SUBMISSION TO THE SENATE INQUIRY INTO MENTAL HEALTH OF THE AUSTRALIAN DEFENCE FORCE (ADF) PERSONNEL WHO HAVE RETURNED FROM COMBAT, PEACEKEEPING OR OTHER DEPLOYMENT.

PREPARED BY BRIAN MCCARTHY, IPSWICH, QUEENSLAND. JUNE 23rd, 2015.

PREAMBLE.

My motivation in presenting this submission is to assist in bringing about much better diagnosis and care than currently exists in the Australian Defence Force (ADF) in relation to mental health issues effecting veterans.
The specific reasons for this submission concern the anti-malarial drug Mefloquine (Lariam), the impact this drug has on the mental health of Veterans and the reluctance of the ADF to identify, diagnose and manage appropriately those veterans impacted.
This submission is constructed in accordance with the terms of reference,
a. The extent and significance of mental ill health and post traumatic stress disorder (PTSD) among returned service personnel.
b. Identification and disclosure policies of the ADF in relation to mental health and PTSD.
d. Mental health evaluation and counselling services available to returned service personnel.
j. Any other matters.

THE FACTS.

- Medical and clinical proof exists that Mefloquine is neurotoxic.
- The manufacturer, Roche, specifically warns of the very significant side effects in black box warnings which are the highest possible warnings.
  "The US Food and Drug Administration (FDA) is advising the public about strengthened and updated warnings regarding neurologic and psychiatric side effects associated with the antimalarial drug mefloquine hydrochloride. A boxed warning, the most serious kind of warning about these potential problems, has been added to the boxed label... Neurologic side effects can occur at any time during drug use, and can last for months to years after the drug is stopped or can be permanent."
  US FDA, Drug Safety Communication, 29th August 2013.
- Mefloquine has been prescribed by the ADF for at least 24 years.
- Mefloquine has been withdrawn from use in intense activity sections of the US Army, eg, special operations such as the Green Beret Forces.
- World research confirms that Mefloquine does cause extreme, adverse reactions.

The extracts below are taken from the testimony of Dr. Remington Nevin to the Senate Committee on Appropriations Subcommittee on Defense, June, 2012.
"Mefloquine causes a severe intoxication syndrome, characterized by vivid nightmares, profound anxiety, aggression, delusional paranoia, dissociative psychosis, and severe

memory loss. Experience has shown that this syndrome, even if rare, can have tragic consequences, both on the battlefield, and on the home front."
"My recent research has helped us to understand this syndrome as a toxic encephalopathy that effects the limbic portion of the brain. With this insight, we now understand the drug's strong links to suicide, and to acts of seemingly senseless and impulsive violence. Yet the new research suggests that even mild Mefloquine intoxication may also lead to neurotoxic brain injury associated with a range of chronic and debilitating psychiatric and neurologic symptoms."
"A recent publication by the Centers for Disease Control suggests that the side effects of Mefloquine may even confound the diagnosis and management of post traumatic stress disorder and traumatic brain injury."
Dr.Nevin has outlined his expertise at the beginning of the paper.
The full paper is ATTACHMENT "A".

The extracts below are taken from a paper presented by Dr. Ashley Croft who is a retired Army Lieutenant Colonel, to the Journal of the Royal Society of Medicine, April 2007.
"A survey of the recent literature shows that Mefloquine has been causally associated with 19 deaths in users, including three suicides."
"Ironically , for a drug that was discovered by the military, soldiers have been amongst the most vocal critics of Lariam. Following a Parliamentary enquiry, Canada's auditor general condemned protocol abuses in which 900 Canadian soldiers deploying to Somalia were prescribed Lariam in 1992-1993, at a time when the drug was still unlicensed in Canada. In the Netherlands, reports of severe adverse drug reactions in soldiers who had used Lariam prophylaxis while undertaking peace keeping duties in Cambodia prompted questions in Parliament and intense public debate. In the US, military epidemiologists have investigated the possible role of Lariam in a series of murders and suicides among soldiers in North Carolina who had served in Afghanistan. Most recently, the Australian military has been threatened with legal action by soldiers reporting severe and disabling symptoms which they attributed to Lariam prophylaxix."
"The case of Lariam and Halfan does not exactly fit the model of scientific irresponsibility which has been highlighted by Chalmers and others. It is not the case with these two antimalaria agents that inconvenient research data on their adverse effects was deliberately withheld from national drug licensing authorities, and from the public. <u>The necessary pre-licensing research was never carried out."</u>
The full paper is ATTACHMENT "B".

