1)	Sleepiness	29 (1.6)	Palpitation	14 (0.8)
Skin rash/dermatitis	92 (5.0)	Weakness	28 (1.5)	Arthralgia	13 (0.7)
Fatigue/lassitude	68 (3.7)	Abdominal pain	25 (1.4)	Fever	12 (0.7)
Sleep disturbance	49 (2.7)	Headache	23 (1.3)	Anorexia	12 (0.7)
Nightmares	41 (2.2)			Anxiety	10 (0.5)
Nausea	40 (2.2)			Constipation	8 (0.4)
Diarrhea	37 (2.0)			Tinnitus	8 (0.4)
				Chest pain	6 (0.3)
				Myalgia	5 (0.3)
				Amnesia	5 (0.3)

Kitchener et al (2005)[74] reported on a trial of mefloquine in 1157 Australian military personnel deployed to East Timor for 6 month periods in 2001 and 2002. Soldiers choosing not to enrol in the mefloquine study received doxycycline.

The most common adverse events relating to malaria prophylaxis with either drug were sleep disturbance, headache, tiredness and nausea. Apart from mild sleep disturbance, which was more common in soldiers taking mefloquine, and mild tiredness, which was more commonly associated with doxycycline, the incidence of these adverse events was similar for both drugs.

[74] Kitchener SJ, Nasveld PE, Gregory RM, Edstein MD. (2005) Mefloquine and doxycycline malaria prophylaxis in Australian soldiers in East Timor. Med J Aust. Feb 21;182(4):168-71.

There were nine serious adverse events (not described) and three withdrawals from the study due to neuropsychiatric reactions possibly related to mefloquine. Two of these cases had prior undisclosed contraindications (a history of auditory hallucinations and a history of epilepsy), and had recurrence of these problems while taking mefloquine. The third soldier experienced depression, episodic anxiety, mild paranoia, short-term memory loss and suicidal ideation. Although he was taken off mefloquine and placed on doxycycline, his mental state continued to deteriorate. He was psychologically evaluated and returned to Australia.

Jaspers et al (1996)[75] reported on adverse events in a battalion of Dutch marines stationed in Cambodia from June until October 1993. In 73 volunteers who used mefloquine as malaria chemoprophylaxis, possible mefloquine-related adverse events were monitored with special emphasis on QT prolongation. All participants started mefloquine chemoprophylaxis with a loading dose (250 mg a day for three days) one week before departure, followed by a weekly dose (250 mg) for approximately 25 weeks.

Spontaneously reported complaints were noted one month before (t -1) and one (t + 1) and three (t + 3) months after the start of mefloquine chemoprophylaxis. Thereafter, specific questions were asked about the use of other medications and adverse events possibly associated with mefloquine (headache, dizziness, ataxia, nausea, diarrhoea, rash, sleeping disorders, visual or auditory disturbances, psychiatric disorders).

Adverse events such as dizziness, headache, coordination problems, and nausea were spontaneously reported in one (1.4%) and three (4.1%) persons at one month and 3 months after starting treatment, respectively. Specific questioning revealed adverse events in nine (12.3%) and five (6.9%) persons, respectively, at the same time points (symptoms not specified). One person was advised by the investigators to reduce the dosage to 250 mg/two weeks because of dizziness and coordination disorders; thereafter, he was free of these complaints. Eight other participants reported dizziness, diarrhoea, and coordination disorders during the 1-3 day period following the loading dose.

Three months after starting chemoprophylaxis, the heart rate at rest and total white blood cell count were significantly lower, while the QTc-interval was longer and levels of liver transaminases significantly increased, although both were still within the normal range. There was no extreme prolongation of the QTc-interval or increased levels of liver transaminases that resulted in a need to stop the chemoprophylaxis.

The authors concluded that mefloquine chemoprophylaxis was safe and well-tolerated in this group and did not interfere with daily military duties. The authors did not follow up on adverse events after cessation of treatment.

[75] Jaspers CA, Hopperus Buma AP, van Thiel PP, van Hulst RA, Kager PA (1996). Tolerance of mefloquine chemoprophylaxis in Dutch military personnel. Am J Trop Med Hyg 55: 230–234.

Cohort studies

Eick-Cost et al (2017)[76] estimated the occurrence of neuropsychiatric outcomes (NPOs) in service members prescribed mefloquine, which was widely prescribed to U.S. military service members until 2009 when use was limited to personnel with contraindications to doxycycline and no contraindications to mefloquine. Active component service members filling a prescription for mefloquine, doxycycline, or atovaquone/proguanil (A/P) between January 1, 2008 and June 30, 2013, were included in the analysis. A total of 367,840 individuals were evaluated (36,538 received mefloquine, 318,421 received doxycycline, and 12,881 received A/P).

The risk of developing incident NPOs and the risk of subsequent NPOs among subjects with a history of the condition were assessed. The risk period for NPOs was defined as the entire duration of the prescription plus 365 days after the end of the prescription. Data from the Defense Medical Surveillance System (DMSS), the Pharmacy Data Transaction Service (PDTS), and the Theater Medical Data Store (TMDS) were used for this study. DMSS is the central repository of medical surveillance data for the U.S. Armed Forces and is maintained by the Armed Forces Health Surveillance Branch. DMSS contains longitudinal data on medical encounters. Ambulatory and inpatient medical encounters occurring in theatre or at fixed medical facilities during a risk period were searched for International Classification of Disease-Clinical Modification, 9th Revision codes for an NPO.

When compared with doxycycline recipients, deployed individuals prescribed mefloquine had an increased risk of incident anxiety (RR 1.12, 95% CI 1.01-1.24). However, the risk of anxiety disorder was significantly reduced in non-deployed individuals (RR 0.70, 95% CI 0.57–0.86). There was no increase in risk of any other NPO in either deployed or non-deployed individuals, including tinnitus.

When compared with A/P recipients, non-deployed mefloquine recipients had an increased risk of posttraumatic stress disorder (RR 1.83, 95% CI 1.07-3.14). However, the risk of posttraumatic stress disorder was not significantly increased in deployed personnel (RR 1.31, 95% CI 0.75–2.29). An increased risk of tinnitus was seen for both deployed and non-deployed mefloquine recipients compared with A/P recipients (RR 1.81, 95% CI 1.18-2.79, RR 1.51, 95% 1.13-2.03 respectively). There was no increase in risk of any other NPO in either deployed or non-deployed individuals.

6% of the mefloquine cohort had an NPO in the year before receiving mefloquine. When comparing individuals with a prior neuropsychiatric history to those without, the ratio of relative risks for adjustment disorder, anxiety, insomnia, and PTSD were higher but not statistically significant for mefloquine compared with doxycycline. Non-significant decreased risks for three outcomes were seen (borderline significant decreased risk for vertigo). It is likely that, with a larger sample size, anxiety (higher risk) and vertigo (lower risk) might reach statistical significance.

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[76] Eick-Cost AA, Hu Z, Rohrbeck P, Clark LL. (2017) Neuropsychiatric Outcomes After Mefloquine Exposure Among U.S. Military Service Members. Am J Trop Med Hyg. Jan 11;96(1):159-166.

In this large, retrospective cohort study of U.S. military service members, rates of NPOs among mefloquine recipients were similar or less than the rates among two other antimalarial prescribed cohorts for the majority of outcomes investigated. Mefloquine recipients were at increased risk of three outcomes (anxiety disorder in deployed but not non-deployed compared to doxycycline, PTSD in non-deployed but not deployed compared to atovaquone-proguanil, and tinnitus in deployed and non-deployed compared to atovaquone-proguanil but not doxycycline). Mefloquine recipients were at decreased risk for six outcomes.

The findings of this study should be interpreted in light of its limitations. The use of electronic medical data archived in DMSS allowed for near complete capture of diagnoses recorded during medical encounters; however, these data are dependent upon the accuracy of ICD-9 coding. Service members may have experienced outcomes for which they never sought medical care, or received care from sources not documented in DMSS. Such outcomes would not be captured in the analysis and would result in under-ascertainment of the NPOs. It is not expected that such misclassification of the outcome would differ by drug type, making the misclassification non-differential and biasing the results toward the null. Potentially one of the most significant limitations of this study is the lack of data on prescription compliance. A strength of this analysis is the large sample size which allowed for investigation of NPOs which are infrequently diagnosed.

TABLE 8 IRR OF EACH NEUROPSYCHIATRIC OUTCOME COMPARING THE MEFLOQUINE COHORT TO THE DOXYCYCLINE COHORT BY DEPLOYMENT STATUS

	Deployed		Nondeployed	
Outcome	Unadjusted IRR (95% CI)	Adjusted IRR* (95% CI)	Unadjusted IRR (95% CI)	Adjusted IRR* (95% CI)
Adjustment disorder	0.50 (0.47–0.54)	0.95 (0.88–1.02)	0.42 (0.37–0.48)	0.69 (0.60–0.80)
Insomnia	0.57 (0.53–0.62)	1.04 (0.95–1.14)	0.45 (0.38–0.53)	0.67 (0.56–0.81)
Anxiety disorder	0.62 (0.56–0.67)	1.12 (1.01–1.24)	0.50 (0.42–0.60)	0.70 (0.57–0.86)
Tinnitus	0.74 (0.67–0.81)	1.02 (0.92–1.13)	0.92 (0.80–1.07)	0.94 (0.80–1.11)
Depressive disorder	0.67 (0.61–0.74)	1.02 (0.92–1.15)	0.47 (0.39–0.57)	0.68 (0.55–0.84)
Vertigo	1.19 (0.93–1.52)	1.05 (0.79–1.40)	0.57 (0.35–0.93)	0.52 (0.31–0.88)
Posttraumatic stress disorder	0.71 (0.64–0.79)	1.08 (0.96–1.22)	0.56 (0.43–0.72)	0.69 (0.52–0.91)
Suicide ideation	0.46 (0.37–0.59)	1.03 (0.79–1.34)	0.36 (0.23–0.57)	0.90 (0.55–1.47)
Convulsions	0.62 (0.45–0.85)	0.83 (0.58–1.19)	0.79 (0.52–1.19)	1.10 (0.69–1.76)
Psychosis	0.38 (0.21–0.69)	0.64 (0.33–1.24)	0.66 (0.28–1.52)	1.13 (0.43–2.97)
Hallucinations	0.23 (0.09–0.63)	0.48 (0.17–1.39)	0.18 (0.02–1.30)	0.24 (0.03–1.99)
Paranoia	0.67 (0.16–2.81)	1.27 (0.24–6.57)	–	–
Suicide	1.01 (0.13–7.83)	0.87 (0.08–9.19)	1.64 (0.18–14.67)	2.94 (0.27–31.67)
Confusion	–	–	1.64 (0.18–14.67)	3.28 (0.21–50.02)

CI = confidence interval; IRR = incidence rate ratio.
*Models adjusted for age, sex, service, grade, year of prescription start; deployed model also adjusted for location and combat exposure.

TABLE 9 IRR OF EACH NEUROPSYCHIATRIC OUTCOME COMPARING THE MEFLOQUINE COHORT TO THE ATOVAQUONE/PROGUANIL COHORT BY DEPLOYMENT STATUS

	Deployed		Nondeployed	
Outcome	Unadjusted IRR (95% CI)	Adjusted IRR* (95% CI)	Unadjusted IRR (95% CI)	Adjusted IRR* (95% CI)
Adjustment disorder	0.91 (0.73–1.13)	1.01 (0.74–1.37)	1.38 (1.13–1.69)	1.31 (0.99–1.74)
Insomnia	0.68 (0.54–0.86)	0.80 (0.58–1.10)	0.94 (0.74–1.19)	1.07 (0.78–1.48)
Anxiety disorder	0.97 (0.71–1.33)	0.97 (0.64–1.48)	1.07 (0.82–1.39)	0.98 (0.67–1.43)
Tinnitus	1.31 (0.93–1.86)	1.81 (1.18–2.79)	1.24 (1.00–1.54)	1.51 (1.13–2.03)
Depressive disorder	1.76 (1.12–2.75)	1.56 (0.89–2.74)	1.25 (0.94–1.67)	1.36 (0.90–2.04)
Vertigo	1.27 (0.51–3.14)	1.24 (0.34–4.54)	0.83 (0.43–1.61)	1.04 (0.43–2.49)
Posttraumatic stress disorder	1.65 (1.04–2.61)	1.31 (0.75–2.29)	1.32 (0.90–1.94)	1.83 (1.07–3.14)
Suicide ideation	2.90 (0.71–11.82)	3.56 (0.45–28.40)	1.04 (0.54–1.98)	1.00 (0.36–2.79)
Convulsions	0.44 (0.21–0.95)	0.39 (0.14–1.12)	2.46 (1.15–5.27)	1.72 (0.60–4.92)
Psychosis	–	–	2.64 (0.53–13.10)	7.18 (1.00–51.65)
Hallucinations	0.18 (0.03–0.97)	0.09 (0.01–1.20)	0.18 (0.02–1.52)	0.43 (0.02–8.40)
Paranoia	–	–	–	–
Suicide	–	–	0.88 (0.06–14.09)	2.59 (0.03–225.47)
Confusion	–	–	–	–

CI = confidence interval; IRR = incidence rate ratio.
*Models adjusted for age, sex, service, grade, year of prescription start; deployed model also adjusted for location and combat exposure.

TABLE 10 IRR OF EACH NEUROPSYCHIATRIC OUTCOME COMPARING INDIVIDUALS WITH A 1-YEAR PRIOR HISTORY TO THOSE WITHOUT: STRATIFIED AND COMPARING MEFLOQUINE AND DOXYCYCLINE

	Diagnosis vs. no diagnosis of the condition in the 1 year before antimalarial medication		Mefloquine IRR compared with doxycycline IRR	
	Mefloquine cohort	Doxycycline cohort		
Outcome*	Adjusted IRR (95% CI)†	Adjusted IRR (95% CI)†	Bootstrap RRR (95% CI)	Permutation test *P* value
Adjustment disorder	5.47 (4.69–6.36)	4.86 (4.73–5.00)	1.13 (0.94–1.34)	0.81
Anxiety	16.95 (13.86–20.73)	13.50 (12.92–14.11)	1.26 (0.98–1.59)	0.17
Insomnia	7.62 (5.57–10.44)	6.66 (6.20–7.15)	1.14 (0.80–1.59)	0.61
Depressive disorder	12.54 (10.04–15.67)	12.58 (12.04–13.14)	1.00 (0.78–1.29)	0.38
PTSD	27.98 (20.71–37.82)	24.60 (23.17–26.12)	1.14 (0.78–1.65)	0.88
Tinnitus	7.52 (5.70–9.91)	8.05 (7.43–8.71)	0.93 (0.69–1.23)	0.60
Vertigo	4.32 (3.15–5.93)	5.90 (5.39–6.46)	0.73 (0.50–1.00)	0.06
Convulsions	122.7 (51.42–292.78)	134.80 (110.13–164.99)	0.91 (0.25–2.34)	0.73

CI = confidence interval; IRR = incidence rate ratio; PTSD = posttraumatic stress disorder; RRR = ratio of rate ratios.
*Outcomes not listed were not diagnosed in the 365 days before prescription.
†Models adjusted for age, sex, service, grade, year of prescription start, deployment status.

Wells et al (2006)[77] used standard military databases for mefloquine prescriptions and hospitalisations to investigate mefloquine safety among US service members from 2002 through 2004. Mefloquine-prescribed and deployed personnel (N= 8,858) were compared with two reference groups. The reference groups comprised US service members who were not prescribed mefloquine and resided in Europe or Japan (N = 156,203) or had been otherwise deployed (N = 232,381). Cox proportional hazards time-to-event modelling was used to compare the hospitalisation experience of these groups.

Follow up time began on return from deployment for mefloquine prescribed members, and for the deployed reference group, on assignment to Europe or Japan, or January 1, 2002, whichever occurred last for the Europe/Japan reference group. Follow- up continued for 12 months or until date of separation from active-duty service, date of next deployment, date of next antimalarial prescription, or end of the study period, March 31, 2004, whichever occurred first.

In comparison with active-duty US service members residing in Europe or Japan, mefloquine-prescribed service members were at statistically significant decreased hazard for any-cause hospitalisation, as well as diseases of the respiratory and digestive systems, musculoskeletal system and connective tissue diseases, injuries and poisonings, ill-defined conditions, and mood disorders. There were no significant differences in risk of mental disorders or nervous system disorders in comparison with either Europe/Japan personnel or deployed personnel.

