

# Evidence for Neurotoxicity from Quinoline Antimalaria Drugs: Four Personal Accounts

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## Abstract

**Background:** The adverse effects of mefloquine and other quinoline antimalaria drugs can be severe and long-lasting. We believe that the trigger for these effects may be drug-induced hepatocellular damage that causes, firstly, a spillage of retinoids into the circulation (and hence a direct toxic effect on the brain and other target organs), and secondly, disruption of the liver-thyroid axis (and hence a pattern of specific bipolar symptoms such as is often seen in thyroid disease). **Methods:** We sought recently-published lay accounts of adverse effects in users of quinoline antimalaria drugs, to test these lay descriptions against our hypothesis on the likely pathogenesis of these effects. **Results:** We found six lay accounts that described four different experiences of adverse effects arising from the prophylactic use of quinoline antimalaria drugs. All four travellers were healthy, at the start of travel. Two of the travellers experienced severe psychoses, and one had a mild psychosis. The fourth traveller, a serving US soldier, killed 16 unarmed Afghan civilians. Analysis of these accounts shows that, based on our hypothesis, all four travellers had at least one risk factor (most commonly, concurrent alcohol use), for developing a severe reaction to their quinoline antimalaria drug. Our hypothesis therefore predicted a severe adverse drug reaction in each of these four travellers. We also identified a hitherto unrecognized risk factor for developing a severe reaction to quinoline antimalaria drugs—namely, the concurrent use of anabolic steroids. **Conclusions:** Lay accounts of drug adverse effects can help initiate or further develop medical hypotheses of their pathogenesis. We advise that the quinoline class of antimalaria drugs should be prescribed cautiously, and that mefloquine should not now be prescribed for malaria prophylaxis, under any circumstances whatsoever. Where persistent adverse effects have resulted from the historical use of quinoline antimalaria drugs, we propose a five-point management strategy that we believe will in most cases cause symptoms to abate rapidly: 1) stop taking the quinoline drug; 2) stop alcohol, and stop all other liver-damaging drugs, including anabolic steroids, hormonal contraception, hormone replacement therapy, recreational drugs, antidepressants, anxiolytics and hypnotics; 3) maintain good hydration, using non-fluoridated drinking water; 4) temporarily eliminate die-

tary vitamin A; as an additional and optional therapeutic measure, 5) lower the concentration of circulating retinoids through phlebotomy, plasmapheresis or hirudotherapy.

## Keywords

Afghanistan, Bales, Lariam, Malaria, Mefloquine, *Pibloktoq*

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## 1. Introduction

Croft and Herxheimer in 2002 [1] and Mawson in 2013 [2] independently advanced two distinct but complementary hypotheses to explain the neurotoxic and other adverse effects associated with mefloquine, a quinoline antimalaria drug. Mefloquine (*i.e.* Lariam, a potent, long-acting blood schizonticide manufactured by F. Hoffmann-LaRoche AG) is chemically related to other quinoline derivatives such as amodiaquine and chloroquine [3]; hence the two hypotheses might reasonably apply to these related antimalaria compounds also.

### 1.1. Croft-Herxheimer (Liver-Thyroid) Hypothesis

Many of the adverse effects of mefloquine (and, by analogy, of other quinoline antimalaria agents also) are a post-hepatic syndrome caused by primary liver damage [1]. The liver plays a key part in the metabolism of thyroid hormones (Weetman, 2010). Mefloquine-induced liver damage disrupts the exquisitely delicate physiological relationship between the liver and the thyroid gland (“the liver-thyroid axis”). Thyroid hormone imbalance then occurs, either as excess or as deficiency of circulating thyroid hormone. Symptomatic thyroid disturbance may result. Thyroid disease is typically bipolar in its mode of presentation (*i.e.* it presents as weight loss *or* weight gain, preference for a cool climate *or* a warm climate, nervousness *or* lethargy, diarrhea *or* constipation, etc.) [4], and this pattern of physiological opposites features commonly in published case reports of mefloquine adverse effects. Previous liver or thyroid disease is a risk factor for developing adverse effects from mefloquine. The mefloquine syndrome presents variously as headache (suggesting a direct toxic effect on the brain, superimposed on disruption of the liver-thyroid axis), gastrointestinal disturbances, nervousness, fatigue, disorders of sleep, mood, memory and concentration, and occasionally frank psychosis [1] [5].