There are many other papers concerning the side effects of Mefloquine easily found on the Internet. Dr. Elspeth Ritchie, a retired army officer, is another significant authority.

My deep seated concern is that the ADF makes no significant, genuine attempt to reach appropriate medical/clinical diagnoses and follow up care and management for those Veterans impacted by Mefloquine.
My correspondence to the then Chief of Army on March 1st, 2015 is self explanatory.
A copy of that letter is ATTACHMENT "C".

The response of the Chief of Army is ATTACHMENT "D".
The response did not indicate that the ADF had any intention of developing an Outreach Programme for Veterans impacted by Mefloquine or for working with and for these Veterans in any positive and appropriate manner.
It is particularly disappointing that the Chief of Army did not respond to my challenge....

"The question is, do you have the moral courage to take up the issue of Mefloquine in the same way that you have supported those women who were so worthy of that support?"

Disappointing by comparison with the way that the Chief of Army responded so openly, positively and publicly to the women in the Army who had endured abuse by their contemporaries. Why do not the Mefloquine Veterans receive the same consideration?

I have attached a copy of a letter from the Assistant Minister for Defence, Stuart Robert. This letter is ATTACHMENT "E".
This letter was in response to a letter from Shayne Neumann MP, the sitting member for Blair. I am a constituent.
I have attached my letter in response. Please note the date. I have confirmed that my letter was delivered, but at the time of writing I have not received the courtesy of a reply.
My letter is ATTACHMENT "F".
The authors of both letters have indicated very clearly that the ADF is not prepared, or willing, to concede that Mefloquine causes very significant mental health issues for some Veterans.
Stuart Robert states, *"I am advised that Major McCarthy's paper, while raising valid concerns, significantly overstates the risks of long term or permanent side effects associated with Mefloquine use."*
Who provided that advice? Why is that advice contrary to the expert opinions of Dr. Remington Nevin, Dr. Ashley Croft and other credible authorities?
Stuart Robert also states, *"The Army Malaria Institute has a standing brief to monitor international literature and the malaria policies of our coalition partners. It is well placed to identify any requirements to change Australian Defence Force malaria policies going forward."*
This is not credible. A simple review on the internet of the international literature by any reasonable person would show clearly that the Army Malaria Institute is not taking note.
Please refer to ATTACHMENTS "A" and "B".

I have a copy of letter from Stuart Robert, Assistant Minister for Defence to Senator Whish Wilson.
This letter is ATTACHMENT "G".
Stuart Robert states,
"The side effects of Mefloquine are well known to the Therapeutic Goods Administration and to Defence, including the neurotoxic side effects as referred to by Mr. McCarthy."
If these side effects are known why are the veterans impacted not being diagnosed and managed appropriately?
"Over the last five years, of the 20,000 ADF members deployed to malarious areas, only an average of 25 members have been prescribed Mefloquine each year."
This statement hides behind a very convenient statistic.

BUT....how many Veterans were prescribed Mefloquine between 1990, when it was introduced into the AD,F and 2015 ?
Whatever the number, were these Veterans debriefed according to what Stuart Robert has described as the process? If so, what were the outcomes? How many Veterans were diagnosed with illnesses attributed to Mefloquine? What rehabilitation and management processes have been provided to these Veterans?
What is the success rate of any rehabilitation and management processes?
What specific illnesses have been diagnosed?
Dr.Remington Nevin writes, *"It is unknown how many of the hundreds of thousands of troops previously exposed to Mefloquine may be suffering from the devasting effects of this neurotoxicity."*

Why does the ADF not want to find out? Why will the ADF not establish a process of discovery?

And now, something extremely important and significant.

The ADF is the employer and the health provider for its total members.
Failure to diagnose accurately and to provide appropriate care is CRIMINAL NEGLIGENCE.

For a definition of Criminal Negligence I have relied on Criminal Courts Queensland.
ATTACHMENT H.