Multivariable Cox proportional hazards analyses were conducted for specific categories of psychiatric and neurologic hospitalizations. Mefloquine-prescribed individuals were at significantly decreased risk of hospitalisations for mood disorders compared with the Europe/Japan reference group (HR 0.37, 95% CI, 0.15–0.90) after adjusting for age, sex, military rank, race/ethnicity, service branch, marital status, occupation, and previous hospitalizations. No other psychiatric or neurologic categories were statistically significant when the mefloquine-prescribed group was compared with either reference group. There was

[77] Wells TS, Smith TC, Smith B, Wang LZ, Hansen CJ, Reed RJ, Goldfinger WE, Corbell TE, Spooner CN, Ryan MA. (2006) Mefloquine use and hospitalizations among US service members, 2002–2004. Am J Trop Med Hyg 74: 744–749.

an elevated, but not statistically significant, hazard for vertiginous syndromes compared with both reference groups, but this was based on only one case in the mefloquine-exposed group.

TABLE 11 HOSPITALIZATIONS AMONG US SERVICE MEMBERS PRESCRIBED MEFLOQUINE, 2002–2003

Category (ICD-9-CM codes)	Cases			Mefloquine vs Europe/Japan*	Mefloquine vs deployed†
	Mefloquine (*n*)	Europe/Japan* (*n*)	Deployed† (*n*)	Hazard ratio (95% CI)‡	Hazard ratio (95% CI)§
Any cause¶	135	7,308	5,868	0.47 (0.39–0.56)	0.94 (0.79–1.12)
Infectious/parasitic (001–139)	11	386	438	1.06 (0.57–1.94)	1.08 (0.59–1.99)
Neoplasms (140–239)	5	240	251	0.90 (0.37–2.21)	1.13 (0.46–2.77)
Endocrine, nutritional, metabolic (240–279)	13	416	493	1.04 (0.59–1.82)	1.34 (0.77–2.35)
Blood and blood-forming organs (280–289)	4	316	360	0.51 (0.19–1.36)	0.65 (0.24–1.74)
Mental disorders (290–319)	37	1,280	1,314	0.76 (0.55–1.07)	1.23 (0.87–1.72)
Nervous system (320–389)	6	312	292	0.58 (0.26–1.32)	0.76 (0.34–1.73)
Circulatory system (390–459)	9	492	577	0.61 (0.31–1.18)	0.69 (0.35–1.34)
Respiratory system (460–519)	9	578	486	0.44 (0.23–0.86)	0.81 (0.42–1.58)
Digestive system (520–579)	23	1,280	1,122	0.52 (0.34–0.79)	0.90 (0.60–1.37)
Genitourinary system (580–629)	13	724	512	0.71 (0.40–1.26)	1.19 (0.67–2.13)
Skin and subcutaneous tissues (680–709)	9	272	294	0.88 (0.43–1.80)	1.31 (0.64–2.69)
Musculoskeletal and connective tissue (710–739)	30	1,149	984	0.68 (0.47–0.98)	1.28 (0.88–1.85)
Ill-defined conditions (780–799)	22	2,255	1,221	0.24 (0.16–0.37)	0.71 (0.46–1.09)
Injury and poisoning (800–999)	47	1,798	1,802	0.63 (0.47–0.84)	1.06 (0.79–1.43)

* US service members who resided in either Europe or Japan during 2002, with no prescription for mefloquine, chloroquine, or more than 14 tablets of doxycycline.
† US service members who deployed for 1 or more months during 2002, with no prescription for mefloquine, chloroquine, or more than 14 tablets of doxycycline.
‡ Hazard ratio for mefloquine-prescribed group, using the Europe/Japan reference group.
§ Hazard ratio for mefloquine-prescribed group, using the deployed reference group.
¶ Excludes complications of pregnancy, childbirth, and the puerperium, congenital anomalies, and certain conditions originating in the prenatal period (ICD-9-CM codes 630–676 and 740–779).

TABLE 12 HOSPITALIZATIONS AMONG US SERVICE MEMBERS PRESCRIBED MEFLOQUINE, SPECIFIC PSYCHOLOGICAL AND NEUROLOGICAL DIAGNOSES, 2002–2003

Category (ICD-9-CM codes)	Cases			Mefloquine vs Europe/Japan*	Mefloquine vs deployed†
	Mefloquine (*n*)	Europe/Japan* (*n*)	Deployed† (*n*)	Hazard ratio (95% CI)	Hazard ratio (95% CI)
Somatoform disorders‡	0	25	10	—	—
Mood disorders§	6	388	412	0.37 (0.15–0.90)	0.50 (0.21–1.22)
Anxiety disorders¶	6	186	185	0.92 (0.40–2.10)	1.27 (0.55–2.91)
Post-traumatic stress disorder (309.81)	1	38	29	0.79 (0.11–5.91)	1.66 (0.21–12.85)
Mixed syndromes#	4	130	151	0.91 (0.33–2.51)	0.99 (0.36–2.73)
Substance use disorders**	19	634	741	0.72 (0.45–1.15)	1.20 (0.75–1.90)
Other disorders††	20	743	551	0.71 (0.45–1.13)	1.54 (0.96–2.46)
Personality disorders (301)	7	364	225	0.46 (0.21–1.05)	1.39 (0.60–3.20)
Adjustment reaction‡‡	13	453	305	0.78 (0.45–1.38)	1.68 (0.95–2.97)
Nystagmus (379.5)	0	0	2	—	—
Vertiginous syndromes (386)	1	4	6	3.17 (0.32–31.18)	5.53 (0.59–52.06)
Dizziness and giddiness (780.4)	0	42	21	—	—
Migraine (346)	3	93	52	1.36 (0.42–4.36)	2.09 (0.63–6.90)

Nested case-control study

Schneider et al (2013)[78] used the UK General Practice Research Database to conduct a follow-up study with a nested case-control analysis. They assessed the risk of developing first-time anxiety, stress-related disorders/psychosis, depression, epilepsy or peripheral neuropathies in patients using mefloquine, chloroquine and/or proguanil, or atovaquone/proguanil for malaria chemoprophylaxis, as compared to unexposed travellers.

A case was considered to have current or past exposure to a study drug (mefloquine, chloroquine and/or proguanil or atovaquone/proguanil) if they received a prescription within 540 days prior to the index date (date the case was diagnosed). A 540-day exposure window was used because any incident neuropsychiatric disorder occurring one and a half years after stopping a drug of interest was unlikely to be associated with former drug use. Controls were patients who did not develop an outcome of interest during follow-up.

[78] Schneider C, Adamcova M, Jick SS, Schlagenhauf P, Miller MK, Rhein HG, Meier CR. (2013) Antimalarial chemoprophylaxis and the risk of neuropsychiatric disorders. Travel Med Infect Dis. Mar-Apr;11(2):71-80.

Cases were defined as people with an incident diagnosis of a neuropsychiatric disorder including anxiety, stress-related disorders or psychosis, depression, epilepsy or peripheral neuropathies during or after anti-malarial drug use. All patients with a diagnosis of malaria prior to the start of anti-malarial drug use, patients with a history of cancer, alcoholism, rheumatoid arthritis; or with an outcome of interest prior to using anti-malarial drugs were excluded.

Within the study population, there were 952 patients with an incident diagnosis of anxiety, stress-related disorder or psychosis, 739 patients with an incident diagnosis of depression, 86 patients with incident diagnosis of epilepsy, and 56 patients with an incident diagnosis of peripheral neuropathy during follow-up.

The risk of neuropsychiatric disorders was similar for users and for non-users of anti-malarial chemoprophylaxis, with evidence for elevated risks in females. The risk of psychosis was non-significantly elevated in mefloquine users, while being non-significantly reduced in users of other antimalarials. Phobia, anxiety and panic attack diagnoses were non-significantly reduced in mefloquine users compared with non-users.

TABLE 13 RISK OF ANXIETY DISORDERS OR DEPRESSION AFTER SELECTED ANTIMALARIALS

Table 3 Odds ratios for anti-malarial drug exposures in relation to anxiety or stress-related disorders or psychosis, depression, epilepsy and neuropathies.

	Cases (%)	Controls (%)	OR (95% CI)	Adj. OR (95% CI)	*P*-value
Anxiety or stress-related disorders or psychosis					
Unexposed	537 (56.4)	2806 (49.1)	1.00 (ref)	1.00 (ref)	
Mefloquine	98 (10.3)	741 (13.0)	0.69 (0.54–0.87)	0.71 (0.56–0.90)	<0.01
Current	41 (4.3)	293 (5.1)	0.73 (0.52–1.03)	0.76 (0.53–1.08)	0.12
Past	57 (6.0)	448 (7.8)	0.67 (0.50–0.89)	0.68 (0.51–0.92)	0.01
Chloroquine/proguanil	47 (4.9)	238 (4.2)	1.04 (0.74–1.46)	1.04 (0.74–1.46)	0.83
Current	18 (1.9)	68 (1.2)	1.41 (0.82–2.41)	1.39 (0.81–2.40)	0.23
Past	29 (3.0)	170 (3.0)	0.90 (0.60–1.36)	0.90 (0.60–1.36)	0.62
Atovaquone/proguanil	266 (27.9)	1888 (33.1)	0.72 (0.61–0.85)	0.73 (0.61–0.86)	<0.01
Current	90 (9.5)	509 (8.9)	0.91 (0.71–1.16)	0.92 (0.72–1.18)	0.52
Past	176 (18.5)	1379 (24.1)	0.65 (0.54–0.78)	0.65 (0.54–0.79)	<0.01
Mixed exposure	4 (0.4)	39 (0.7)	0.53 (0.19–1.48)	0.56 (0.20–1.58)	0.27
Depression					
Unexposed	423 (57.2)	2181 (49.2)	1.00 (ref)	1.00 (ref)	
Mefloquine	68 (9.2)	640 (14.4)	0.54 (0.41–0.71)	0.54 (0.41–0.71)	<0.01
Current	16 (2.2)	248 (5.6)	0.33 (0.19–0.55)	0.32 (0.19–0.54)	<0.01
Past	52 (7.0)	392 (8.8)	0.67 (0.49–0.92)	0.68 (0.50–0.94)	0.02
Chloroquine/proguanil	33 (4.5)	159 (3.6)	1.07 (0.71–1.59)	1.06 (0.71–1.59)	0.78
Current	6 (0.8)	47 (1.1)	0.66 (0.28–1.58)	0.70 (0.29–1.66)	0.41
Past	27 (3.7)	112 (2.5)	1.23 (0.79–1.92)	1.21 (0.77–1.90)	0.41
Atovaquone/proguanil	210 (28.4)	1421 (32.0)	0.75 (0.62–0.91)	0.75 (0.62–0.91)	<0.01
Current	40 (5.4)	368 (8.3)	0.55 (0.39–0.78)	0.56 (0.40–0.80)	<0.01
Past	170 (23.0)	1053 (23.7)	0.83 (0.68–1.02)	0.83 (0.67–1.02)	0.07
Mixed exposure	5 (0.7)	33 (0.7)	0.80 (0.31–2.06)	0.84 (0.32–2.19)	0.72

TABLE 14 RISK OF PSYCHIATRIC DIAGNOSES BY TYPE OF ANTIMALARIAL

Table 4 Odd ratios for anti-malarial drug exposure in relation to psychosis, phobia, anxiety or panic attacks.

	Cases (%)	Controls (%)	OR (95% CI)	Adj. OR (95% CI)	*P*-value
Psychosis					
Unexposed	19 (42.2)	136 (50.4)	1.00 (ref)	1.00 (ref)	
Mefloquine	10 (22.2)	31 (11.5)	2.40 (0.98–5.86)	2.17 (0.85–5.59)	0.11
Chloroquine/Proguanil	1 (2.2)	12 (4.4)	0.59 (0.07–5.00)	0.47 (0.05–4.11)	0.49
Atovaquone/Proguanil	15 (33.3)	90 (33.3)	1.12 (0.52–2.37)	0.97 (0.44–2.14)	0.93
Mixed exposure	0 (0.0)	1 (0.4)	NA	NA	NA
Phobia					
Unexposed	92 (56.4)	464 (47.4)	1.00 (ref)	1.00 (ref)	
Mefloquine	16 (9.8)	114 (11.7)	0.70 (0.38–1.27)	0.73 (0.40–1.34)	0.30
Chloroquine/proguanil	7 (4.3)	35 (3.6)	1.04 (0.43–2.49)	1.06 (0.44–2.60)	0.89
Atovaquone/proguanil	48 (29.4)	360 (36.8)	0.66 (0.45–0.97)	0.64 (0.43–0.96)	0.03
Mixed exposure	0 (0.0)	5 (0.5)	NA	NA	NA
Anxiety					
Unexposed	293 (58.6)	1463 (48.8)	1.00 (ref)	1.00 (ref)	
Mefloquine	50 (10.0)	422 (14.1)	0.59 (0.43–0.82)	0.60 (0.43–0.83)	<0.01
Chloroquine/proguanil	23 (4.6)	130 (4.3)	0.87 (0.54–1.42)	0.86 (0.53–1.40)	0.54
Atovaquone/proguanil	131 (26.2)	962 (32.1)	0.66 (0.53–0.84)	0.66 (0.52–0.84)	<0.01
Mixed exposure	3 (0.6)	23 (0.8)	0.63 (0.19–2.13)	0.66 (0.20–2.24)	0.51
Panic attack					
Unexposed	121 (56.3)	657 (50.9)	1.00 (ref)	1.00 (ref)	
Mefloquine	18 (8.4)	150 (11.6)	0.64 (0.37–1.11)	0.68 (0.39–1.17)	0.17
Chloroquine/proguanil	10 (4.7)	52 (4.0)	1.04 (0.51–2.09)	1.06 (0.52–2.14)	0.87
Atovaquone/proguanil	65 (30.2)	423 (32.8)	0.84 (0.60–1.17)	0.86 (0.61–1.21)	0.38
Mixed exposure	1 (0.5)	8 (0.6)	0.67 (0.08–5.43)	0.88 (0.11–7.16)	0.90
Other					
Unexposed	12 (41.4)	86 (49.4)	1.00 (ref)	1.00 (ref)	
Mefloquine	4 (13.8)	24 (13.8)	1.10 (0.31–3.94)	1.80 (0.48–6.79)	0.38
Chloroquine/proguanil	6 (20.7)	9 (5.2)	5.17 (1.42–18.77)	6.39 (1.55–26.40)	0.01
Atovaquone/proguanil	7 (24.1)	53 (30.5)	0.96 (0.33–2.77)	1.04 (0.32–3.37)	0.94
Mixed exposure	0 (0.0)	2 (1.1)	NA	NA	NA

Other: Posttraumatic stress disorder, adjustment disorder, reaction to severe stress.
OR: odds ratio; adj. OR: odds ratio adjusted for smoking, BMI; 95% CI: 95% confidence interval.

In an earlier study using the UK General Practice Research Database **Meier et al (2004)**[79] assessed risk of first time psychiatric diagnoses. In this analysis they compared current users to past users, rather than non-users.

Compared to chloroquine and/or proguanil, there was a non-significant twofold increase in risk of panic attacks (RR 2.3, 95% CI 0.8-6.4) in current users. Current users of mefloquine were at increased risk of psychosis and panic attacks compared to past users.

The incidence rate for psychosis was 1.1000 person years (95% CI 0.3-2.9) and for panic attacks it was 3/1000 person-years (95% CI 1.6-5.7).

Adverse event reports

Nevin and Leoutsakos (2017)[80] used latent class modelling to identify a distinct neuropsychiatric syndrome class associated with mefloquine use. Latent class modelling is a

[79] Meier CR, Wilcock K, Jick SS (2004) The risk of severe depression, psychosis or panic attacks with prophylactic antimalarials. Drug Saf.;27(3):203-13.
[80] Nevin RL, Leoutsakos JM. (2017) Identification of a Syndrome Class of Neuropsychiatric Adverse Reactions to Mefloquine from Latent Class Modeling of FDA Adverse Event Reporting System Data. Drugs R D. Mar;17(1):199-210.

statistical method used to infer unobserved constructs from a set of observed data. The data source was symptoms reported to the US Food and Drug Administration Adverse Event Reporting System (FAERS).