Symptoms of mefloquine toxicity tend to abate spontaneously once the drug is discontinued, *provided that concurrent chemical insults to the liver are also discontinued, or corrected.* These concurrent chemical insults may include:

- 1) Alcohol,
- 2) Dehydration,
- 3) An oral contraceptive pill, or hormonal replacement therapy,
- 4) Recreational drugs,
- 5) Other liver-damaging co-medications.

Co-medications in the last of the above sub-categories likely to be especially hazardous in mefloquine users are, firstly, those medicines that cause hepatocellular injury *and*

also are thyroid hormone antagonists (e.g. amiodarone, benzodiazepine, calcium channel blockers, phenytoin); and secondly, other quinine analogues taken concurrently with mefloquine, such as fluoroquinolone antibiotics [1]. It should not be necessary to treat mefloquine adverse effects through specific drug therapy; administering further drugs could in fact make mefloquine's adverse effects worse, or cause them to become permanent [1].

In those commonly-reported cases where the adverse effects of mefloquine persist for months, or years, the explanation often lies in the fact that after stopping mefloquine the mefloquine-damaged individual continues to take alcohol, or liver-damaging prescription drugs such as antidepressants, or (in the case of women) hormonal contraception [1].

## 1.2. Mawson (Endogenous Hypervitaminosis A) Hypothesis

Vitamin A is stored mainly in the liver, in potentially poisonous concentrations [2]. A condition known as *pibloktoq* (or "Arctic hysteria") has been described in Inuit people and attributed to hypervitaminosis A after their gorging on vitamin A-rich polar bear or seal liver [6]. *Pibloktoq* manifests as irrational and sometimes violent acts, followed by amnesia for the event [7]. It affects dogs, as well as humans [6].

The adverse effects of mefloquine (and, presumably, of other quinoline antimalaria drugs also) may result from drug-induced liver damage that provokes an endogenous syndrome analogous to hypervitaminosis A, and that is characterized by the spillage of toxic retinoid compounds into the circulation. At a cellular level the mechanisms contributing to this physiological harm may include:

- 1) Mefloquine-induced dehydrogenase inhibition,
- 2) The accumulation of retinoids in the liver,
- 3) Retinoid-induced hepatocellular damage,
- 4) The spillage of stored retinoids into the circulation,
- 5) The transport of retinoid compounds to the gut and brain, in toxic concentrations.

This same hypothesis plausibly explains Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN); these should be considered as overlapping manifestations on a spectrum of acute drug-induced conditions associated with severe blistering, skin peeling, and multi-organ damage [8]. Of interest, SJS was attributed to mefloquine, early in the drug's prescribing history [9]. Likewise, TEN has been attributed to chloroquine, in a user who concurrently took pyrimethamine plus dapsone (*i.e.* Maloprim), aspirin and propranolol [10].

As with the Croft-Herxheimer hypothesis, Mawson's hypothesis suggests that simply stopping mefloquine will usually suffice to bring about a swift remission of unwanted drug effects, where these have occurred. Symptom worsening could also potentially be arrested by lowering the concentration of circulating retinoids through phlebotomy or plasmapheresis, or else through pharmacological measures to limit the further expression of these substances [8].

## 1.3. The Current State of Knowledge

The Croft-Herxheimer-Mawson hypothesis has not been tested formally—for example, in a case-control study incorporating both detailed symptom ascertainment, and thy-

roid and liver biochemistry (including retinoid profiles) in a population of quinoline antimalaria drug users. Hence, the hypothesis remains speculative. If valid, the model may explain the pathogenesis of other disease states, such as primary biliary cirrhosis [11] and dengue haemorrhagic fever [12].

Notwithstanding the above, adverse effects from the quinoline class of antimalaria drugs continue to be commonly reported, in both the scientific [13] [14] [15] and lay literature. We undertook to explore the latter resource for evidence that might serve to support (or alternatively to discredit) our as yet untested hypothesis on the pathogenesis of the neurotoxic and other adverse effects associated with quinoline antimalaria drugs.

## 2. Methods

During 2013-2016 we non-systematically searched the published lay literature in different formats (books, newspapers, magazines) for accounts describing adverse effects from quinoline antimalaria drugs, in lay users of these drugs. We selected and analyzed those reports with sufficient detail to enable us to judge the apparent concordance with or divergence from our pre-existing hypotheses of adverse event causation related to this class of drugs. We identified these lay accounts serendipitously; none of the accounts was or is now indexed on any standard scientific bibliographical database, such as Pubmed or Embase.