It is the duty of every person who has (in his charge or) under his control anything ...of such a nature that, in the absence of care or precaution in its use or management the life, safety or health of any person may be endangered, to use reasonable care and take reasonable precautions to avoid that danger; and he is held to have caused any consequences which result to the life or health of any person by reason of any omission to perform that duty.
To establish that the defendant is guilty of (manslaughter or other offence) through criminal negligence, the prosecution must prove, beyond reasonable doubt, that the defendant
owed the prescribed duty of care;
omitted to perform that duty; and
thereby caused the (death or other event).

In presenting this submission I challenge positively those conducting the Inquiry to ensure that specific, extremely appropriate questions relating to the consequences of the side effects of Mefloquine in the ADF be directed to,
The Chief of the ADF,
The Surgeon General of the ADF,
The previous Chief of Army,
The present Chief of Army,
The Minister for Defence,
The Assistant Minister for Defence,
The Minister for Veteran Affairs.

Such questions should include the following,

Have you ever had a face to face discussion with a Veteran who is suffering with the side effects of Mefloquine?
Have you ever had a face to face discussion with the spouse/partner/parent of a Veteran suffering with the side effects of Mefloquine?
If the answer to these two questions is "yes", how did you respond emotionally and professionally?
(It is very important to remember how Lieutenant General Morrison explained very publicly how he felt after he had met with the women in the Army who had been abused.)
Please explain what are the specific details of the specific side effects of Mefloquine.
(According to Stuart Robert Defence knows about the side effects of Mefloquine.)
What is the specific number of Veterans who have been prescribed with Mefloquine by the ADF?
How many of those Veterans in the previous question have presented with symptoms of adverse side effects of Mefloquine?
Can you provide specific details of how those who presented with side effects of Mefloquine were diagnosed accurately and provided with specific rehabilitation and management?

The following questions should be directed specifically to Stuart Robert in relation to his statements in correspondence,
"...the potentially very small number of members with unrecognised or permanent side effects....."
What is the potentially small number compared with those prescribed with Mefloquine since it was introduced?
What is meant by "*unrecognised*"? Does this mean that the ADF has not diagnosed specifically?
Does this "*very small number*", if it can be quantified, mean that those members within that number are not entitled to consideration, diagnosis, rehabilitation and management?
If the answer is "No", why?
If the answer is "Yes", what programme/s have been put in place by the ADF? When?
Finally. Why have you (all of those listed above) hidden behind bland, smokescreen style, verbal and written statements which attempt to justify that the ADF does not need to be concerned with the adverse side effects and consequences of Mefloquine?

To Stuart Robert and the Chief of Army.....Why have you not replied to the correspondence from Brian McCarthy?

In researching the Internet comprehensively for the last twelve months I have read numerous articles about Mefloquine and its side effects. I have attached one of these articles by Denise Williams, written in June 2014. This article has been carefully researched and importantly it has been written in plain English. It represents a very fair and accurate summary of the issues surrounding Mefloquine. Attention should be given to the last two paragraphs.
Each member conducting the Inquiry should read this article.
ATTACHMENT I

CONCLUSION.

I have recent documentary evidence that a Veteran who presented to an Army GP with very significant symptoms of the side effects of Mefloquine was told by the Army GP not to be concerned about anything untoward happening in relation to Mefloquine use because it was approved by Therapeutic Goods Administration. This statement was made in front of the Veteran's Commanding Officer. I can produce the appropriate details if requested to do so by the Inquiry.

Was the Army GP careless, ill informed, or directed by Army Medical Command?

I believe that the Army GP was seriously negligent.

Many Veterans are suffering the side effects of Mefloquine. My son, Major Stuart McCarthy, is one of them. I have watched and listened to him unfold emotionally and psychiatrically over a very long period as he struggles to convince the ADF of the seriousness of his illnesses. Stuart is just one of far too many Veterans who have been misdiagnosed and mismanaged.

I am doing what I can to bring these circumstances to an end for all Veterans impacted by the side effects of Mefloquine.

I wish to be called to the Inquiry as a witness so that, in response to appropriate questioning, I can explain very personally how I have been drawn into the issues which surround the side effects of Mefloquine. Importantly and significantly I want to explain the frustration which I have experienced at the hands of the Assistant Minister for Defence and the senior leadership of the Army. I cannot possibly measure the frustration felt by all those Veterans impacted but I believe that my voice from outside the ADF will contribute in a very positive way to significant, beneficial change.