Symptoms were classified using the Medical Dictionary for Regulatory Activities (MedDRA) neurologic and psychiatric high-level group terms. MedDRA vocabulary translates reported reactions into standard terminology known as lowest level terms, and groups these into medically similar or equivalent preferred terms (PTs). The MedDRA further categorizes PTs multiaxially into one or more of 26 top-level system organ classes (SOCs), and within each SOC, to typically one of a few dozen distinct high-level group terms (HLGTs), thus making the presence or absence of reactions categorized at the SOC or HLGT level of potential utility as indicators in latent class modelling.

Two study datasets were created from the pooled dataset: the primary dataset consisting of mefloquine, atovaquone-proguanil, and doxycycline cases; and a control dataset consisting of chloroquine and loperamide cases.

The syndrome class identified by modelling included a very high probability of symptoms of deliria (82.7%) including confusion and disorientation, and a moderate probability of other severe psychiatric and neurologic symptoms including dementia and amnesia (18.6%) and seizures (18.1%). The syndrome class was also associated with symptoms of anxiety, depression, sleep disturbance, and abnormal dreams, dizziness, vertigo, and paresthesias.

Based on the most-likely class assignment, the prevalence of the syndrome class in the primary study dataset was 10.3% with mefloquine, 6.0% with loperamide, 3.5% with doxycycline, 3.3% with chloroquine and 2.0% with atovaquone-proguanil.

The syndrome class was most likely to be associated with mefloquine (OR 3.92, 95% CI 2.91-5.28) and loperamide (OR 2.17, 95% CI 0.78-6.04), though the association with loperamide was non-significant. It was less likely to be associated with atovaquone-proguanil (OR 0.35, 95% CI 0.14-0.85), doxycycline (OR 0.38, 95% CI 0.28-.51) or chloroquine (OR 0.46, 95% CI 0.17-1.28).

This study’s methods could not determine the sequence or chronicity of these symptoms. More serious reactions associated with mefloquine such as psychosis were not included among the characteristic features of the syndrome. One of the authors, Dr Remington Nevin, discloses that he has been retained as a consultant and expert witness in legal cases involving claims of antimalarial toxicity.

TABLE 15 CONDITIONAL PROBABILITIES BY CLASS, TWO-CLASS HLGT-LEVEL LATENT CLASS MODEL

	Syndrome	Non-syndrome
Communication disorders and disturbances	0.182	0.017
Deliria (including confusion)	0.827	0.006
Dementia and amnestic conditions	0.186	0.023
Depressed mood disorders and disturbances	0.318	0.052
Neuromuscular disorders	0.090	0.028
Peripheral neuropathies	0.082	0.019
Psychiatric disorders NEC	0.314	0.015
Seizures (including subtypes)	0.181	0.032

HLGT high-level group term, *NEC* not elsewhere classified

Ringqvist et al (2015)[81] described long term effects of mefloquine in 73 subjects who reported to a Danish national register for mefloquine associated side effects. 16 subjects had a previous personal or family history of psychiatric disorder.

Subjects reported a range of symptoms, including gastrointestinal symptoms, dizziness, fatigue, abnormal vision, vertigo, headache, skin symptoms, numbness of the arms and legs, tinnitus, fever, leg cramps and hair loss.

Using a 90-item symptoms questionnaire (SCL-90-R), clinically significant scores for anxiety, phobic anxiety and depression were found in 55%, 51%, and 44% of the mefloquine group. Cases of hypomania/mania in the acute phase were 5.5%. Substantial acute phase psychotic symptoms were found in 15% and were time-limited (longest 2-3 months). Illusions/hallucinations were more frequently observed among women. One subject reported delusional mood and delusions of reference for 9-11 months.

Significant long-term mental health effects were demonstrated for the SF-36 subscales mental health (MH), role emotional (RE), and vitality (VT) in the mefloquine group compared to Danish norms. The authors suggest that this could have been due to neurotoxic effects but could also be the result of having a stressful life event (the adverse drug reaction) or other unmeasured life events. The authors acknowledge that bias could have been introduced by retrospective collection of symptoms and non-random selection of study subjects.

[81] Ringqvist Å, Bech P, Glenthøj B, Petersen E. (2015) Acute and long-term psychiatric side effects of mefloquine: a follow-up on Danish adverse event reports. Travel Med Infect Dis. Jan-Feb;13(1):80-8.

TABLE 16 PHYSICAL SYMPTOMS IN ASSOCIATION WITH MEFLOQUINE EXPOSURE

Table 3 Physical symptoms in association with mefloquine exposure in a group ($n = 73$) experiencing adverse reactions to mefloquine.

Physical complaint	Percentage of total ($n = 73$) indicating symptoms
Gastrointestinal symptoms	57%
Dizziness	57%
Fatigue	49%
Abnormal vision	49%,
Palpitations	42%
Vertigo	38%
Headache	36%
Skin symptoms	36%
Numbness of arms and legs	30%
Tinnitus	18%
Fever	16%
Leg cramps	14%
Loss of hair	12%
Hearing loss	12%
Reduced nociception of the skin	10%
Involontary movements	10%

TABLE 17 SUBJECTS ESTIMATION OF DURATION OF SYMPTOMS

Table 5 Subjects' estimation of duration of physical symptoms, nightmares, cognitive dysfunction, and symptoms in response to mefloquine in the SCL-90-R. The study population consisted of 73 cases reported for adverse side effects to mefloquine.

	Cases indicating symptoms	1–2 days	3 days – 3 weeks	1–3 months	4–8 months	9 months – 3 years	Still symptoms
Nightmares	43	2	11	12	5	4	9
Cognitive dysfunction	42	2	10	7	3	6	14
SCL-90-R	68	2	18	12	6	13	17

Case series/ case reports

Jain et al (2016)[82] describe the case of a 30-year-old man of Pakistani descent with sudden onset of dizziness and diplopia following the administration of mefloquine who developed macular changes diagnosed as acute central serous chorioretinopathy by angiography and optical coherence tomography.

On suspicion of malaria, he had been treated by a local physician with 2500 mg of chloroquine over 3 days, followed by 15 mg of primaquine daily over 14 days, and then with 1500 mg of mefloquine in three divided doses over 24 hours. Apart from symptoms related to his initial febrile illness, he was asymptomatic until he received mefloquine. Its introduction was associated with an onset of diplopia, blurred vision in his right eye, dizziness, nausea, and vomiting after intake of the first dose, with blurred vision progressing over the course of

[82] Jain M, Nevin RL, Ahmed I. (2016) Mefloquine-associated dizziness, diplopia, and central serous chorioretinopathy: a case report. J Med Case Rep. Oct 31;10(1):305.

dosing. All medicines were discontinued and the symptoms resolved over a period of 11 weeks, with a mild recurrence at 1 year.

This is the first report of a confirmed case of unilateral central serous chorioretinopathy associated with use of mefloquine. Principally on the basis of parsimony in explaining all symptoms simultaneously, the authors postulate that mefloquine, either alone or in synergy with other quinoline antimalarial drugs, caused dizziness, diplopia, and serous chorioretinopathy through transient focal effects on specific structures of the patient's central nervous system. They further suggest that this effect may potentially indicate susceptibility to other neuropsychiatric effects of mefloquine.

Livezey et al (2016)[83] report the case of a 32-year-old male United States military service member who was referred to the Walter Reed National Military Medical Center Toxicology and Clinical Pharmacology Clinic. He developed neuropsychiatric symptoms 2 weeks after starting mefloquine 250 mg/week for malaria prophylaxis. He continued to take the medication for the next 4 months while on deployment. Four months into the deployment, the patient experienced a traumatic event (enemy gun fire).

Initial symptoms included vivid dreams and anxiety, as well as balance problems. These symptoms persisted and progressed over the next 4 years to include vertigo, emotional lability, and poor short-term memory.

Vestibular testing by audiology showed no evidence of peripheral vestibulopathy. An MRI of the internal auditory canals was unremarkable. Rotary chair testing results showed rare findings of hyperactive vestibulo-ocular reflex (VOR) gains and an abnormally low VOR phase. These findings were reported to be consistent with migraines, motion sickness or a central vestibulopathy. The patient was referred for vestibular rehabilitation therapy.

The authors conclude that there was a probable relationship between the patient's initial symptoms and mefloquine exposure, but that the cause of his progression of symptoms over the course of 4 years is more difficult to ascertain. The experience of a traumatic event and the presence of re-experiencing, avoidance, negative cognitions and mood, and hyperarousal suggest a differential diagnosis of PTSD, although this does not explain the dizziness.

McEvoy et al (2015)[84] report the first published case of depersonalisation/derealisation disorder following exposure to mefloquine. The patient was a 31 year old previously well Peace Corps volunteer who developed symptoms of depersonalisation shortly after the second dose of an interrupted course of mefloquine. Despite stopping the medication, the depersonalisation persisted intensely for several weeks. Over the next 2 to 3 months with active treatment involving medication and psychotherapy, his symptoms gradually resolved.

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[83] Livezey J, Oliver T, Cantilena L. (2016) Prolonged Neuropsychiatric Symptoms in a Military Service Member Exposed to Mefloquine. Drug Saf Case Rep. 2016 Dec;3(1):7.
[84] McEvoy K; Anton B; Chisolm MS. (2015) Depersonalization/derealization disorder after exposure to mefloquine. Psychosomatics. 56(1):98-102, Jan-Feb.

In this case, there is no direct evidence that DDD was caused by mefloquine. However, the temporal relationship between depersonalisation/derealisation symptom-onset and mefloquine use, the established potential to cause psychiatric symptoms, and the relative paucity of other risks for the development of depersonalisation symptoms suggest a possible causal relationship between DDD and mefloquine.

Maxwell et al (2015)[85] describe a case of chloroquine intoxication that appeared to be prolonged by subsequent use of multiple psychotropic medication. They suggest that there may be increased susceptibility to quinoline antimalarial intoxication in some individuals.

Nevin (2012)[86] report an adverse reaction to mefloquine chemoprophylaxis in a previously healthy 24 year old man who travelled to Africa. The relationship of the author to the case is unclear, as he does not state whether or not he was the treating doctor. The reference to returning home to the US for a week of training, needing to by on standby for short notice for travel to Africa, being sent home after 5 weeks and taking a course of primaquine suggests that the patient may have been a member of the US military.

Within 12 hours of taking his first 250 mg dose of mefloquine for malaria prophylaxis, the patient developed symptoms of anxiety over the next 2 days, followed by the development of psychosis, short-term memory impairment, confusion, personality change, disequilibrium and vertigo. Despite these symptoms he continued taking mefloquine for a total of 7 weeks, and also took a 14 day course of primaquine.

An MRI was essentially normal and an ENT specialist suspected central vestibular dysfunction based on the pattern of nystagmus. Approximately six months after symptom onset the patient's hallucinations had fully resolved, but he reported continued deficits in short-term spatial and working memory with rare episodes of spatial disorientation described as "dizzy" spells, with episodes of tinnitus, vertigo, and severe disequilibrium occurring approximately every day to every other day, frequently heralded by frontal headache, and occasionally associated with palpitations and anxiety. Ten months after symptom onset and at the conclusion of reported follow-up, the patient remained restricted from driving due to persistent episodes of vertigo and disequilibrium, and also complained of continuing memory impairment and new onset visual illusions.

The author proposes that the symptoms in this case represent an idiosyncratic neurotoxic syndrome of progressive limbic encephalopathy and multifocal brainstem injury caused by mefloquine gap junction blockade:

> In recent studies in a rat model, high dose mefloquine also caused similar permanent, dose dependent lesions in the nucleus gracilis, nucleus cuneatus, and the solitary tract. From this, it is tempting to speculate that mefloquine neurotoxic brainstem injury might represent a related

[85] Maxwell NM, Nevin RL, Stahl S, Block J, Shugarts S, Wu AH, Dominy S, Solano-Blanco MA, Kappelman-Culver S, Lee-Messer C, Maldonado J, Maxwell AJ. (2015) Prolonged neuropsychiatric effects following management of chloroquine intoxication with psychotropic polypharmacy. Clin Case Rep. Jun;3(6):379-87.

[86] Nevin RL (2012) Limbic encephalopathy and central vestibulopathy caused by mefloquine: a case report. Travel Med Infect Dis. 2012 May;10(3):144-51.

> idiosyncratic effect preceded by prodromal limbic symptoms and manifesting primarily among those susceptible to this encephalopathy. The possibility that mefloquine might cause subclinical or otherwise overlooked damage to brainstem and limbic structures is further supported by earlier observations with other quinolines.

Peterson et al (2011)[87] report the case of a 27-year-old male active-duty US military service member who developed severe depression, psychotic hallucinations, and neuropsychological sequelae following the prophylactic use of the antimalarial medication mefloquine. The patient clearly should not have been prescribed mefloquine, since he had a recent history of depression and was taking antidepressant medications (sertraline) and diazepam as needed at the time of his deployment to the Middle East.

Symptoms of depression began after the third dose of mefloquine and increased so that shortly after his fifth weekly dose, the patient began experiencing florid visual hallucinations, difficulty speaking, vivid nightmares, hypnopompic sleep paralysis, intense feelings of depression with uncontrollable crying, and strong suicidal ideations. At this point the mefloquine was ceased and he was shortly thereafter evacuated back to the US. The article does not report on the patient's response to treatment or duration of symptoms.

In a series of 54 patients of one institution treated for malaria with mefloquine, **Ronn et al 1998**[88], reported that neuropsychiatric symptoms were transient in all but 2 cases, both of whom required "extended hospitalisation" (duration not specified).

Fifteen patients (28%) had one or more neuropsychiatric adverse reactions, albeit mostly mild to moderate, including; hallucinations, nightmares, depression, anxiety, sleeplessness and mania. The majority of reactions were transient, peaked at 3 days and resolved spontaneously, except in two patients: one female patient suffered from hallucinations, paranoia and mania, another patient had severe nightmares and depression, requiring extended hospitalisation for both. These patients had no personal or family history of neuropsychiatric disorder, alcohol abuse or drug history, nor was there any evidence of concomitant infections.

Lobel et al (1998)[89] describe two cases of mefloquine overdosage. In one case 250 mg was taken daily instead of weekly for 61 days, with the associated development of confusion, agitation, ataxia, dizziness, speech difficulties and high frequency hearing loss. One year after ceasing treatment, all symptoms except hearing loss had resolved. In the other case 250 mg of mefloquine was taken daily for 3 weeks and then 2 to 3 times per week for 23 weeks. After 3 months he noted weakness, depression, disorientation and paraesthesia, with symptoms persisting for one year.

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[87] Peterson AL, Seegmiller RA, Schindler LS (2011). Severe neuropsychiatric reaction in a deployed military member after prophylactic mefloquine. Case Rep Psychiatry 2011: 350–417.
[88] Rønn AM, Rønne-Rasmussen J, Gøtzsche PC, Bygbjerg IC. (1998) Neuropsychiatric manifestations after mefloquine therapy for Plasmodium falciparum malaria: comparing a retrospective and a prospective study. Trop Med Int Health. Feb;3(2):83-8.
[89] Lobel HO, Coyne PE, Rosenthal PJ. (1998) Drug overdoses with antimalarial agents: prescribing and dispensing errors. JAMA. Nov 4;280(17):1483.

Lysack et al (1998)[90].describe an adverse reaction to mefloquine and chloroquine in a 23 year old traveller who took these drugs for prophylaxis. After the first dose of mefloquine, taken upon arrival in India, the man experienced anxiety, depression, and sleep disturbances. One week later, after the second dose, visual and auditory hallucinations, paranoia, and suicidal ideation developed. He also experienced severe fatigue, vertigo, ataxia, tinnitus, and anorexia. These symptoms worsened after the third dose. Concerned that the symptoms could be related to mefloquine, he discontinued the drug.

One week after the third dose of mefloquine, he was prescribed and ingested 300 mg chloroquine base (500 mg chloroquine phosphate salt) for malaria prophylaxis. Three hours after-wards, the man had what he described as a severe anxiety attack. Ten hours after ingesting the chloroquine, he experienced an acute neurological adverse event, consisting of prodromal anxiety accompanied by severe tinnitus, paresthesia, and paresis initially.

At 9 months later the patient reported persisting episodic fatigue, vertigo, tinnitus, depression, and suicidal ideation. A comprehensive neurological evaluation was undertaken. The physical examination, audiogram, electroencephalogram, and magnetic resonance encephalogram showed no abnormalities. However, an electronystagmogram did reveal a peripheral weakness in the left vestibular apparatus. The depression and suicidal ideation resolved without treatment 12 months after discontinuation of the antimalarial drugs. At the time of writing, mild to moderate fatigue, vertigo, and tinnitus had not resolved.