## 3. Results

### Case Reports

We identified four published experiences of adverse effects from quinoline antimalaria drugs that were reported between 2013-2016 in six separate lay accounts, in sufficient detail for us to undertake a comparative analysis of their content.

One report (Case Study One) [16] described mefloquine use in a 29-year old male traveller; a second report (Case Study Two) [17] [18] described either amodiaquine or chloroquine use in a 43-year old male traveller; a third report (Case Study Three) [19] [20] described probable mefloquine use in a 38-year old male traveller, against a probable background of previous, prolonged chloroquine use; a fourth report (Case Study Four) [21] described mefloquine use in a young male writer. All four travellers were ostensibly healthy, prior to their index experience of drug-induced adverse effects.

All of the six lay accounts we identified, representing four different experiences of quinoline drug-related harm, were written for a predominantly lay readership. None of the accounts included any reference to or apparent knowledge of our respective hypotheses [1] [2] [8] [11] [12].

The general characteristics of the four case studies are summarized at **Table 1**.

A comparative analysis of the content of the four case studies is at **Table 2**.

## 4. Discussion

We analyzed four recently-published case reports drawn from the non-specialist lay literature, describing the adverse effects of quinoline antimalaria drugs. We sought evidence that could illuminate our untested hypotheses on how these adverse effects are

**Table 1.** General characteristics of four published lay accounts of adverse effects from quinoline antimalaria drugs.

	Nationality [ <i>occupation</i> ] of subject	Context of the account	Quinoline antimalaria drug used	Main drug-related symptoms reported
<b>Case Study One [12]</b>	US [ <i>writer</i> ]	Autobiography	Mefloquine	Amnesia
<b>Case Study Two [9] [18]</b>	British [ <i>comedian</i> ]	Autobiography, newspaper reports	Amodiaquine? Chloroquine?	Paranoia
<b>Case Study Three [2] [20]</b>	US [ <i>soldier</i> ]	Newspaper reports	Probable mefloquine use Probable prior chloroquine use	Paranoia, extreme violence (multiple homicide)
<b>Case Study Four [22]</b>	British [ <i>comedian</i> ]	Magazine article	Mefloquine	Mild psychosis, sleep disturbance

generated, and on how they might be mitigated, or treated. To our knowledge, this exercise has not been performed previously, even though it has been accepted for some years that clinical case studies, including those normally regarded as purely anecdotal [22] [23] [24], can provide useful information for generating or refining scientific hypotheses, in the absence of high-level evidence from randomized controlled trials or from systematic reviews of trials.

The case studies show that, in addition to the users having each taken quinoline antimalaria drugs, a number of additional risk factors (as predicted by the Croft-Herxheimer-Mawson model) were present in each case. This supports our hypothesis on the pathogenesis of adverse effects with this class of drugs, since we would have predicted *a priori* that the four subjects would each have been at high risk of a severe adverse reaction from their prescribed antimalaria medication.

The fact that a prolonged period of drug-related harm was reported in Case Study One, Two and Four (the outcome in Case Study Three is unknown) was also foreseeable. Our hypothesis would have predicted a quicker and more complete recovery from the unwanted effects of the quinoline drugs taken, had psychotropic drugs *not* been used (as they plainly were, at least in Case Study One and Two) in an attempt to treat those effects.

Case Study Three is of special interest because of the extreme consequences (the self-confessed murder of 16 Afghan civilians) that were attributed in the published lay accounts to the subject's use of a quinoline antimalaria drug. Following a newspaper Freedom of Information request to the FDA, there now exists in the public domain [25] a redacted Adverse Event Report that plainly relates to this user, and which indicates that he was taking mefloquine at the time of his homicidal acts (Figure 1). In the years immediately preceding 2012 it is highly likely that this military user had been taking chloroquine, as malaria prophylaxis during three successive deployments to Iraq. This will have pre-sensitized him to the effects of mefloquine, we believe. This individual's concurrent use of anabolic steroids, a class of drugs metabolized in the liver and known