THE CRIMINAL NEGLIGENCE OF THE ADF IN RELATION TO MEFLOQUINE MUST STOP NOW!

23/06/2015.

ATTACHMENT "A"

Testimony of Dr. Remington Nevin, MD, MPH
Preventive Medicine Physician and Epidemiologist

to the
Senate Committee on Appropriations
Subcommittee on Defense

Wednesday, June 6th, 2012, 10am
Dirksen 192

Good morning Mr. Chairman and members of the Committee. My name is Dr. Remington Nevin. I am a board certified Preventive Medicine physician, epidemiologist, and medical researcher. I am a graduate of the Uniformed Services University School of Medicine; the Johns Hopkins Bloomberg School of Public Health; and the residency program in Preventive Medicine at the Walter Reed Army Institute of Research, where I was awarded the distinguished George M. Sternberg Medal. I have published extensively in medical and scientific journals, and my research has informed and broadly influenced military public health policy for the past seven years.

I am here today to testify on an important issue which I fear may become the 'Agent Orange' of our generation: a toxic legacy that affects our troops, and our veterans. This is a critical issue that is in desperate need of research funding.

I am referring to the harmful effects of the antimalarial drug mefloquine, also known as Lariam®, which was first developed over 40 years ago by the Walter Reed Army Institute of Research.

Mefloquine causes a severe intoxication syndrome, characterized by vivid nightmares, profound anxiety, aggression, delusional paranoia, dissociative psychosis, and severe memory loss. Experience has shown that this syndrome, even if rare, can have tragic consequences, both on the battlefield, and on the home front.

My recent research has helped us understand this syndrome as a toxic encephalopathy that affects the limbic portion of the brain. With this insight, we now understand the drug's strong links to suicide, and to acts of seemingly senseless and impulsive violence. Yet new research suggests that even mild mefloquine intoxication may also lead to neurotoxic brain injury

associated with a range of chronic and debilitating psychiatric and neurologic symptoms.

It is unknown how many of the hundreds of thousands of troops previously exposed to mefloquine may be suffering from the devastating effects of this neurotoxicity. However, I can tell you that I am contacted nearly every day by military patients and veterans, from the United States, and from around the world, seeking diagnosis and care for their symptoms. Their compelling and often heart-wrenching stories can be found regularly in media reports worldwide. Invariably, these patients are frustrated by a lack of resources and information specific to their condition.

A recent publication by the Centers for Disease Control suggests that the side effects of mefloquine may even confound the diagnosis and management of posttraumatic stress disorder and traumatic brain injury.

Given our research commitments to posttraumatic stress and traumatic brain injury, the first two signature injuries of modern war, this observation calls for a similarly robust research agenda into mefloquine neurotoxic brain injury, to ensure that patients with these conditions are receiving accurate diagnosis and the very best medical care.

Some concrete actions for facilitating this research include:

1. Expanding the scope and mission of the Defense Centers of Excellence and the National Intrepid Center of Excellence to include the evaluation and care of patients suffering side effects from mefloquine; and

2. Funding a dedicated mefloquine research center at a civilian medical school or school of public health, to attract the very best minds to this problem, and to coordinate broad investigations into the pathophysiology, epidemiology, clinical diagnosis, and treatment of mefloquine intoxication and neurotoxic brain injury.

A commitment to this research, roughly commensurate with our initial investment in mefloquine's development, will allow us to mitigate the effects of the toxic legacy it has left behind. If this issue is left unaddressed, mefloquine could become our next 'Agent Orange', but it does not have to. With appropriate

action, mefloquine neurotoxic brain injury could join posttraumatic stress and traumatic brain injury as the third recognized signature injury of modern war, and as a result, receive the same level of commitment shown for these first two conditions.

I would again like to thank you Mr. Chairman, and members of the Committee, for the opportunity to appear before you and bring this issue to your attention. I should emphasize in closing that the opinions I expressed today are my own and do not necessary reflect those of the U.S. Army. This concludes my prepared statement and I am happy to answer any questions that you may have.