This case raises the possibility that the continuation of malaria prophylaxis with chioroquine during an adverse reaction to mefloquine may aggravate symptoms and delay their resolution.

In a series of 12 patients with neuropsychiatric effects, **Weinke (1991)**[91] reported a maximum duration of effect of 10 days, and 5 patients may have had additive effects from taking concurrent chloroquine or quinine. All patients recovered fully without sequelae.

Loken and Haymaker (1949)[92] report a case of accidental pamaquine poisoning in which approximately 20 times the therapeutic dose of the drug was given in one day. Death occurred 7 days thereafter. Pamaquine is an 8-aminoquinoline drug that was used to prevent relapse of vivax malaria, and is in the same quinolone subclass as primaquine. The patient had also received quinacrine and quinine at standard dosage, but was without any symptoms of toxicity. However, the combination may have indirectly worsened the pamaquine poisoning.

Early clinical symptoms included apprehension, cyanosis, nausea, and generalized pains. Late symptoms included numbness of the face, difficulty in speaking, dyspnoea, and palatal paralysis. Methemoglobinemia and hemoglobinuria occurred soon after the ingestion of the

[90] Lysack JT, Lysack CL, Kvern BL. (1998) A severe adverse reaction to mefloquine and chloroquine prophylaxis. Aust Fam Physician. Dec;27(12):1119-20.
[91] Weinke T, Trautmann M, Held T, Weber G, Eichenlaub D, Fleischer K, Kern W, Pohle HD. (1991) Neuropsychiatric side effects after the use of mefloquine. Am J Trop Med Hyg. Jul;45(1):86-91.
[92] Loken A, Haymaker W. (1949) Pamaquine poisoning in man, with a clinicopathologic study of one case. Am J Trop Med Hyg. May;29(3):341-52.

pamaquine. At autopsy there was ischemic necrosis with reactive change in a small area of the basis pontis, and mild to moderate degenerative changes in the globus pallidus, nuclei of the extraocular nerves, vestibular nuclei, and cerebral cortex.

The authors comment that despite the large dosage of pamaquine the pathologic changes in the central nervous system were few. Some of the changes were consistent with hypoxia from methaemoglobinaemia, but the changes in brainstem nuclei were similar to those reported by Schmidt and Schmidt (1948) in rhesus monkeys given pamaquine. The cause of death was thought to be prolonged hypoxia and complicating pneumonia.

Animal studies

Yu et al (2011)[93] examined the effect of mefloquine on organotypic cultures of the macula of the utricle from postnatal day 3 rats to determine if mefloquine might be toxic to the vestibular system. Mefloquine has been suggested as being ototoxic based largely on case reports where it has been associated with hearing loss, tinnitus, vertigo, and dizziness.

Mefloquine treatment in clinically relevant doses caused a loss of utricular hair cells, with a dose-response effect. Hair cell nuclei in mefloquine-treated utricles showed evidence of apoptosis.

This finding is consistent with earlier studies of inner ear toxicity. Using zebrafish larvae to screen for ototoxicity with more than a 1000 FDA approved drugs, mefloquine was identified as toxic to hair cells in lateral line sensory organ (Chiu et al 2008). An earlier study by this group using postnatal cochlear organotypic cultures, reported that mefloquine caused a dose-dependent loss of cochlear hair cells and spiral ganglion neurons (Ding et al 2009).

While these results indicate that mefloquine is toxic to vestibular hair cells in postnatal day 3 vestibular organ cultures, it remains to be seen whether it is toxic *in vivo* either in postnatal or adult animals. Mefloquine vestibulotoxicity *in vivo* will depend on many factors, such as dose and duration of treatment, uptake of the compound across the blood-brain barrier and individual susceptibility.

There have been several reports of hearing loss, tinnitus and dizziness in patients taking mefloquine (Karbwang et al 1994, Phillips-Howard and ter Kuile 1995, Fusetti et al 1999, Wise and Toovey 2007), though another study have failed to identify hearing and vestibular problems in healthy volunteers (Carrara et al 2008).

The authors propose several mechanisms by which mefloquine might cause cellular death in the vestibular system. Mefloquine is a potent blocker of certain connexins which are transmembrane proteins that assemble to form gap junctions. They are highly expressed in the brain and vestibular system.

[93] Yu D, Ding D, Jiang H, Stolzberg D, Salvi R. (2011) Mefloquine damage vestibular hair cells in organotypic cultures. Neurotox Res. Jul;20(1):51-8.

Mefloquine is also a potent blocker of L-type calcium channels which are expressed in the vestibular system. Finally, mefloquine and related anti-malarial drugs such as quinine and chloroquine, generate toxic reactive oxygen and nitrogen species which could induce cell death. The latter hypothesis was supported by a demonstration that mefloquine induces oxidative stress and neurodegeneration in rat cortical neurons.[94] However, the precise relationship between the disruption of calcium homeostasis and increase in oxidative stress is unknown.[95]

Dow et al (2011)[96] studied next generation quinoline methanols (NGQMs) that do not accumulate in the central nervous system (CNS). CNS levels of NGQMs relative to mefloquine were measured, aiming to find compounds which exhibited a five-fold reduction CNS levels relative to mefloquine (the difference in levels between treatment and prophylaxis levels of mefloquine). Of the compounds tested, diamine quinoline methanols were the most promising, but further optimisation of this property together with assessment of potency and half-life would be needed.

Milatovic et al (2011)[97] studied rat cortical neurons and confirmed that mefloquine neurotoxicity is associated with apoptotic response and oxidative injury, mediated in part by non-receptor tyrosine kinase 2.

Dow et al (2006)[98] investigated the potential neurological effects of mefloquine in six 7-week-old female rats given a single oral dose of the compound. Potential mefloquine-induced neurological effects were monitored using a standard functional observational battery, automated open field tests, automated spontaneous activity monitoring, a beam traverse task, and histopathology.

Doses of 45, 187, 327, and 574 mg/kg were selected. Mefloquine doses of 45 and 187 mg/kg were found to generate plasma mefloquine concentrations of the same order of magnitude as those observed after prophylaxis and treatment in humans, respectively. Adverse effects in humans generally occur more frequently at the treatment dose (1,250 mg) than at the prophylaxis dose (250 mg).

Mefloquine induced dose-related changes in endpoints associated with spontaneous activity and impairment of motor function and caused degeneration of specific brain stem nuclei (nucleus gracilis). The nucleus gracilis is a component of the dorsal column system which

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[94] Hood JE, Jenkins JW, Milatovic D, Rongzhu L, Aschner M. (2010) Mefloquine induces oxidative stress and neurodegeneration in primary rat cortical neurons. Neurotoxicology. Sep;31(5):518-23.
[95] Hood JE, Jenkins JW, Milatovic D, Rongzhu L, Aschner M. (2010) Mefloquine induces oxidative stress and neurodegeneration in primary rat cortical neurons. Neurotoxicology. Sep;31(5):518-23
[96] Dow GS, Milner E, Bathurst I et al (2011).Central nervous system exposure of next generation quinoline methanols is reduced relative to mefloquine after intravenous dosing in mice. Malar J. Jun 6;10:150.
[97] Milatovic D, Jenkins JW, Hood JE, Yu Y, Rongzhu L, Aschner M. (2011) Mefloquine neurotoxicity is mediated by non-receptor tyrosine kinase. Neurotoxicology. Oct;32(5):578-85.
[98] Dow G, Bauman R, Caridha D, Cabezas M, Du F, Gomez-Lobo R, Park M, Smith K, Cannard K. (2006) Mefloquine induces dose-related neurological effects in a rat model. Antimicrob Agents Chemother. Mar;50(3):1045-53.

transfers proprioceptive signals. Increased spontaneous motor activity was observed only during the rats' normal sleeping phase, suggesting a correlate to mefloquine-induced sleep disorders.

These dose and concentration-related endpoints may be clinically relevant, but the threshold dose for many of the neurological effects in this study was 187 mg/kg. This dose is 7.2-fold higher in mg/kg terms than that used for malaria treatment of humans (25 mg/kg maximum total dose).

The authors identified only one other report of mefloquine-induced neurological effects in animal models in the scientific literature (Shepherd et al 1988). These authors reported clonic convulsions and aggression after sequential daily dosing of mefloquine at 300 mg/kg in mice. The relevance of the dosing regime used to clinical practice is unclear, and plasma mefloquine concentrations were not determined.

de Lagerie et al (2009)[99] investigated the influence of cerebral malaria on the cerebral uptake of mefloquine, in an experimental mouse model. After a single intraperitoneal dose, mefloquine concentrations were measured by liquid chromatography in blood and brains of mice infected with *Plasmodium berghei* ANKA and compared with that of non-infected mice.

Mefloquine brain concentrations were significantly decreased in cerebral malaria mice versus healthy mice, by about 40%. Therefore, an increase of central toxicity due to mefloquine should not be expected during cerebral malaria. These findings could be explained by a decrease in cerebral blood flow, and cerebral hypoperfusion has been previously evidenced during cerebral malaria in humans and in an animal model.

Summary and conclusions

Background

Concerns have been raised that mefloquine, although usually considered a second or third line option for malaria prophylaxis, may be unsuitable for use in the military context (McCarthy 2015, Nevin 2015, Quinn 2016). These concerns relate in part to the well-recognised acute neuropsychiatric effects of mefloquine, which are particularly problematic in an environment in which weapons are available and unimpaired judgement and fine motor skills are needed. Nevin and Ritchie (2015) suggest that these effects might be attributed to psychiatric disorders.

It has also been postulated that mefloquine might cause long term effects on the brain (Quinn 2016, Nevin 2014, Ritchie et al 2013), amounting to a condition that has been variously termed "mefloquine toxicity syndrome", "chronic mefloquine toxicity syndrome", "mefloquine intoxication syndrome", "chronic mefloquine-induced encephalopathy" and "chemically-acquired brain injury". Nevin (2012) proposes that mefloquine causes limbic encephalopathy, explaining symptoms of confusion, memory impairment and psychosis, with or without associated multifocal brainstem injury, explaining symptoms of dizziness and vertigo.

[99] de Lagerie SB, Fernandez C, German-Fattal M et al (2009) Impact of cerebral malaria on brain distribution of mefloquine. Drug Metabolism Letters. 3(1):15-7.

The US Food and Drug Administration (FDA) issued a drug safety communication in 2013, with their main concern being reports of persistent vestibular adverse effects in mefloquine users. This assessment was based on adverse event reports from the FDA Adverse Event Reporting System and case reports in the published literature. Dizziness, loss of balance, tinnitus, or vertigo persisted for months to years after mefloquine was discontinued, and permanent vestibular damage was diagnosed in some cases. Patients who experienced vestibular symptoms usually had concomitant psychiatric symptoms such as anxiety, confusion, paranoia, and depression, some of which were persistent.

Mefloquine has been included as a factor in 14 Statements of Principles where there was at least a reasonable hypothesis that the relevant condition can occur: acquired cataract, anxiety disorder, bipolar disorder, depressive disorder, epileptic seizure, heart block, myasthenia gravis, peripheral neuropathy, psoriasis, sensorineural hearing loss, schizophrenia, suicide and attempted suicide, tinnitus and trigeminal neuropathy.

Basis for defining disease and assessing epidemiology
In order to determine whether chemically-acquired brain injury with long-lasting health effects can also occur as a result of exposure to a substance, it is necessary to consider whether there is any sound medical-scientific evidence showing a consistent pathology in humans that is associated with an enduring pattern of symptoms. Such evidence is available for acquired brain injury from exposure to lead (de Souza et al 2013) and solvents (Beckley et al 2013).

While animal studies can provide evidence of biological mechanisms, this type of evidence needs to be confirmed by pathological and epidemiological in humans because of interspecies differences, the high doses which tend to be used in animal studies, and the difficulty of relating animal behaviours to human symptoms. Studies of a variety of quinoline compounds conducted in animals as part of a wartime search for effective antimalarials demonstrated that toxicities were specific to each compound tested, and that there were considerable interspecies differences in toxicities (Schmidt and Schmidt 1948 and 1949).

The most informative epidemiological studies of long term neurological and psychiatric effects are cohort and case-control studies in which there is a specified period of follow up. These types of study employ a comparison group, thus accounting for the fact that symptoms can occur in people for reasons other than the exposure of interest. Information on longer term effects can also be obtained from adverse events registers and case reports, but because they lack a comparison group it is difficult to determine from these studies if symptoms are due to a drug exposure or to other illnesses or exposures, and whether or not they are more common than in people not exposed to the drug.

The term “neuropsychiatric effects” is vague, and it is not clear if it is meant to encompass only psychiatric illness, neurological symptoms and signs or a broad range of physical symptoms and cognitive problems. Reported neuropsychiatric symptoms include anxiety, panic attacks, agitation, aggression, acute psychosis, depression, forgetfulness, sleep disturbance, nightmares, dizziness/vertigo, fatigue, abnormal vision, headache and tinnitus (Australian Medicines Handbook 2017, Ringqvist et al 2015, Fujii et al 2007). The symptom of

most concern to the FDA has been persistent vestibular adverse effects. Therefore, sound medical-scientific evidence concerning a broad range of neurological and psychiatric effects has been considered.

Clinical trials

There have been several randomised controlled trials in both military and civilian populations (Gonzalez et al 2014, Nasveld et al 2010, Schlagenhauf et al 2003, van Riemsdijk et al 2002, Boudreau et al 1993). While none reported neuropsychiatric events which they rated as severe or requiring hospitalisation, these studies do not include long term follow up, so are not informative for potential chronic effects.

Similarly, there is a body of literature reporting on the findings of non-randomised, uncontrolled clinical trials or cohort studies, which are not designed to assess long term sequelae. Many of these trials have been conducted in military populations in order to establish the effects of mefloquine in relation to efficacy, safety, compliance or effects on work functioning in a deployment situation. These include studies in soldiers from Australia (Kitchener et al 2005), the US (Saunders et al 2015), Japan (Fujii et al 2007), the UK (Terrell et al 2015, Adshead 2014) and Holland (Jaspers et al 1996).

Fujii et al (2007) reported one case of psychosis, and Kitchener et al (2005) reported three withdrawals due to acute neuropsychiatric reactions possibly related to mefloquine. Overall, the trials concluded that mefloquine was well tolerated despite some mild to moderate adverse effects. Two trials in military populations reported that it did not compromise work function (Terrell et al 2015, Boudreau et al 1993). A randomised trial of 119 Dutch travellers found that measures of concentration impairment showed no significant difference in change between subjects taking atovaquone plus proguanil and those taking mefloquine (van Riemsdijk et al 2002).

Cohort and case-control studies

Of particular relevance to the question of long term effects were three studies based on prescriptions of mefloquine and longitudinal data on specified adverse events; two large cohort studies in US military populations (Eick-Cost et al 2017, Wells et al 2006) and a nested case-control study using data from the UK General Practice Research Database (Schneider et al 2013). These three studies all found similar or decreased risk of neuropsychiatric outcomes for mefloquine-prescribed groups compared to control groups.

Eick-Cost et al (2017) compared those prescribed mefloquine with those prescribed doxycycline or atovaquone-proguanil, in both deployed and non-deployed groups. The risk period included the duration of the prescription and 365 days after the end of the prescription. Mefloquine recipients were at increased risk of three outcomes but only in particular subgroups (anxiety disorder in deployed but not non-deployed compared to doxycycline only, PTSD in non-deployed but not deployed compared to atovaquone-proguanil only, and tinnitus in deployed and non-deployed compared to atovaquone-proguanil only). Mefloquine recipients were at decreased risk for six outcomes.

Wells et al (2006) compared deployed, mefloquine-prescribed groups with non-antimalarial prescribed groups who were either deployed or non-deployed, with follow up between 12 to 27 months. Mefloquine-prescribed individuals were at significantly decreased risk of hospitalisations for mood disorders compared with the Europe/Japan reference group. No other psychiatric or neurologic categories were significant different when the mefloquine-prescribed group was compared with either reference group.

Schneider et al (2013) compared users of antimalarial chemoprophylaxis with non-users over a 540 day period. The risk of psychosis was non-significantly elevated in mefloquine users, while being non-significantly reduced for users of other antimalarials. Phobia, anxiety and panic attack diagnoses were non-significantly reduced in mefloquine users compared with non-users.