**Table 2.** Detailed analysis of three published lay accounts of adverse effects from quinoline anti-malaria drugs.

	Date when adverse drug reactions occurred	Risk factors present?*	Treatment administered	Symptom duration
Case Study One [16]	October 2002	<p><b>1. Alcohol.</b> Yes. Narrative account declares regular use of beer.</p> <p><b>2. Dehydration.</b> Likely. Symptoms emerged after some months' residence in India.</p> <p><b>3. Contraceptive pill/hormonal therapy.</b> No.</p> <p><b>4. Recreational drugs.</b> Yes. Prior drug misuse declared.</p> <p><b>5. Other liver-damaging agents.</b> None described.</p> <p><b>6. Other risk factors.</b> None described.</p>	Hospitalisation (3 days) Sedative drugs administered	>11 years (gradually abating)
Case Study Two [17] [18]	December 1989	<p><b>1. Alcohol.</b> Yes. Narrative account describes regular use of beer, brandy, champagne, vodka, whisky.</p> <p><b>2. Dehydration.</b> Likely. Symptoms worsened after long flight to Kenya.</p> <p><b>3. Contraceptive pill/hormonal therapy.</b> No.</p> <p><b>4. Recreational drugs.</b> Yes. Narrative account describes prior use of LSD.</p> <p><b>5. Other liver-damaging agents.</b> Yes. Previous use of morphine.</p> <p><b>6. Other risk factors.</b> Yes. Prior hepatitis A. Also, following the onset of adverse drug effects, the quinoline antimalaria drug (either amodiaquine or chloroquine) was accidentally administered in overdose for several days, while the user was hospitalized.</p>	Hospitalisation (2 months) Antipsychotic medication (chlorpromazine hydrochloride) administered	>2 months (gradually abating)
Case Study Three [19] [20]	March 2012	<p><b>1. Alcohol.</b> Yes. Narrative account describes concurrent use of whisky (Jack Daniels).</p> <p><b>2. Dehydration.</b> Likely. Symptoms emerged acutely after some months' residence in Afghanistan.</p> <p><b>3. Contraceptive pill/hormonal therapy.</b> No (but see 5 below).</p> <p><b>4. Recreational drugs.</b> No.</p> <p><b>5. Other liver-damaging agents.</b> Yes. Concurrent use of a synthetic anabolic steroid (stanozolol), for muscle building.</p> <p><b>6. Other risk factors.</b> Yes. There was probable prior use of chloroquine in Iraq, over a period of, potentially, several years. In addition, traumatic brain injury (a putative risk factor) had been experienced in the past.</p>	Unknown	Unknown

Continued

<p><b>Case Study Four [21]</b></p>	<p>1995 (approximately)</p>	<p><b>1. Alcohol.</b> Use of alcohol not declared.  <b>2. Dehydration.</b> Yes. Sheet sleeping bag became soaked at night. Symptoms were associated with long overland bus journeys.  <b>3. Contraceptive pill/hormonal therapy.</b> No.  <b>4. Recreational drugs.</b> Not declared.  <b>5. Other liver-damaging agents.</b> None described.  <b>6. Other risk factors.</b> Anxiety (a putative risk factor) had been experienced in the past. Otherwise, none described.</p>	<p>Stopped taking the pills</p>	<p>5 months</p>
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\*The risk factors for developing severe and/or prolonged adverse effects from antimalaria quinoline drugs are those proposed in our hypothesis papers [1] [2] [8] [11] [12]; not all the proposed risk factors are widely accepted, as yet.



**FDA - Adverse Event Reporting System (FAERS)**  
**FOIA Case Report Information**

**Case ID: 8504150**

**Case Information:**

Case Type: EXPEDITED (15-DAY)    eSub: Y    HP: Y    Country: USA    Outcomes: OT    (A)NDA/BLA: 019591 /  
 FDA Rcvd Date: 11-Apr-2012    Mfr Rcvd Date: 29-Mar-2012    Mfr Control #: US-ROCHE-1054403

**Patient Information:**

Age:                      Sex:                      Weight:

**Suspect Products:**

#	Product Name	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	LARIAM				PRODUCT USED FOR UNKNOWN INDICATION		

  

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler
1	LARIAM							

**Event Information:**

Preferred Term ( MedDRA Version #: 16.0 )                      Start Date                      End Date                      ReC  
 HOMICIDE

**Event/Problem Narrative:**

Initial Information for this Spontaneous case, AER number 1054403, was received on 29/Mar/2012 from a Pharmacist and concerns a patient of unknown demographics who was treated with Mefloquine Hydrochloride (Lariam) for an unknown indication. Medical history included TBI (Traumatic brain injury). No concurrent illnesses were reported. No concomitant medications or past drugs were reported. On an unknown date, the patient started Mefloquine Hydrochloride (dose, form and frequency not reported). On an unknown date the patient who was a soldier in the US Army developed homicidal behavior and led to Homicide killing 17 Afghans. It was reported that this patient was administered Mefloquine in direct contradiction to US military rules that Mefloquine should not be given to soldiers who had suffered TBI (Traumatic brain injury) due to its propensity to cross blood brain barriers inciting psychotic, homicidal or suicidal behavior. The outcome of Homicide was not Reported. There was insufficient information regarding the therapy ongoing status of Mefloquine Hydrochloride. The reporter did not provide the seriousness criteria of the event of Homicide and its causal relationship with Mefloquine Hydrochloride. The company assessed the event of Homicide as medically significant. No further information was available.