-END-

ATTACHMENT "B"

JRSM JOURNAL OF THE ROYAL SOCIETY OF MEDICINE

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A lesson learnt: the rise and fall of Lariam and Halfan

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INTRODUCTION

Go to:

Lariam (pharmacological name mefloquine) is an antimalaria drug discovered by the US Army shortly after the Vietnam War, and subsequently marketed worldwide by F. Hoffmann-La Roche. The first reported trials of mefloquine were in prisoners, and were performed at the Joliet Correctional Center, Illinois, in 1975, and at the Maryland House of Correction in 1976.[1,2]

Halfan (pharmacological name halofantrine) is an antimalaria drug chemically related to mefloquine and quinine. Like Lariam, Halfan emerged from the US Army's huge post-Vietnam antimalaria drug discovery programme.[3] Halfan was first described in the literature in November 1982.[4] During the 1980s and 1990s, Halfan was marketed by Smith Kline Beecham.

There is no question that safe and effective antimalaria drugs were needed in the second half of the twentieth century, once it became apparent that the *Plasmodium* had developed resistance to the mainstay of antimalaria therapy, namely chloroquine. Chloroquine resistance was observed first in Thailand in 1957, then on the Colombian-Venezuelan border in 1959, and in Kenya and Tanzania in 1978.[5] Within a decade of Lariam and Halfan being marketed, however, the safety of both these novel agents was in doubt.

This essay looks at the unusual developmental history of Lariam and Halfan, explains the circumstances under which both drugs rose in esteem with policy makers and prescribers and then fell into disfavour with consumers, and summarizes the lessons learnt in the process. These lessons need to be recorded and acted upon, to prevent a repetition of the same mistakes with the next generation of antimalaria compounds.

BACKGROUND

Go to:

Both Lariam and Halfan were discovered at the Experimental Therapeutics Division of the Walter Reed Army Institute of Research (WRAIR) in Washington DC.[3] In the earliest published reports, these two drugs had not yet been named, and they were still referred to by their respective Walter Reed experimental numbers: WR 142 490 and WR 171 669.[1,4] Lariam and Halfan were the two main progeny of the WRAIR malaria drug discovery programme, which ran from 1963 until 1976.

Over a 15-year period, vast resources were voted by the US federal government to fund WRAIR's antimalaria drug research, which at the time was the largest drug discovery programme ever mounted. The political driving force behind the programme was the severe clinical setback experienced by the US military during the Vietnam War, when at one stage 1% of US combat troops were succumbing to malaria each day.[6] Because of the size and urgency of the research task, WRAIR collaborated with numerous governmental, academic and commercial organizations, including 175 external contractors.[7]

From the early 1960s onwards, WRAIR screened over 250 000 potential antimalaria compounds.[8] Lariam was number 142 490 in this long series, and Halfan was number 171 669. Because the US military was and remains forbidden by Congress from operating in the commercial sector, WRAIR engaged the holding companies F. Hoffmann-La Roche and Smith Kline Beecham to market these two promising novel agents.

The precise details of the three-way business agreement between WRAIR, the US federal government and the two multinational drug companies which marketed Lariam and Halfan have not been made public. It appears, however, that all of WRAIR's phase I and phase II clinical trial data on Lariam and Halfan were delivered as a free good to F. Hoffmann-La Roche and to Smith Kline Beecham. Drug approval was swiftly granted by the Food and Drug Administration (FDA): Lariam was approved in 1989 and Halfan in 1992.

From the perspective of the two drug companies chosen to act as the marketing arm of WRAIR, the primary commercial potential of Lariam and Halfan lay in their ability to prevent malaria in tourists and business travellers to the tropics. Prior to their obtaining FDA approval, however, no randomized Phase III tolerability study was carried out on either drug in a normal study population of healthy civilian volunteers.[9] Likewise, there was no serious attempt prior to licensing to explore the potential drug-drug interactions of either Lariam and Halfan; some of the fatal drug reactions which followed may have been a direct consequence of the resulting gap in the prescribers' knowledge base.

Within months of their being licensed, major safety concerns around Lariam and Halfan began to emerge. These two compounds should have been welcomed by the public as being safe, effective and lifesaving pharmaceutical weapons in a world where international travel was increasing exponentially and where chloroquine-resistant malaria seemed to be spreading just as rapidly.[10] Instead, consumers viewed the two new drugs with disquiet, and later with concern and alarm.