Case series and case reports

Most studies report that acute reactions to mefloquine occur after the initial few doses (Castelli et al 2010), and tolerance develops over subsequent days or weeks (Riemsdijk et al 2002, Ronn et al 1998, Weinke 1991). Given that mefloquine has been used by more than 35 million travellers for chemoprophylaxis worldwide,[100] there is a strong likelihood that even rare effects would be able to be detected with reasonable frequency if a causal relationship existed. Nevertheless, there are relatively few case reports of long term adverse effects given the high level of usage.

In a study using cases reported to a Danish adverse event reporting system, Ringqvist et al (2015) described long term effects of mefloquine in 73 subjects who reported mefloquine associated side effects. 33 subjects reported that nightmares and cognitive dysfunction persisted beyond 9 months. This group of subjects was not randomly selected and there could be alternative explanations for the symptoms other than prolonged neurotoxic effects. The non-specific nature of the reported symptoms means that plausible alternative explanations could include anxiety arising from an acute reaction, use of other medications or exposure to unmeasured stressful life events. Because data were collected retrospectively, there may have been a bias towards recall of symptoms of concern, and it is uncertain when the symptoms first began in relation to taking mefloquine. Duration of symptoms could not be compared with a control group. There was no assessment of other potential causes of the symptoms.

There are occasional case reports of psychiatric effects lasting longer than a few months (Ronn et al 1998, unspecified duration; Lysack et al 1998, 12 months). There were three case reports in which, amongst other symptoms, persistent vertigo was reported (Lysack et al 1998, Nevin 2012, Livezey et al 2016) and one in which persistent hearing loss after mefloquine overdosage was reported (Lobel et al 1998). In two cases central vestibular dysfunction was suspected (Nevin 2012, Livezey et al 2016), though an MRI was normal in both cases. There is a case report demonstrating damage to various parts of the brain in a person who was

[100] Schlagenhauf P, Adamcova M, Regep L, Schaerer MT, Rhein HG. (2010) The position of mefloquine as a 21st century malaria chemoprophylaxis. Malar J. Dec 9;9:357.

given 20 times the therapeutic dose of pamaquine, a historical drug belonging to the 8-aminoquinoline subclass and related most closely to primaquine (Loken and Haymaker 1949).

Biological mechanisms

The precise mechanism by which mefloquine might cause damage to the brain or vestibular system is unclear, but severe hypothesis have been suggested. These include blockage of calcium channels and induction of toxic reactive oxygen species (Yu et al 2011), membrane channel blockade (Quinn 2015), apoptotic response and oxidative injury (Milatovic et al 2011), liver toxicity and hypervitaminosis A (Mawson 2013) and induction of autophagy (Shin et al 2012).

Animal studies have investigated a possible central mechanism for dizziness and vertigo, showing damage to brainstem nuclei in rats given mefloquine (Dow et al 2006). However, rhesus monkeys given lethal and sublethal doses of the 8-aminoquinoline primaquine did not specifically demonstrate degenerative changes in the vestibular nuclei (Schmidt and Schmidt 1951). Primaquine was much less neurotoxic that the historical quinoline compound Plasmocid in rhesus monkeys (Schmidt and Schmidt 1948). While Plasmocid affected multiple brainstem nuclei at lethal doses, the auditory and vestibulo-cerebellar systems were much less affected by subfatal doses. At one quarter the maximum tolerated dose, only scattered degenerating cells were observed in the vestibular nuclei.

Other studies have focussed on potential peripheral effects of mefloquine on the vestibulocochlear system. Carrara et al (2008) assessed the effects on auditory function of a standard 3-day oral dose of artesunate combined with mefloquine for treatment of acute uncomplicated falciparum malaria. Among the 93 patients, neither audiometric or the auditory brainstem responses tests showed clinical evidence of auditory toxicity seven days after receiving treatment. In an experimental study, Yu et al (2011) examined the effect of mefloquine on organotypic cultures of the macula of the utricle from rats to determine if mefloquine might be toxic to the vestibular system. Hair cell nuclei in mefloquine-treated utricles showed evidence of apoptosis, which was consistent with earlier studies of inner ear toxicity. However, vestibulotoxicity of mefloquine *in vivo* would depend on many factors, including dose and duration of treatment, uptake of the compound across the blood-brain barrier and individual susceptibility.

The occurrence of acute neuropsychiatric reactions in a minority of mefloquine users suggests that individual susceptibility is likely, but no biomarkers or genotypes of susceptibility have yet been confirmed (Nevin and Ritchie 2016). There is no imaging modality which has been able to reliably diagnose damage in the human brain after taking mefloquine.

Limitations of the available epidemiology

One of the difficulties with attributing persistent symptoms to mefloquine is the lack of comparative studies and the non-specific nature of the reported symptoms. While there often is a probable relationship between a patient's initial symptoms and mefloquine exposure, the cause of progression of symptoms over the subsequent periods is difficult to ascertain. Without a comparison group, it is possible that symptoms could be attributed to causes other than neurotoxicity, especially when these symptoms are common in the general population

and overlap with other disorders, including posttraumatic stress disorder and depression. In relation to military cases, McCarthy (2015) points out that many reported symptoms are not reasonably distinguishable from normal psychological or physiological reactions to psychological or environmental stressors prevalent in military settings where mefloquine is used.

Dizziness and vertigo are highly prevalent symptoms which can be attributed to a number of different pathological mechanisms, including disorders of the inner ear or labyrinth and general medical, cardiac, neurological, endocrinological, and psychological disorders. A systematic review of balance disorders in the general community (Murdin and Schilder 2014[101]) identified a prevalence of dizziness severe enough to interfere with normal activities in the last month of around 11%. For symptoms of vertigo that interfere with daily activities, lifetime prevalence has been estimated at 3.0 to 7.8%. Two studies estimated 12-month incidence of de novo vertigo attacks at 0.76% and 1.4%.

There is no case definition for chronic mefloquine toxicity syndrome and no unique or distinctive group of symptoms has yet been specified (Nevin 2014, McCarthy 2015). Nevin and Leoutsakos (2017) sought to identify a distinct neuropsychiatric syndrome class associated with mefloquine using latent class modelling of US Food and Drug Administration Adverse Event Reporting System data. This technique produced a syndrome defined by a very high probability of symptoms of deliria (82.7%), including confusion and disorientation, and a moderate probability of other severe psychiatric and neurologic symptoms, including dementia and amnesia (18.6%) and seizures (18.1%). The syndrome was more strongly associated with mefloquine than with other drugs, but was not specific to mefloquine or antimalarials. This study's methods could not determine whether any of these reported symptoms preceded the more serious characteristic symptoms of this syndrome class (eg psychosis), nor could it determine the chronicity of these symptoms.

Summary and conclusions

In summary, the attribution of chronic brain injury as a result of having taken mefloquine is postulated on the basis of acute neuropsychiatric symptoms, with some case reports and adverse event reports of persistence of a variety of commonly experienced symptoms, some pathology identified from animal studies and putative biological mechanisms. No studies have measured cognitive performance in people who have taken mefloquine and reported ongoing symptoms, so it is not known whether they demonstrate neurocognitive deficits capable of meeting the DSM-5 criteria for a neurocognitive disorder.

The three available comparative studies of longer term effects, while retrospective, show similar or decreased risk of neuropsychiatric outcomes for mefloquine-prescribed groups compared to control groups. There is no test for the postulated condition, no pathology has been demonstrated in the brain of people who have taken mefloquine and reported ongoing symptoms, and no pattern of symptoms unique to past or current mefloquine users has been identified.

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[101] Murdin L, Schilder AGM (2014). Epidemiology of balance symptoms and disorders in the community: a systematic review. Otology & Neurotology, 36: 387-92.

Therefore, at present there are insufficient data to define a specific chronic toxic encephalopathy which could be defined and causally attributed to taking mefloquine (Grade 5a). To show that chronic effects are due to mefloquine and not some other cause, prospective, controlled studies measuring rates, patterns and duration of symptoms in comparison with a non-exposed group are needed. Prospective studies eliminate the problem of increased recall of symptoms due to having an illness or to adverse publicity. Other methods which would assist in the confirmation of a specific chronic toxic encephalopathy attributable to mefloquine would include a working case definition in which the frequency, duration and pattern of symptoms is specified, evidence of neurocognitive deficits in comparison to a control group before and after taking mefloquine, and evidence of a specific and consistent pathology in the human brain from an imaging modality or other test.

The above conclusion does not imply that symptoms experienced by people who have taken mefloquine are not real. Some people are reporting that they are experiencing a range of symptoms, which may be causing varying levels of distress and disability and require treatment. Some evidence as to effective treatment for illnesses presenting with multiple chronic symptoms is available[102], but further studies may be needed to identify more effective treatments.

Tafenoquine

Reviews

Novitt-Moreno et al (2017)[103] provided a safety assessment of tafenoquine for antimalarial prophylaxis based on 5 clinical trials, including 1 conducted in deployed military personnel (Nasveld et al 2010) and 4 in non-deployed residents (civilian populations in Africa, the UK and the USA), which also incorporated placebo and mefloquine comparator groups. The clinical regimen was 200 mg of tafenoquine orally for 3 days as a loading dose, followed by 200 mg once per week.

Adverse events that occurred at ≥ 1% incidence in both tafenoquine sub-groups (deployed and non-deployed) and at a higher frequency than placebo included diarrhoea, nausea, vomiting, gastroenteritis, nasopharyngeal tract infections, and back/neck pain.

In all studies, the majority of adverse events were mild and considered unrelated to the study drugs. Among the tafenoquine overall population, non-deployed residents were similar to placebo subjects in overall incidence of adverse events (67.6% vs. 64.1%, respectively).

In contrast, the percentage of subjects with adverse events was markedly higher in the deployed ADF subgroup (94.9%) than in the non-deployed residents (67.6%). However, a much higher percentage of adverse events in the deployed ADF subjects were considered to be unrelated to treatment (86.7%) than in the non-deployed residents (53.0%). Military

[102] Institute of Medicine (2013). Gulf War and Health: Volume 9. Treatment for chronic multisymptom illness. The National Academies Press. Washington D.C.
[103] Novitt-Moreno A, Ransom J, Dow G, Smith B, Read LT, Toovey S (2017) Tafenoquine for malaria prophylaxis in adults: An integrated safety analysis, Travel Medicine and Infectious Disease.

subjects experience a number of physical and psychological stressors which place them at higher risk for neuropsychological adverse effects than civilian populations, especially problems related to sleep.

Previous trials that have utilised tafenoquine at higher exposures than the clinical regimen in these clinical trials have reported the adverse effects of gastrointestinal distress, as well as reversible asymptomatic methaemoglobinemia, together with haemolytic anaemia in rare individuals with G6PD deficiency who were admitted to the trials in error.

Ebstie et al (2016)[104] discuss the potential for tafenoquine in the treatment and relapse prevention of *P. vivax* malaria. They conclude that data on the relative safety of tafenoquine over primaquine in patients with G6PD deficiency are lacking. However, tafenoquine could be a safer drug in terms of QT prolongation compared with other quinoline antimalarial drugs, probably due to short duration of treatment with tafenoquine.

Brueckner et al (1998)[105] state that preclinical studies have demonstrated that tafenoquine has greater efficacy and less toxicity compared with primaquine. They report the first human randomised, double-blind, placebo-controlled study designed to evaluate the safety, tolerance and pharmacokinetics of tafenoquine. The drug was administered to 48 men in single oral doses ranging from four to 600 mg (base).

Gastrointestinal side effects (heartburn, gas, vomiting, and diarrhoea) were only seen in those receiving study drug, and occurred only at higher doses (300-600 mg). Methemoglobinemia, haemolytic anemia, thrombocytopenia, or changes in white blood cell counts or ECGs were not observed. The elimination half-life was 14 days. The authors concluded that the safety, efficacy and pharmacokinetic properties of this drug made it an excellent candidate for further testing as a prophylactic, radical curative, and terminal eradication drug.

Randomised controlled trials

Rajapakse et al (2015)[106] conducted a Cochrane review of three randomised clinical trials of tafenoquine for relapse prevention in people with *P. vivax* infection (Llanos-Cuentos et al

[104] Ebstie YA, Abay SM, Tadesse WT, Ejigu DA. (2016) Tafenoquine and its potential in the treatment and relapse prevention of Plasmodium vivax malaria: the evidence to date. Drug Des Devel Ther. Jul 26;10:2387-99.
[105] Brueckner RP, Lasseter KC, Lin ET and Schuster BG (1998). First-time-in -humans safety and pharmacokinetics of WR238605, a new antimalarial. Am. J. Trop. Med. Hyg. 58 (5) pp645-649.
[106] Rajapakse S, Rodrigo C, Fernando SD. (2015) Tafenoquine for preventing relapse in people with Plasmodium vivax malaria. Cochrane Database Syst Rev. Apr 29;4:CD010458.

2014[107], Walsh et al 1999[108], Walsh et al 2004[109]). They found no difference in rates of adverse events between tafenoquine groups and controls.

Green et al (2014)[110] conducted a Phase I, single-blind, randomised controlled study to investigate whether tafenoquine at supratherapeutic and therapeutic concentrations prolonged cardiac repolarisation in 260 healthy volunteers. Tafenoquine did not have a clinically meaningful effect on cardiac repolarization.

Leary et al (2009)[111] conduced a randomised, double-blind, placebo-controlled study to assess the effect of tafenoquine, 200 mg weekly for 6 months on ophthalmic and renal safety in 120 healthy volunteers. This trial was carried out after observations in previous clinical trials that tafenoquine may be associated with the development of corneal deposits and elevations in serum creatinine.

There was no effect on night vision or other ophthalmic indices measured. Persons taking tafenoquine also showed no difference in mean change in glomerular filtration rate after 6 months of dosing.

Hale et al (2003)[112] conducted a randomised, double-blind, placebo-controlled chemoprophylaxis trial with adult residents of northern Ghana to determine the minimum effective weekly dose of tafenoquine for the prevention of infection by *Plasmodium falciparum*. Relative to the placebo, all four tafenoquine dosages demonstrated significant protection against *P. falciparum* infection, with a dose-response effect.

There was little difference between study groups in the adverse events reported. Physical complaints involving the musculoskeletal, gastrointestinal, and respiratory systems collectively accounted for 52% - 70% of the total adverse events that prompted health clinic visits in each group. No serious adverse events were considered by study physicians to be related to the study drug, and no deaths occurred. There was no evidence of a relationship between tafenoquine dosage and reports of physical complaints or the occurrence of abnormal laboratory parameters. The authors concluded that tafenoquine dosages of 50, 100, and 200 mg/week were safe, well tolerated, and effective.

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[107] Llanos-Cuentas A, Lacerda MV, Rueangweerayut R, et al (2014). Tafenoquine plus chloroquine for the treatment and relapse prevention of plasmodium vivax malaria (DETECTIVE): a multicentre, double-blind, randomised, phase 2b dose-selection study.
[108] Walsh DS, Looareesuwan S, Wilairantana P, et al (1999). randomised dose-ranging study of the safety and efficacy or WR238605 (tafenoquine) in the prevention of relapse of plasmodium vivax malaria in Thailand. J Infect Dis, 180(4): 1282-7.
[109] Walsh DS, Eamsila C, Sasiprapha T, et al (2004). Efficacy of monthly tafenoquine for prophylaxis of plasmodium vivax and multidrug-resistant p. falciparum malaria. J Infect Dis, 190(8): 1456-63.
[110] Green JA, Patel AK, Patel BR, et al (2014).Tafenoquine at therapeutic concentrations does not prolong fridericia-corrected QT interval in healthy subjects. J Clin Pharmacol, 54(9): 995-1005.
[111] Leary KJ, Riel MA, Roy MJ, et al (2009). A randomised, double-blind, safety and tolerability study to assess the ophthalmic and renal effects of tafenoquine 200 mg weekly versus placebo for 6 months in healthy volunteers. Am J Trop Med Hyg, 81(2), p. 356-362.
[112] Hale BR, Owusu-Agyei S, Fryauff DJ, et al (2003). A randomised, double-blind, placebo-controlled, dose-ranging trial of tafenoquine for weekly prophylaxis against plasmodium falciparum. Clin Infect Dis, 36(5): 541-9.

Lell et al (2000)[113] conducted a randomised, double-blind study in Gabon to assess the efficacy and safety of tafenoquine in different doses for prevention of *Plasmodium falciparum* malaria. 426 participants aged 12-20 were randomly assigned tafenoquine or placebo daily for 3 days. 417 received initial curative treatment with halofantrine, and 410 completed the assigned prophylaxis regimen. Follow-up was for 70 days.