FDA - Adverse Event Reporting System (FAERS)  
FOIA Case Report Information

Case ID: 8504150

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?
Medical History Product(s)	Start Date	End Date	Indications
			Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
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Concomitant Products:

#	Product Name	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event
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Reporter Source:

Study Report?: No      Sender Organization: ROCHE

Literature Text:

**Figure 1.** Adverse Drug Report filed on 29 March 2012 with the manufacturer of mefloquine (*i.e.* Lariam), F. Hoffmann-La Roche. The subject of this redacted ADR was Staff Sergeant Robert Bales, US Army. Initial newspaper reports suggested that he massacred 17 unarmed civilians in Afghanistan’s Kandahar province, on a single night in March 2012. The subsequent military police investigation showed that the death toll was in fact 16 civilians.

to cause liver damage [1], is likely to represent an additional risk factor for his development of a severe reaction to mefloquine. This putative additional risk factor in the pathogenesis of severe and/or prolonged reactions to quinoline antimalaria drugs has not previously been highlighted, either by us or by other researchers.

### 5. Conclusions

The quinoline class of antimalaria drugs includes amodiaquine, chloroquine, mefloquine and tafenoquine. It has been known for decades that this class of drugs can precipitate unwanted neuropsychiatric effects [5]. Mefloquine appears to be the most dangerous of these drugs, since it is neurotoxic in animal models [26], and has been associated with sudden and irrational acts of extreme violence in humans [27]; Case Study Three in our lay series typifies this. The pharmacology of mefloquine is imperfectly un-

derstood [28]. Until it is properly elucidated, we recommend that mefloquine should not be prescribed as malaria prophylaxis *under any circumstances whatsoever*.

Where quinoline antimalaria drugs have been given historically, and drug-induced adverse effects have occurred and have persisted, we suggest a five-point management strategy that we believe will in most cases result in rapid symptom abatement. Our suggested management strategy for treating long-lasting quinoline adverse effects is as follows.

### **5.1. Stop the Quinoline Drug**

The incriminated quinoline agent should be stopped immediately, and should not ever be taken again, by that individual. If the drug-damaged individual is a traveller in a malaria-endemic zone, it will be necessary for that traveler to immediately start taking an alternative, non-quinoline antimalaria agent (e.g. doxycycline monohydrate, or atovaquone-proguanil), as malaria prophylaxis.

### **5.2. Stop All Alcohol**

Alcohol should be stopped completely for a month. At the same time, all other liver-damaging drugs that are not essential to life (e.g. anabolic steroids, hormonal contraception, hormone replacement therapy, recreational drugs, antidepressants, anxiolytics and hypnotics) should be discontinued.

### **5.3. Maintain Good Hydration**

Hydration should be maintained by drinking plain water, and not through drinking coffee or tea, both of which are dehydrating [1]. Non-fluoridated drinking water only (e.g. bottled spring water) should be used, since fluoride in drinking water can damage the liver [29].

### **5.4. Eliminate Vitamin a from the Diet**

For one month, dietary sources of vitamin A should be eliminated. The richest food source for vitamin A is liver, but it is also found in milk, cheese, egg yolks and fish oils [30]; all these foodstuffs should be avoided. Deficiency is unlikely to result in the short or medium term, since the liver contains enough stored vitamin A to last two years [30].

### **5.5. Reduce Circulating Retinoids (Optional)**

In extreme cases of quinoline-induced damage, the concentration of circulating retinoids could be lowered, under careful medical supervision. This could be achieved through phlebotomy, plasmapheresis or hirudotherapy (*i.e.* leech therapy) [31].

## **Acknowledgements**

We thank Dr Remington Nevin, ex-US Army, for his helpful comments in relation to Case Study Three. We also acknowledge our late colleague Dr Andrew Herxheimer, who wrote sagely on mefloquine's adverse effects and on many related topics and would have been an enthusiastic third author of this paper, we believe, but who sadly died just

before we conceived the idea for it.

## Conflict of Interests

AC has given expert testimony in historic Court cases involving quinoline drugs, and he has advised government enquiries into the use of Lariam in soldiers.

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