THE SITUATION TODAY

Go to:

Though still prescribed in most countries, both for preventing and treating malaria, Lariam is now known to cause neurotoxicity.[11] This unexpected property came to prominence in the mid-1990s, when national pharmacovigilance centres, initially in Europe, began to receive recurring reports of neuropsychiatric adverse effects caused by this new antimalaria agent. In the Netherlands during 1998 and 1999, mefloquine was respectively the most and the second most cited drug in spontaneous reports of drug-related illness made to the Lareb Pharmacovigilance Foundation.[12] Around the same time, it was reported that 60% of all the mefloquine occurrences notified to the WHO's Uppsala Monitoring Centre cited neuropsychiatric disturbance secondary to the drug.[12]

Belatedly, three randomized controlled trials were carried out in healthy volunteer populations, and were reported between 2001-2003.[13-15] The studies confirmed mefloquine's potential for causing psychological illness, and all three study reports described an excess of neuropsychiatric adverse effects in the mefloquine arm.[13-15] Around the same time an analysis of the cause of illness in 4524 travellers returning from sub-Saharan Africa to the northern hemisphere found that, excluding diarrhoea and fever as causes, mefloquine was the fifteenth most common cause of post-travel illness.[16] A case control study of 564 Dutch travellers between 1997 to 2000 found a threefold increase in the incidence of psychiatric events with mefloquine use (OR 3.5, 95% CI 1.4-8.7), and a very high risk of psychiatric events in women users of the drug (OR 47.1, 95% CI 3.8-578.6).[17] A survey of the recent literature shows that mefloquine has been causally associated with 19 deaths in users, including three suicides (Table 1).[18-26]

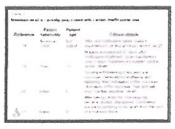

Table 1

Nineteen deaths causally associated with Lariam (mefloquine) use

By 2004, public concern in the US was such that the FDA took the exceptional step of insisting that a patient medication guide be given to all recipients of mefloquine prescriptions.[27,28] The FDA thus followed the example of the Committee on Safety of Medicines, which had advised British doctors in 1996 to warn patients about the incidence of neuropsychiatric adverse effects with mefloquine. As was pointed out in the *British Medical Journal*, this advice overturned accepted clinical practice in the UK, which at that time was to warn patients about common adverse effects only.[29,30]

Also unexpectedly, Halfan was found after licensing to cause ventricular dysrhythmias that were often fatal.[23,31-33] This unforeseen property of the drug (unforeseen because unresearched) came to light serendipitously, in a prospective electrocardiographic study of Karen patients that was reported in the *Lancet* in 1993.[34] Halfan is no longer recommended by WHO for the self-treatment of malaria, and the drug is not listed for

this indication in the *British National Formulary* or in other national pharmacopoeias. Halfan is not now approved in any country for malaria prophylaxis.[35] The 2006 edition of *Goodman and Gilman* states that:

> *'Because halofantrine displays erratic bioavailability, potentially lethal cardiotoxicity, and extensive cross-resistance with mefloquine, its use generally is not [now] recommended.'*[36]

The disappointing performance in clinical practice of these two drugs, developed at enormous cost to the US taxpayer, could not have been anticipated 30 years ago. Or could it?

WHAT WENT WRONG?

Go to:

Both Lariam and Halfan are products of what has been called 'the military-industrial complex'. This is an overused term, but one that describes a real entity.

The partnership between industry and the military has achieved some astonishing technical feats—witness the placing of a man on the moon. In the area of patient care, however, the health and wellbeing of consumers of health care is protected by regulations which, however imperfect and seemingly cumbersome, are derived from decades of use and experience. These regulations reach forward in time, protecting future cohorts of patients from prescriber-induced harm, but also slowing up pharmaceutical innovations which in some cases may be needed urgently. Powerful lobbies, impatient of delay (and acting in what they may see as the public's best interests) may be tempted to disregard those regulations. The clinical consequences of doing so may be unforeseen, however.