Tafenoquine was effective and well tolerated. There were 180 adverse events which were thought by the study doctors to be at least possibly related to the study drug. These were in general mild and self-limiting and none were considered serious. Analyses for adverse events were done 1 week (29 participants) and 4 weeks (65 participants; table 3) after the end of study drug intake as well as at the end of the study (170 events). Although abdominal pain was reported more commonly in the tafenoquine groups than in the placebo group, and the frequency was highest in the tafenoquine 250 mg group, the difference was not significant and there was no clear dose relation. No other symptom was significantly associated with the study drug.

ADF clinical trials

The ADF, via the Army Malaria Institute, appears to have conducted four clinical trials involving tafenoquine:

Nasveld et al (2010)[114] undertook a randomised double blind clinical trial between 2001 and 2002 to assess the safety and efficacy of tafenoquine versus mefloquine. The trial involved 654 participants who were deployed to East Timor and took the treatment for 6 months.

There was a high incidence of vortex keratopathy (benign corneal deposits), but vision was not impaired in any subject and the condition was fully resolved by one year. The study found no significant differences between the mefloquine and tafenoquine groups in the incidence or nature of treatment related adverse events during the prophylactic phase.

Only one subject on tafenoquine reported a severe adverse event (diarrhoea and abdominal pain) suspected to be related to treatment. Common neuropsychiatric effects were mild and included vertigo, somnolence, abnormal dreams and dizziness. Adverse events during the 6 month follow up phase were not reported in this paper.

Elmes et al (2008)[115] conducted an open-label, randomised, parallel-group clinical study of post-exposure malaria prophylaxis in 1512 male and female members of the ADF who had

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[113] Lell B, Faucher J-F, Missinou MA, et al (2000). Malaria chemoprophylaxis with tafenoquine: a randomised study. Lancet, 355(9220): 2041-5.

[114] Nasveld PE, Edstein MD, Reid M, Brennan L, Harris IE, Kitchener SJ, Leggat PA, Pickford P, Kerr C, Ohrt C, Prescott W; Tafenoquine Study Team. (2010) Randomised, double-blind study of the safety, tolerability, and efficacy of tafenoquine versus mefloquine for malaria prophylaxis in nonimmune subjects. Antimicrob Agents Chemother. Feb;54(2):792-8

[115] Elmes NJ, Nasveld PE, Kitchener SJ, et al (2008). The efficacy and tolerability of three different regimens of tafenoquine versus primaquine for post-exposure prophylaxis of plasmodium vivax malaria in the southwest pacific. Trans R Soc Trop Med.

been in Bougainville and Timor-Leste for a period of at least 2 months. Recruitment for the study was carried out between February 1999 and April 2000 and subjects were followed-up for presentation of parasitaemia for 12 months from the last dose of medication. The subjects had been taking daily doxycycline chemoprophylaxis for the duration of their deployment. Subjects received one of three tafenoquine 3 day regimens or daily primaquine plus doxycycline over 14 days in Bougainville and in Timor-Leste.

Relapse rates were lower or similar in the tafenoquine treated groups compared to the primaquine treated groups in both countries. The most frequent adverse events reported across all groups were nausea, abdominal distress and diarrhoea. There was a dose-dependent reduction in adverse events with a reduced dose of tafenoquine, with the lowest dose (total 600 mg over 3 days) producing rates of adverse events equivalent to that of primaquine plus doxycycline. No serious adverse events were reported.

Kitchener et al (2007)[116] undertook a small pilot study to assess the efficacy and safety of tafenoquine for the treatment of recurrent *P.vivax* malaria (31 patients were enrolled and commenced study medication and 27 patients completed the full tafenoquine treatment).

Treatment was terminated early for four patients when all tafenoquine clinical trials were suspended by the sponsor because of an unexpected adverse event (vortex keratopathy) occurring in a long-term prophylaxis trial being conducted concurrently. There were no serious adverse events reported in this study and no withdrawals because of adverse events. Only one patient subsequently relapsed.

In an earlier open label trial, **Nasveld et al (2002)[117]** compared the effectiveness of tafenoquine (400 mg/day for 3 days) versus primaquine (22.5 mg/day for 14 days) for post-exposure prophylaxis of *P. vivax* malaria. The study involved 586 ADF personnel completing their 2-4 month deployments to Bougainville Island between November 1998 and September 1999.

Tafenoquine was equally effective as the longer course of primaquine in preventing *P.vivax* malaria. Both drugs were associated with gastrointestinal disturbances such as nausea and abdominal pain. Tafenoquine produced more adverse events than primaquine. The adverse events associated with tafenoquine tended to be of greater intensity. However, they were transient in nature, generally “non-troubling” and did not interfere with the volunteers’ daily activities. No serious adverse events were reported.

[116] Kitchener S, Nasveld P, Edstein MD (2007). Short report: tafenoquine for the treatment of recurrent plasmodium vivax malaria. Am J Trop Med Hyg, 76(3): 494-6.
[117] Nasveld P, Kitchener S, Edstein M, et al (2002). Comparison of tafenoquine (WR238605) and primaquine in the post-exposure (terminal) prophylaxis of vivax malaria in Australian Defence Force personnel. Trans R Soc Trop Med Hyg, 96(6): 683-4.

Animal study

Dow et al (2017)[118] conducted a neurobehavioral study in rats with histopathological assessment of the brain. The clinical, haematological, behavioural, motor activity, and neurohistopathologic changes induced by different dose levels of tafenoquine were evaluated following single supertherapeutic dose administration. For context, the human dosing regimen is a 10 mg/kg load followed by 3.3 mg/kg weekly (in a 60 kg person).

Tafenoquine at doses up to the minimum lethal dose (500 mg/kg single dose) in adult rats did not exhibit any dose-related histopathological changes in the brain. The main adverse effects noted in the maximum tolerated dose study were dose-related reductions in red blood cell parameters, and increases in liver enzymes with threshold doses as low as 125 mg/kg.

In humans, gastrointestinal disturbance is the dose-limiting toxicity in individuals who are G6PD-normal while haemolytic toxicity is the dose-limiting toxicity in G6PD deficiency. Keratopathy had no effect on vision acuity and fully resolved within 6-12 months. The authors concluded that, as in humans, adverse events other than neurotoxicity were dose-limiting for tafenoquine in rats.

Summary and conclusions

Tafenoquine has been trialled in the shorter term for prophylaxis (up to 6 months) or *P. vivax* post-exposure prophylaxis. Randomised, controlled trials support the safety and efficacy of tafenoquine for malaria prophylaxis (Novitt-Moreno et al 2017, Leary et al 2009, Hale et al 2003, Lell et al 2000, Nasveld et al 2010) and post-exposure prophylaxis (Rajapakse et al 2015, Elmes et al 2008). One subject taking tafenoquine in one of the ADF clinical trials (Nasveld et al 2010) reported a severe adverse event (diarrhoea and abdominal pain). Other adverse events were mild and self-limiting, with gastrointestinal effects being the most common. Clinical trials do not report on adverse effects beyond the duration of the trial, so longer term effects of tafenoquine are unknown.

Two known side effects of tafenoquine are vortex keratopathy and haemolytic anaemia in people with G6PD deficiency. Vortex keratopathy is a benign and reversible condition, and therefore not likely to cause ongoing disability. It did occur in two of the ADF trials, but vision was not impaired in any subject and the condition was fully resolved by one year (Nasveld et al 2010, Kitchener et al 2007). Haemolytic anaemia in people with G6PD deficiency is also usually reversible and subjects were screened for this defect in the clinical trials conducted by the ADF.

A study of adverse effects of high dose tafenoquine in rats (Dow et al 2017) did not provide evidence of neurological toxicity, and suggested that, as in humans, dose-limiting toxicities are gastrointestinal disturbances and haemolysis, rather than neurological effects.

[118] Dow G, Brown T, Reid M, Smith B and Toovey S (2017) Tafenoquine is not neurotoxic following supertherapeutic doses in rats. Travel Medicine and Infectious Diseases.

These studies do not identify any evidence that tafenoquine causes long term signs, symptoms or pathology suggestive of chronic neurological damage in humans. Gastrointestinal disturbance and haemolysis in those with G6PD deficiency are the main acute toxicities reported and are likely to be dose-limiting. At present there are insufficient data to define a specific chronic toxic encephalopathy which could be causally attributed to taking tafenoquine (Grade 5a).

Primaquine

Reviews

Recht et al (2014)[119] reviewed the evidence on the risks associated with primaquine use for a World Health Organisation (WHO) report. Evidence for the safety of primaquine comes from case reports, clinical studies and observations during mass drug administration. In 12 mass drug administration programmes, primaquine was given to more than 9 million people in various regions of the world.

Efforts to limit the spread of artemisinin resistance and to eliminate malaria in some parts of the world have renewed interest in the use of single-dose primaquine because of its transmission-blocking effects in falciparum malaria. A significant obstacle to its use is concern about its safety in populations with G6PD deficiency.

The authors reviewed all studies to which they had access, both published (by screening the PubMed database) and unpublished (in the archives and historical collection of the WHO), in which the safety of pamaquine and primaquine was evaluated, regardless of the regimen administered. They also included published and unpublished reports of deaths, haemolysis and other severe adverse events, such as haemoglobinuria and renal failure, resulting from use of these drugs, even if they were not part of a formal study.

In 78 studies of the safety of primaquine (27 in mass drug administration studies and 51 other studies) and 141 published case reports, a total of 219 severe adverse events were attributed to primaquine.

Most of the events were acute haemolytic anaemia. A single case report from the USA in 1980[120] described depression and psychosis in a 55-year-old man with malaria who was treated with chloroquine and then primaquine at 15 mg daily, starting the day before discharge from hospital. The day after the second dose of primaquine, he was extremely depressed, anorectic, confused and forgetful and imagined events that had not occurred; none of these symptoms had been present before, and all disappeared within 24 h of discontinuation of primaquine.

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[119] Recht J, Ashley EA, White NJ (2014) Safety of 8-Aminoquinoline Antimalarial Medicines. Geneva: World Health Organization;. Downloadable at: http://www.who.int/malaria/publications/atoz/9789241506977/en/.

[120] Schlossberg D. (1980) Reaction to primaquine. Annals of Internal Medicine, Vol 92:435.

Of the other events, one was severe urticaria, two were methaemoglobinaemia, one was severe anaemia and 67 were hospitalizations for unknown reasons, which could have included some cases of acute haemolytic anaemia.

In 1985, a doctoral thesis in France described mass administration of antimalarial drugs in Nicaragua in 1973–1983 to almost 2 million people (excluding infants). Chloroquine and primaquine were given over 3 days (adult dose, 15 mg primaquine per day, 600 mg chloroquine on day 1 and 450 mg of each on days 2 and 3; children were given proportionally less in age blocks). An undetermined number of cases of vertigo and rare cases of psychomotor agitation and transitory neurological problems resulting in cessation of treatment were reported.

In addition to reviewing published data, the authors extracted all case reports submitted to the Uppsala Monitoring Centre, the WHO collaborating centre for international drug monitoring (http://www.who-umc.org), between 1969 and 30 July 2012 in which primaquine was suspected to be a causative or interacting factor for the reaction. A total of 1429 reports on 4560 reactions or events were submitted to the Centre from all WHO regions.

There were three reports of acute psychosis, in two of which the patients were also taking mefloquine. One report in Malaysia in 2008 was in a 27-year-old woman who received primaquine at 15 mg daily for 5 days with chloroquine. Both drugs were assessed as possible causes of her psychosis and anaemia; quinine was listed as a concomitant cause. Chloroquine is known to cause psychosis rarely. The second report was from the USA of a 35-year-old man who received primaquine and mefloquine daily for 41 days (well above the recommended dosage).The adverse reactions reported included psychosis, manic reaction, neurosis and aggressive behaviour. The third case, from the USA in 2010, was of an 11-year-old girl with psychotic disorder and mania who had received mefloquine, artesunate and primaquine; risperidone was listed as concomitant medication.

Hill et al (2006)[121] examined the evidence for the recommendation concerning use of primaquine. Primaquine phosphate has been used for preventing relapse of *Plasmodium vivax* and *P. ovale* malaria since the early 1950s, based on its ability to kill latent (hypnozoite) and developing liver stages of these parasites.

There are three uses for primaquine in malaria: radical cure of established infection with *P. vivax* or *P. ovale* malaria; presumptive anti-relapse therapy (terminal prophylaxis) in persons with extensive exposure to these parasites; and primary prophylaxis against all malaria species.

The review found that the most common mild/moderate adverse drug reactions were abdominal pain, nausea, vomiting. The most severe reactions were haemolysis in persons with G6PD deficiency. Methemoglobinemia occurs, but is not reported to be clinically

[121] Hill DR, Baird JK, Parise ME, Lewis LS, Ryan ET, Magill AJ. (2006) Primaquine: report from CDC expert meeting on malaria chemoprophylaxis I. Am J Trop Med Hyg. Sep;75(3):402-15.

significant at dosages used for prophylaxis. In studies, 0–2% of persons have reported a severe reaction and 0–2% have discontinued prophylaxis because of ADRs.

In relation to neuropsychiatric adverse events the authors found that "psychomotor effects have not been noted and neuropsychiatric changes seem to be rare, with only a single case report of depression and psychosis after primaquine use."

Meta-analysis

Kolifarhood et al (2017)[122] conducted a systematic review and meta-analysis of studies concerning the prophylactic effectiveness and toxicity of primaquine. Five randomised controlled trials, one non-randomised controlled trial and one uncontrolled before-and-after study were included in the review.

Overall, a 74% reduction in the incidence of parasitaemia by primaquine versus other prophylactic regimens was estimated. The trials showed non-inferiority of primaquine compared to other chemoprophylactic regimens concerning gastrointestinal and neuropsychiatric side effects. All studies reviewed recommended primaquine as a well-tolerated prophylactic regimen for persons without G6PD deficiency.

The authors concluded that for persons without G6PD deficiency, who are not pregnant, primaquine is the most effective presently available prophylactic antimalarial for *P. vivax* malaria and comparable to such regimens as doxycycline, mefloquine and atovaquone-proguanil for the prevention of *P. falciparum* malaria.

ADF clinical trials

Head to head trials of primaquine and tafenoquine were conducted because of concerns over high relapse rates of *P. vivax* malaria in Australian military personnel returning from duties in the Pacific region. These returning soldiers had been given 14 day courses of primaquine, at either 22.5 mg daily or 30mg daily for terminal prophylaxis. It was thought that the high relapse rates might be due to resistance to primaquine or poor compliance with the 14 day regime. One trial (Nasveld et al 2002) compared the standard primaquine regime with 400 mg of tafenoquine once daily over 3 days. A subsequent trial (Elmes et al 2008) additionally examined the tolerability and efficacy of different tafenoquine regimes.

Elmes et al (2008)[123] conducted an open-label, randomised, parallel-group clinical study of post-exposure malaria prophylaxis in 1512 male and female members of the ADF who had been in Bougainville and Timor-Leste for a period of at least 2 months. Recruitment for the study was carried out between February 1999 and April 2000 and subjects were followed-up for presentation of parasitaemia for 12 months from the last dose of medication. The subjects had been taking daily doxycycline chemoprophylaxis for the duration of their deployment.

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[122] Kolifarhood G, Raeisi A, Ranjbar M et al (2017) Prophylactic efficacy of primaquine for preventing Plasmodium falciparum and Plasmodium vivax parasitaemia in travelers: A meta-analysis and systematic review. Travel Med Infect Dis. 2017 Apr 24. pii: S1477-8939(17)30068-6.
[123] Elmes NJ, Nasveld PE, Kitchener SJ, et al (2008). The efficacy and tolerability of three different regimens of tafenoquine versus primaquine for post-exposure prophylaxis of plasmodium vivax malaria in the southwest pacific. Trans R Soc Trop Med.

Subjects received one of three tafenoquine 3 day regimens or daily primaquine plus doxycycline over 14 days in Bougainville and in Timor-Leste.

Relapse rates were lower or similar in the tafenoquine treated groups compared to the primaquine treated groups in both countries. The most frequent adverse events reported across all groups were nausea, abdominal distress and diarrhoea. Tafenoquine produced more adverse events than primaquine, though rates were similar to those on the lowest dose regime of tafenoquine (200 mg once daily).

TABLE 18 ADVERSE EFFECTS OF TAFENOQUINE AND PRIMAQUINE

Table 2 Comparison of the rates of adverse events between healthy subjects administered 3 d courses of tafenoquine and a 14 d course of primaquine plus doxycycline for post-exposure vivax malaria prophylaxis

Adverse events (AE)[a]	Tafenoquine 400 mg od[b] (*n* = 242)	Tafenoquine 200 mg bid[c] (*n* = 161)	Tafenoquine 200 mg od[b] (*n* = 406)	Primaquine 7.5 mg tid[d] (*n* = 464)
Nausea	57, 5[e] (25.6)	28, 3 (19.3)	31, 1 (7.9)	43, 4 (10.1)
Abdominal distress	33, 9 (17.4)	14, 3 (10.6)	22, 4 (6.4)	14, 1 (3.2)
Diarrhoea	18, 5 (9.5)	22, 2 (14.9)	16, 3 (4.7)	8, 2 (2.2)
Reflux	14, 0 (5.8)	10, 0 (6.2)	2, 0 (0.5)	10, 0 (2.2)
Vomiting	7, 4 (4.5)	2, 2 (2.5)	1, 1 (0.5)	4, 1 (1.1)
Flatulence	4, 0 (1.7)	4, 0 (2.5)	2, 0 (0.5)	5, 0 (1.1)
Headache	17, 1 (7.4)	5, 0 (3.1)	3, 1 (1.0)	8, 1 (1.9)
Lethargy	5, 1 (2.5)	1, 2 (1.9)	7, 0 (1.7)	8, 0 (1.7)
Any GI AE	111 (45.9)	65 (40.4)	69 (17.0)	75 (16.2)
Tafenoquine concentrations (ng/ml)[f]				
With AE	619 ± 122 (*n* = 92)	631 ± 136 (*n* = 56)	317 ± 65 (*n* = 72)	
Without AE	609 ± 138 (*n* = 87)	630 ± 120 (*n* = 80)	321 ± 64 (*n* = 311)	

Values in parentheses are percentages.
[a] No. subjects with mild and moderate adverse events, respectively (% of subjects with combined mild and moderate adverse events).
[b] Once daily.
[c] Twice daily.
[d] Thrice daily for primaquine plus doxycycline 100 mg daily.
[e] One severe adverse event.
[f] Mean (± SD) plasma tafenoquine concentrations measured between 8 and 14 h after last drug administration on day 3.

In an earlier open label trial, **Nasveld et al (2002)**[124] compared the effectiveness of tafenoquine (400 mg/day for 3 days) versus primaquine (22.5 mg/day for 14 days) for post-exposure prophylaxis of *P. vivax* malaria. The study involved 586 ADF personnel completing their 2-4 month deployments to Bougainville Island between November 1998 and September 1999.

Tafenoquine was equally effective as the longer course of primaquine in preventing *P.vivax* malaria. Both drugs were associated with gastrointestinal disturbances such as nausea and abdominal pain. Tafenoquine produced more adverse events than primaquine. The adverse events associated with tafenoquine tended to be of greater intensity. However, they were transient in nature, generally “non-troubling” and did not interfere with the volunteers’ daily activities. No serious adverse events were reported.

[124] Nasveld P, Kitchener S, Edstein M, et al (2002). Comparison of tafenoquine (WR238605) and primaquine in the post-exposure (terminal) prophylaxis of vivax malaria in Australian Defence Force personnel. Trans R Soc Trop Med Hyg, 96(6): 683-4.

Clinical trial

Clayman et al (1952)[125] report on the adverse effects of primaquine given to a prison population, including subjects both with and without malaria. Daily doses ranged from 10 to 240 mg, administered for 5 to 14 days. In addition, single doses of 30 mg of primaquine were given weekly and semiweekly for 52 weeks, together with chloroquine. Adverse effects were gastrointestinal symptoms and methaemoglobinaemia, especially at higher doses. The long term regimen also caused gastrointestinal symptoms, but no other adverse effects were reported. Neurotoxic effects were not reported, even in those given 240 mg (16 times the normal dose).

Case reports

Loken and Haymaker (1949)[126] report a case of accidental pamaquine poisoning in which approximately 20 times the therapeutic dose of the drug was given in one day. Death occurred 7 days thereafter. Pamaquine is an 8-aminoquinoline drug that was used to prevent relapse of vivax malaria, and is in the same quinolone subclass as primaquine. The patient had also received quinacrine and quinine at standard dosage, but was without any symptoms of toxicity. However, the combination may have indirectly worsened the pamaquine poisoning.

Early clinical symptoms included apprehension, cyanosis, nausea, and generalized pains. Late symptoms included numbness of the face, difficulty in speaking, dyspnoea, and palatal paralysis. Methemoglobinemia and hemoglobinuria occurred soon after the ingestion of the pamaquine. At autopsy there was ischemic necrosis with reactive change in a small area of the basis pontis, and mild to moderate degenerative changes in the globus pallidus, nuclei of the extraocular nerves, vestibular nuclei, and cerebral cortex.

The authors comment that despite the large dosage of pamaquine the pathologic changes in the central nervous system were few. Some of the changes were consistent with hypoxia from methaemoglobinaemia, but the changes in brainstem nuclei were similar to those reported by Schmidt and Schmidt (1948) in rhesus monkeys given pamaquine. The cause of death was thought to be prolonged hypoxia and complicating pneumonia.

Animal studies

Schmidt and Schmidt (1948[127], **1949**[128], **1951**[129]**)** reported on the neurotoxicity of various 8-aminoquinolines in rhesus monkeys and other animals. These studies were undertaken during wartime research for more effective antimalarial drugs.

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[125] Clayman CB, Arnold J, Hockwald RS, Yount EH, Edgcomb JH, Alving AS. (1952) Toxicity of primaquine in Caucasians. J Am Med Assoc.Vol 149(17):1563-8.
[126] Loken A, Haymaker W. (1949) Pamaquine poisoning in man, with a clinicopathologic study of one case. Am J Trop Med Hyg. May;29(3):341-52.
[127] Schmidt I, Schmidt L. (1948) Neurotoxicity of the 8-aminoquinolines; lesions in the central nervous system of the rhesus monkey induced by administration of plasmocid. J Neuropathol Exp Neurol. Oct;7(4):368-98.
[128] Schmidt I, Schmidt L. (1949) Neurotoxicity of the 8-aminoquinolines; reactions of various experimental animals to plasmocid.J Comp Neurol. Dec;91(3):337-67.
[129] Schmidt IG, Schmidt LH. (1951) Neurotoxicity of the 8-aminoquinolines. III. The effects of pentaquine, isopentaquine, primaquine, and pamaquine on the central nervous system of the rhesus monkey. Neuropathol Exp Neurol. 1951 Jul;10(3):231-56.

The 1951 report includes the effects of primaquine in rhesus monkeys. Subfatal intoxication produced low grade injury to the dorsal motor, supraoptic and paraventricular nuclei and fatal intoxication produced somewhat more extensive but not extremely severe lesions in these areas. Functional disturbances were not observed, which may have been due to neuron sparing or to masking by other effects. The authors were of the opinion that "the injury these drugs produce at subfatal doses does not appear extensive enough to constitute a therapeutic hazard."

The 1948 report covers the signs and pathology caused by lethal and sublethal doses of Plasmocid (6-methoxy-8-3-diethylaminoproplyoamino-quinoline) in rhesus monkeys. The authors state that the different 8-aminoquinolines evoked different types of toxic reactions in the rhesus monkey, with some affecting the heart and circulation, others suppressing myeloid activity in the blood and bone marrow, and others affecting the nervous system.

Plasmocid was the most active compound in inducing disturbances in the central nervous system. Functional disturbances included hyperesthesis, nystagmus, loss of pupillary reflexes, vertigo, ataxia, lack of muscular coordination, difficulty in walking and sometimes strabismus and apparent loss of vision. Signs occurred in a dose-response manner, with not toxic reactions observed at the lowest dose.

In the central nervous system, degenerative changes were observed in the nucleus dorsalis, multiple nuclei of the brainstem and in the midbrain, diencephalon and corpus striatum. The corresponding pathways were the proprioceptive, auditory, vestibulo-cerebellar, visual reflex, and extrapyramidal pathways. The auditory and vestibulo-cerebellar systems were much less affected by the subfatal doses. At one quarter the maximum tolerated dose, only scattered degenerating cells were observed in the vestibular nuclei. The cerebellar cortex was not affected and the cerebral cortex was largely unaffected.

The authors did not find any evidence of haemorrhagic lesions, suggesting that the damage was not caused by circulatory impairment. Rather, they considered the likely mechanism to be a specific toxic reaction to selected neurons.

The 1949 paper reports that there were marked differences in the effects of minimum fatal doses of Plasmocid between rhesus, cynomolgus and magabey monkeys, and dogs, rats and mice. Rhesus, and cynomolgus monkeys exhibited severe degenerative lesions involving the brain stem, cerebellum and spinal cord, while mangabey monkeys showed the same general pattern but less susceptibility. Dogs showed no signs and no lesions in the areas which were affected in monkeys, but there was severe degeneration in the dorsal motor nucleus. Rats and mice tolerated much larger doses than the other animals, with major sign being paralysis of the tongue and lower jaw.

Summary and conclusions

A comprehensive World Health Organisation (WHO) review reports on the risks associated with the use of primaquine (Recht et al 2014). Evidence for the safety of primaquine comes from case reports, clinical studies and observations during mass drug administration. The

report confirmed that the most common and serious adverse reaction to this drug is haemolytic anaemia due to G6PD deficiency. There were four case reports of acute psychosis in patients taking primaquine in combination with chloroquine or mefloquine.

A CDC review (Hill et al 2006) likewise reported that neuropsychiatric changes seem to be rare, with only a single case report of depression and psychosis after primaquine use. This case was one of the four cases reported in the WHO review (Schlossberg 1980). A meta-analysis of randomised controlled trials (Kolifarhood et al 2017) concluded that primaquine is a safe and effective drug for malaria prevention, and non-inferior to other chemoprophylactic regimens concerning gastrointestinal and neuropsychiatric side effects.

Two clinical trials involving members of the Australian Defence Force compared the effects and efficacy of primaquine and tafenoquine (Elmes et al 2008, Nasveld et al 2002). The most frequent adverse events reported across all groups were nausea, abdominal distress and diarrhoea. No serious adverse events were reported. None of these reports or trials were designed to assess the long term adverse effects of primaquine.

Fatal and subfatal doses of primaquine produced lesions in specific areas of the brain of rhesus monkeys, but the lesions were not considered severe and had no functional effect (Schmidt and Schmidt 1951). The authors concluded that "there was little likelihood that significant neuronal injury would result from use of primaquine in doses such as are employed for malaria therapy." The authors found that there was considerable variation in the types of toxic reactions caused by different 8-aminoquinoline compounds. Primaquine was much less toxic than Plasmocid, one of the other candidate 8-aminoquinolines they tested (Schmidt and Schmidt 1948). There was also considerable interspecies differences in toxic effects, with monkeys being much more susceptible to specific neuronal injuries than dogs, rats and mice (Schmidt and Schmidt 1949).

High and very high doses of primaquine given to humans in a 1952 clinical trial did not produce any neurotoxic effects, despite doses 16 times higher than the standard dose (Clayman et al 1952). There is a 1949 case report of a fatal overdose of a related 8-aminoquinoline compound pamaquine (Loken and Haymaker 1949). Over 20 times the therapeutic dose caused methemoglobinemia, hemoglobinuria, focal changes in the pons and some mild to moderate degenerative changes in parts of the brainstem and cerebral cortex.

These studies do not identify any evidence that primaquine causes long term signs, symptoms or pathology suggestive of chronic neurological damage in humans taking recommended or above recommended doses. Gastrointestinal disturbance and haemolysis in those with G6PD deficiency are the main acute toxicities reported. At present there are insufficient data to define a specific chronic toxic encephalopathy which could be causally attributed to taking primaquine (Grade 5a).

Bibliography

Adshead S. (2014) The adverse effects of mefloquine in deployed military personnel. J R Nav Med Serv. Vol 100(3):232-7.

American Psychiatric Association (2013) Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. Arlington VA, pp.591-643.

Ashley et al. (2014) Primaquine: the risks and the benefits. Malaria Journal, 13:418. Available at http://www.malariajournal.com/content/13/1/418. Accessed 13-2-17.

Australian Institute of Health and Welfare (2007) Disability in Australia: acquired brain injury. Bulletin 55. Available at http://www.aihw.gov.au/WorkArea/DownloadAsset.aspx?id=6442453666%20. Accessed 6-3-17.

Australian Medicines Handbook (2017) Mefloquine. Available at https://amhonline.amh.net.au/chapters/chap-05/antiprotozoals/antimalarials/mefloquine. Accessed 6-3-17.

Beckley J, Woodward J (2013) Volatile Solvents as Drugs of Abuse: Focus on the Cortico-Mesolimbic Circuitry. Neuropsychopharmacology. Dec; 38(13): 2555–2567.

Boudreau E, Schuster B, Sanchez J, et al (1993). Tolerability of prophylactic lariam regimens. Tropical medicine and parasitology, 44(3): 257-265.

Brueckner RP, Lasseter KC, Lin ET and Schuster BG (1998). First-time-in -humans safety and pharmacokinetics of WR238605, a new antimalarial. Am. J. Trop. Med. Hyg. 58 (5) pp645-649.

Carrara VI, Phyo AP, Nwee P et al (2008) Auditory assessment of patients with acute uncomplicated Plasmodium falciparum malaria treated with three-day mefloquine-artesunate on the north-western border of Thailand. Malaria Journal. 7:233.

Castelli F, Odolini S, Autino B et al (2010) Malaria Prophylaxis: A Comprehensive Review. Pharmaceuticals (Basel) October; 3(10): 3212–3239.

Clayman CB, Arnold J, Hockwald RS, Yount EH, Edgcomb JH, Alving AS. (1952) Toxicity of primaquine in Caucasians. J Am Med Assoc.Vol 149(17):1563-8.

de Lagerie SB, Fernandez C, German-Fattal M et al (2009) Impact of cerebral malaria on brain distribution of mefloquine. Drug Metabolism Letters. 3(1):15-7.

de Souza A, Narvencar KP, Desai PK, D'Costa Z, Nilajkar G. (2013) Adult lead encephalopathy. Neurological Research. 35(1):54-8, Jan.

Dow G, Bauman R, Caridha D, Cabezas M, Du F, Gomez-Lobo R, Park M, Smith K, Cannard K. (2006) Mefloquine induces dose-related neurological effects in a rat model. Antimicrob Agents Chemother. Mar;50(3):1045-53.

Dow G, Brown T, Reid M, Smith B and Toovey S (2017) Tafenoquine is not neurotoxic following supertherapeutic doses in rats. Travel Medicine and Infectious Diseases.

Dow GS, Liu J, Lin G, Hetzell B, Thieling S, McCarthy WF, Tang D, Smith B. (2015) Summary of anti-malarial prophylactic efficacy of tafenoquine from three placebo-controlled studies of residents of malaria-endemic countries. Malar J. Nov 26;14(1):473.

Dow GS, Milner E, Bathurst I et al (2011).Central nervous system exposure of next generation quinoline methanols is reduced relative to mefloquine after intravenous dosing in mice. Malar J. Jun 6;10:150.

Ebstie YA, Abay SM, Tadesse WT, Ejigu DA. (2016) Tafenoquine and its potential in the treatment and relapse prevention of Plasmodium vivax malaria: the evidence to date. Drug Des Devel Ther. Jul 26;10:2387-99.

Eick-Cost AA, Hu Z, Rohrbeck P, Clark LL. (2017) Neuropsychiatric Outcomes After Mefloquine Exposure Among U.S. Military Service Members. Am J Trop Med Hyg. Jan 11;96(1):159-166.

Elmes NJ, Nasveld PE, Kitchener SJ, et al (2008). The efficacy and tolerability of three different regimens of tafenoquine versus primaquine for post-exposure prophylaxis of plasmodium vivax malaria in the southwest pacific. Trans R Soc Trop Med.

FDA Drug Safety Communication: FDA approves label changes for antimalarial drug mefloquine hydrochloride due to risk of serious psychiatric and nerve side effects. (2013). Available at: http://www.fda.gov/Drugs/DrugSafety/ucm362227.htm.