As stated above, the underpinning safety and pharmacokinetic studies which should have been performed prior to the licensing of Lariam and Halfan, on the main intended target group for both drugs (namely, tourists and business travellers), were never carried out.[9]

In the case of Lariam, the first randomized controlled trial of the drug in a mixed population of general travellers was not reported until 2001.[13] Of the study participants randomized to receive mefloquine, 67.1% reported ≥1 adverse event, and in 6% of mefloquine users these events were severe (defined as requiring medical advice). Had this same understanding of mefloquine been available prior to its licensing, as it should have been, it is certain that the FDA and the other national licensing authorities which approved Lariam for use prophylactically, in and around 1989, would not at the time have endorsed this drug.[37]

It seems probable that in the late 1980s and early 1990s the FDA and other national licensing bodies were influenced, perhaps subliminally, by the powerful military-industrial-governmental lobby into over-hasty decisions to approve the marketing of both Lariam and Halfan. These two drugs were authorized for public use on the basis of an incomplete knowledge base, and at too early a stage in the normal cycle of drug development.

Post-marketing surveillance of Lariam and Halfan took the place of normal, responsible, pre-licensing research into the safety of these two agents.

Travel medicine experts in most countries were slow to recognize the danger signals associated with Lariam and Halfan, and for many years the public's concern about Lariam, in particular, was dismissed as 'media hype'. A senior WRAIR scientist, writing in 2001, deplored what he called '... the "herd mentality" of mefloquine associated psychoses', and stated defiantly that 'mefloquine (Lariam®) remains the prophylaxis of choice for US soldiers and travellers.'[38] As late as 2005 a reviewer in the *New England Journal of Medicine*, also an employee of the US military for over 20 years, continued to maintain, in the face of compelling empirical and experimental evidence to the contrary, that Lariam was a 'well tolerated' drug.[39] However, by the following year a US military research team, based partly at WRAIR, conceded that:

'Walter Reed Army Institute of Research is currently investigating mefloquine analogues, seeking one with similar efficacy but reduced neuropsychiatric toxicity.'[3]

The victims of this pharmacological muddle have been those many business travellers, embassy staff, tourists, aid workers, missionaries, soldiers and others who were well at the start of their journeys into malaria-endemic areas, were prescribed Lariam or Halfan by their physicians, and who then suffered unforeseen (because unresearched) harms from their chemoprophylaxis.

Effectively, all users of Lariam and Halfan, from the point of licensing onwards, have been involved in a natural experiment to determine the true safety margin, at current dosages, of these two poorly understood antimalaria

drugs. Consumers have been unwitting recruits to this longitudinal study, rather than informed partners.[9,40] The rapid public rejection of Lariam and Halfan could have been anticipated, since users of malaria chemoprophylaxis differ from normal patients in that they are by definition healthy people, and on this account they are unwilling to accept even relatively minor drug-related harms.[41]

Ironically, for a drug that was discovered by the military, soldiers have been amongst the most vocal critics of Lariam. Following a Parliamentary enquiry, Canada's auditor general condemned protocol abuses in which 900 Canadian soldiers deploying to Somalia were prescribed Lariam in 1992-1993, at a time when the drug was still unlicensed in Canada.[42] In the Netherlands, reports of severe adverse drug reactions in soldiers who had used Lariam prophylaxis while undertaking peacekeeping duties in Cambodia prompted questions in Parliament and intense public debate.[43] In the US, military epidemiologists have investigated the possible role of Lariam in a series of murders and suicides among soldiers in North Carolina who had served in Afghanistan.[44] Most recently, the Australian military has been threatened with legal action by soldiers reporting severe and disabling symptoms which they attributed to Lariam prophylaxis.[45]

THE FUTURE

Go to:

Sir Iain Chalmers has pointed out how the biased under-reporting of research harms and sometimes kills patients.[46] The under-reporting of research, he states, is essentially a form of misconduct, since it can lead to seriously misleading recommendations for clinical practice and for new research.[47]

The case of Lariam and Halfan does not exactly fit the model of scientific irresponsibility which has been highlighted by Chalmers and others. It is not the case, with these two antimalaria agents, that inconvenient research data on their adverse effects was deliberately withheld from national drug licensing authorities, and from the public. The necessary pre-licensing research was simply never carried out.