Fujii T, Kaku K, Jelinek T, Kimura M (2007). Malaria and mefloquine prophylaxis use among Japan Ground Self- Defense Force personnel deployed in east Timor. J Travel Med 14: 226–232.

Gogtay NJ, Ferner RE. (2015) Mefloquine for malarial prophylaxis in military personnel. BMJ. Nov 3;351:h5797.

González et al (2014) Intermittent preventive treatment of malaria in pregnancy with mefloquine in HIV-negative women: a multicentre randomized controlled trial. PLoS Med. 2014 Sep 23;11(9):e1001733.

González R, Hellgren U, Greenwood B, Menéndez C. (2014) Mefloquine safety and tolerability in pregnancy: a systematic literature review. Malar J. Feb 28;13:75.

Green JA, Patel AK, Patel BR, et al (2014).Tafenoquine at therapeutic concentrations does not prolong fridericia-corrected QT interval in healthy subjects. J Clin Pharmacol, 54(9): 995-1005.

Hale BR, Owusu-Agyei S, Fryauff DJ, et al (2003). A randomised, double-blind, placebo-controlled, dose-ranging trial of tafenoquine for weekly prophylaxis against plasmodium falciparum. Clin Infect Dis, 36(5): 541-9.

Hill DR, Baird JK, Parise ME, Lewis LS, Ryan ET, Magill AJ. (2006) Primaquine: report from CDC expert meeting on malaria chemoprophylaxis I. Am J Trop Med Hyg. Sep;75(3):402-15.

Hood JE, Jenkins JW, Milatovic D, Rongzhu L, Aschner M. (2010) Mefloquine induces oxidative stress and neurodegeneration in primary rat cortical neurons. Neurotoxicology. Sep;31(5):518-23.

Institute of Medicine (2013). Gulf War and Health: Volume 9. Treatment for chronic multisymptom illness. The National Academies Press. Washington D.C.

Jacquerioz FA, Croft AM. Drugs for preventing malaria in travellers. Cochrane Database Syst Rev. 2009 Oct 7;(4):CD006491.

Jain M, Nevin RL, Ahmed I. (2016) Mefloquine-associated dizziness, diplopia, and central serous chorioretinopathy: a case report. J Med Case Rep. Oct 31;10(1):305.

Jaspers CA, Hopperus Buma AP, van Thiel PP, van Hulst RA, Kager PA (1996). Tolerance of mefloquine chemoprophylaxis in Dutch military personnel. Am J Trop Med Hyg 55: 230–234.

Kitchener S, Nasveld P, Edstein MD (2007). Short report: tafenoquine for the treatment of recurrent plasmodium vivax malaria. Am J Trop Med Hyg, 76(3): 494-6.

Kitchener SJ, Nasveld PE, Gregory RM, Edstein MD. (2005) Mefloquine and doxycycline malaria prophylaxis in Australian soldiers in East Timor. Med J Aust. Feb 21;182(4):168-71.

Kolifarhood G, Raeisi A, Ranjbar M et al (2017) Prophylactic efficacy of primaquine for preventing Plasmodium falciparum and Plasmodium vivax parasitaemia in travelers: A meta-analysis and systematic review. Travel Med Infect Dis. 2017 Apr 24. pii: S1477-8939(17)30068-6.

Leary KJ, Riel MA, Roy MJ, et al (2009). A randomised, double-blind, safety and tolerability study to assess the ophthalmic and renal effects of tafenoquine 200 mg weekly versus placebo for 6 months in healthy volunteers. Am J Trop Med Hyg, 81(2), p. 356-362.

Lee E (2017) Overview of neurologic complications of non-platinum cancer chemotherapy. UpToDate. Available at https://www.uptodate.com/contents/overview-of-neurologic-complications-of-non-platinum-cancer-chemotherapy/print?source=search_result&search=solvent%20encephalopathy&selectedTitle=16~150. Accessed 6-03-17.

Lee SJ, Ter Kuile FO, Price RN, Luxemburger C, Nosten F. Adverse effects of mefloquine for the treatment of uncomplicated malaria in Thailand: A pooled analysis of 19, 850 individual patients. PLoS One. 2017 Feb 13;12(2):e0168780.

Lell B, Faucher J-F, Missinou MA, et al (2000). Malaria chemoprophylaxis with tafenoquine: a randomised study. Lancet, 355(9220): 2041-5.

Levin A (2013). FDA warning highlights mefloquine's mental health risks. Psychiatr News, 48(18): 1.

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

Llanos-Cuentas A, Lacerda MV, Rueangweerayut R, et al (2014). Tafenoquine plus chloroquine for the treatment and relapse prevention of plasmodium vivax malaria (DETECTIVE): a multicentre, double-blind, randomised, phase 2b dose-selection study.

Lobel HO, Coyne PE, Rosenthal PJ. (1998) Drug overdoses with antimalarial agents: prescribing and dispensing errors. JAMA. Nov 4;280(17):1483.

Loken A, Haymaker W. (1949) Pamaquine poisoning in man, with a clinicopathologic study of one case. Am J Trop Med Hyg. May;29(3):341-52.

Lysack JT, Lysack CL, Kvern BL. (1998) A severe adverse reaction to mefloquine and chloroquine prophylaxis. Aust Fam Physician. Dec;27(12):1119-20.

Mawson A. (2013) Mefloquine use, psychosis, and violence: a retinoid toxicity hypothesis. Medical Science Monitor. 19:579-83, Jul 15.

Maxwell NM, Nevin RL, Stahl S, Block J, Shugarts S, Wu AH, Dominy S, Solano-Blanco MA, Kappelman-Culver S, Lee-Messer C, Maldonado J, Maxwell AJ. (2015) Prolonged neuropsychiatric effects following management of chloroquine intoxication with psychotropic polypharmacy. Clin Case Rep. Jun;3(6):379-87.

Milatovic D, Jenkins JW, Hood JE, Yu Y, Rongzhu L, Aschner M. (2011) Mefloquine neurotoxicity is mediated by non-receptor tyrosine kinase. Neurotoxicology. Oct;32(5):578-85.

McCarthy S (2015). Malaria prevention, mefloquine neurotoxicity, neuropsychiatric illness, and risk-benefit analysis in the Australian Defence Force. Journal of Parasitology Research, available at https://www.hindawi.com/journals/jpr/2015/287651/. Accessed 20-4-17.

McEvoy K; Anton B; Chisolm MS. (2015) Depersonalization/derealization disorder after exposure to mefloquine. Psychosomatics. 56(1):98-102, Jan-Feb.

Meier CR, Wilcock K, Jick SS (2004) The risk of severe depression, psychosis or panic attacks with prophylactic antimalarials. Drug Saf.;27(3):203-13.

MIMS (2015) Larium. Full product information. Available at https://www.mimsonline.com.au.

Murdin L, Schilder AGM (2014). Epidemiology of balance symptoms and disorders in the community: a systematic review. Otology & Neurotology, 36: 387-92.

Naranjo CA, Busto U, Sellers EM, Sandor P, et al (1981). A method for estimating the probability of adverse drug reactions. Clinical Pharmacology - Therapeutics, 30(2) pp 239-245.

Nasveld P, Kitchener S, Edstein M, et al (2002). Comparison of tafenoquine (WR238605) and primaquine in the post-exposure (terminal) prophylaxis of vivax malaria in Australian Defence Force personnel. Trans R Soc Trop Med Hyg, 96(6): 683-4.

Nasveld PE, Edstein MD, Reid M, Brennan L, Harris IE, Kitchener SJ, Leggat PA, Pickford P, Kerr C, Ohrt C, Prescott W; Tafenoquine Study Team (2010) Randomised, double-blind study of the safety, tolerability, and efficacy of tafenoquine versus mefloquine for malaria prophylaxis in nonimmune subjects. Antimicrob Agents Chemother. Feb;54(2):792-8.

Nevin (2015) Mefloquine and Posttraumatic Stress Disorder. In Textbook of Military Medicine. Forensic and ethical issues in military behavioural health. EC Ritchie (ed). Borden Institute. Washington DC. Pp. 277-296.

Nevin R, Ritchie E (2016) The mefloquine toxicity syndrome: A significant potential confounder in the diagnosis and management of PTSD and other chronic deployment-related neuropsychiatric disorders. In Post-Traumatic Stress Disorder and Related Diseases in Combat veterans (In Press). Springer International: Switzerland.

Nevin RL (2009). Epileptogenic potential of mefloquine chemoprophylaxis- a pathogenic hypothesis. Malaria Journal, 8- 188

Nevin RL (2012) Limbic encephalopathy and central vestibulopathy caused by mefloquine: a case report. Travel Med Infect Dis. 2012 May;10(3):144-51.

Nevin RL (2012). [Comment] Mefloquine Blockade of Connexin 36 and Connexin 43 Gap Junctions and Risk of Suicide. Biol Psychiatry, 71: e1-e2.

Nevin RL (2014). Idiosyncratic quinoline central nervous system toxicity: historical insights into the chronic neurological sequelae of mefloquine. Int J Parasitol Drugs Drug Resist, 4: 118-25.

Nevin RL, Croft AM. (2016) Psychiatric effects of malaria and anti-malarial drugs: historical and modern perspectives. Malar J. 2016 Jun 22;15:332.

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

Nevin RL. (2016) Bias in military studies of mefloquine. Journal of Travel Medicine. 23(2):tav028, Feb.

Novitt-Moreno A, Ransom J, Dow G, Smith B, Read LT, Toovey S (2017) Tafenoquine for malaria prophylaxis in adults: An integrated safety analysis, Travel Medicine and Infectious Disease.

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

Prescrire International (2014). Mefloquine: persistent vestibular disorders. Prescrire International, 23(150): 157.

Quinn J (2015) Complex Membrane Channel Blockade: A Unifying Hypothesis for the Prodromal and Acute Neuropsychiatric Sequelae Resulting from Exposure to the Antimalarial Drug Mefloquine. Journal of Parasitology Research. Article ID 368064, http://dx.doi.org/10.1155/2015/368064.

Rajapakse S, Rodrigo C, Fernando SD. (2015) Tafenoquine for preventing relapse in people with Plasmodium vivax malaria. Cochrane Database Syst Rev. Apr 29;4:CD010458.

Recht J, Ashley EA, White NJ (2014) Safety of 8-Aminoquinoline Antimalarial Medicines. Geneva: World Health Organization;. Downloadable at: http://www.who.int/malaria/publications/atoz/9789241506977/en/.

Ricard D, Taillia H, Renard JL. (2009) Brain damage from anticancer treatments in adults. Current Opinion in Oncology. 21(6):559-65, Nov.

Ringqvist Å, Bech P, Glenthøj B, Petersen E. (2015) Acute and long-term psychiatric side effects of mefloquine: a follow-up on Danish adverse event reports. Travel Med Infect Dis. Jan-Feb;13(1):80-8.

Ritchie EC, Block J, Nevin RL. (2013) Psychiatric side effects of mefloquine: applications to forensic psychiatry. J Am Acad Psychiatry Law.;41(2):224-35.

Rønn AM, Rønne-Rasmussen J, Gøtzsche PC, Bygbjerg IC. (1998) Neuropsychiatric manifestations after mefloquine therapy for Plasmodium falciparum malaria: comparing a retrospective and a prospective study. Trop Med Int Health. Feb;3(2):83-8.

Ryan D, SC (2013) Memorandum. Available at http://www.rma.gov.au/foi/what.htm.

Saunders DL; Garges E; Manning JE; Bennett K; Schaffer S; Kosmowski AJ; Magill AJ. (2015) Safety, Tolerability, and Compliance with Long-Term Antimalarial Chemoprophylaxis in American Soldiers in Afghanistan. American Journal of Tropical Medicine & Hygiene. 93(3):584-90, Sep.

Schlagenhauf P, Adamcova M, Regep L, Schaerer MT, Rhein HG. (2010) The position of mefloquine as a 21st century malaria chemoprophylaxis. Malar J. Dec 9;9:357.

Schlagenhauf P, Tschopp A, Johnson R, Nothdurft HD, Beck B, Schwartz E, Herold M, Krebs B, Veit O, Allwinn R, Steffen R. (2003) Tolerability of malaria chemoprophylaxis in non-immune travellers to sub-Saharan Africa: multicentre, randomised, double blind, four arm study. BMJ. Nov 8;327(7423):1078.

Schlossberg D. (1980) Reaction to primaquine. Annals of Internal Medicine, Vol 92:435.

Schmidt I, Schmidt L. (1948) Neurotoxicity of the 8-aminoquinolines; lesions in the central nervous system of the rhesus monkey induced by administration of plasmocid. J Neuropathol Exp Neurol. Oct;7(4):368-98.

Schmidt I, Schmidt L. (1949) Neurotoxicity of the 8-aminoquinolines; reactions of various experimental animals to plasmocid.J Comp Neurol. Dec;91(3):337-67.

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

Schneider C, Adamcova M, Jick SS, Schlagenhauf P, Miller MK, Rhein HG, Meier CR. (2013) Antimalarial chemoprophylaxis and the risk of neuropsychiatric disorders. Travel Med Infect Dis. Mar-Apr;11(2):71-80.

Shin JH, Park SJ, Jo YK et al (2012) Suppression of autophagy exacerbates Mefloquine-mediated cell death. Neuroscience Letters. 515(2):162-7, May 02.

Silva AP, Martins T, Baptista S, Goncalves J, Agasse F, Malva JO. (2010) Brain injury associated with widely abused amphetamines: neuroinflammation, neurogenesis and blood-brain barrier. Current Drug Abuse Reviews. 3(4):239-54, Dec.

Terrell AG, Forde ME, Firth R, Ross DA. (2015) Malaria Chemoprophylaxis and Self-Reported Impact on Ability to Work: Mefloquine Versus Doxycycline. J Travel Med. Nov-Dec;22(6):383-8.

The International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Australian Modification, Eighth Edition (2013) World Health Organisation (2010), modified by the National Casemix and Classification Centre, Australian health Services Research Institute, University of Wollongong, Sydney.

Toovey S. (2009) Mefloquine neurotoxicity: a literature review. Travel Med Infect Dis. Jan;7(1):2-6.

van Riemsdijk MM, Sturkenboom MC, Ditters JM, Ligthelm RJ, Overbosch D, Stricker BH (2002). Atovaquone plus chloroguanide versus mefloquine for malaria prophylaxis: a focus on neuropsychiatric adverse events. Clin Pharmacol Ther 72: 294–301.

van Riemsdijk MM, Sturkenboom MC, Pepplinkhuizen L, Stricker BH (2005). Mefloquine increases the risk of serious psychiatric events during travel abroad: a nationwide case-control study in The Netherlands. J Clin Psychiatry 66: 199–204.

Walsh DS, Eamsila C, Sasiprapha T, et al (2004). Efficacy of monthly tafenoquine for prophylaxis of plasmodium vivax and multidrug-resistant p. falciparum malaria. J Infect Dis, 190(8): 1456-63.

Walsh DS, Looareesuwan S, Wilairantana P, et al (1999). randomised dose-ranging study of the safety and efficacy or WR238605 (tafenoquine) in the prevention of relapse of plasmodium vivax malaria in Thailand. J Infect Dis, 180(4): 1282-7.

Weinke T, Trautmann M, Held T, Weber G, Eichenlaub D, Fleischer K, Kern W, Pohle HD. (1991) Neuropsychiatric side effects after the use of mefloquine. Am J Trop Med Hyg. Jul;45(1):86-91.

Wells TS, Smith TC, Smith B, Wang LZ, Hansen CJ, Reed RJ, Goldfinger WE, Corbell TE, Spooner CN, Ryan MA. (2006) Mefloquine use and hospitalizations among US service members, 2002–2004. Am J Trop Med Hyg 74: 744–749.

WHO (2017) Essential Medicines. Available at http://www.who.int/medicines/services/essmedicines_def/en/. Accessed 6-3-17.

WHO Model List of Essential Medicines, 19th list (2015). Available at http://www.who.int/medicines/publications/essentialmedicines/EML_2015_FINAL_amended_NOV2015.pdf?ua=1. Accessed 6-3-17.

WHO (2017) Safety Monitoring of Medicinal Products: Guidelines for Setting Up and Running a Pharmacovigilance Centre. Available at http://apps.who.int/medicinedocs/en/d/Jh2934e/15.html. Accessed 19-5-17.

Yu D, Ding D, Jiang H, Stolzberg D, Salvi R. (2011) Mefloquine damage vestibular hair cells in organotypic cultures. Neurotox Res. Jul;20(1):51-8.