The prime lesson from the Lariam and Halfan experience is that drugs intended primarily for use by healthy people must be genuinely well tolerated, and indeed they must demonstrate much better tolerability under their actual conditions of use than would normally be required for, say, antimitotic agents. Future research studies of malaria chemoprophylaxis must address the unanswered questions and outstanding gaps in the evidence.[48] In particular, planned research studies must be carried out on the population of interest (that is, on tourists and business travellers) and not on a convenience sample of prisoners, or soldiers.[49]

Despite the public outcry about Lariam and Halfan, it is extraordinary that no real attempt has yet been made to properly explore the adverse effects of these two drugs in terms of what causes these effects, who is likely to experience them, how long the effects typically last, how the effects can be mitigated, and how they should be managed if they do occur.

There are several plausible mechanisms through which the unwanted effects of Lariam and Halfan, which are structurally related quinoline derivatives, might be mediated. Croft and Herxheimer suggested in 2002 that many of the adverse effects of mefloquine may be a post-hepatic syndrome caused by primary liver damage, with a subset of mefloquine users also experiencing thyroid disturbance.[50] More recently, Aarnoudse and colleagues have hypothesized that the neuropsychiatric effects of mefloquine are associated with polymorphisms in the MDR1/ABCB1 gene that encodes for the efflux pump P-glycoprotein.[51] Both theories remain speculative, however, since the rigorous studies needed to test the respective hypotheses have not yet been carried out.

Because the harms of mefloquine have never been adequately investigated, and because there appears to be no incentive for the manufacturer of Lariam ever to do this, it is likely that mefloquine, which like halofantrine is a potentially important weapon in the limited pharmaceutical arsenal against malaria, will be discarded along with its sister drug. A recent British review of the treatment options for malaria does not mention mefloquine at all.[52] This apparent willingness to casually sideline two undoubtedly lifesaving drugs represents a waste of resources, and a loss also to future travellers and patients. Researchers, policy makers and prescribers must learn from this experience or be condemned to repeat it. Many of the individual medical tragedies detailed in the table need never have occurred. Powerful institutional pressures must never again override the needs and rights of patients.[46,47]

Notes

Go to:

Competing interests None declared.

Acknowledgments This essay was the Prize Winner in the RSM Section of Pharmaceutical Medicine & Research Prize Essay Competition 2006. I am grateful to the sponsors of the Prize and to all those fellow scientists who helped me develop the ideas outlined in this essay. The opinions expressed here are my own.

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ATTACHMENT 'C'

Lieutenant General David Morrison

Chief of Army.

Canberra.

Ist March 2015.

Dear Lieutenant General Morrison,

I have written to you because of the intense concern which I have for my son Major Stuart McCarthy.

This correspondence consists of four components.

1. An outline of the health issues with which Stuart has been trying to cope for a considerable period of time. This includes a copy of a paper written by Stuart which is included for your information (Attachment A) and a copy of a longer document carefully and thoroughly researched by Stuart (Attachment B).
2. A brief statement of the relationship which I have with Stuart.
3. A brief statement of my professional background prior to retirement.
4. A specific and unambiguous request for you to intervene and to initiate a process through which the Army will provide substantial professional and medical support and rehabilitation for Stuart and the many soldiers like him who are coping with the illness which Stuart has identified and described in detail.

Outline of the health issues.

Attachments A and B are self explanatory and require no elaboration by me.

I have copies of emails exchanged between Stuart and a senior army medical officer General Brennan. In the very least the responses received from General Brennan are dismissive and despite the fact that Stuart has reached out for help, none of any consequence has been provided. Copies of these emails can be made available at your request but they should be available to you from the records of General Brennan.

Stuart has also sent emails to General Leahy but has not received the courtesy of responses.

It is reasonable for me to form the opinion that neither of the Generals care.

My relationship with Stuart.

Stuart is the elder of my two sons. My wife and I were extremely proud when Stuart graduated from Duntroon Military College and began a career as an Officer in the Australian Army. That pride has never diminished and has been enhanced by numerous factors over the past twenty five years which include that I have on occasion read reports of Stuart's performance written by his commanding officers, particularly those related to overseas postings.

My wife and I live less than ten minutes from Stuart's home and as a result we have regular connections with Stuart and his family. Stuart has a great sense of family; his own family, that of my wife and I and that of his brother who lives in London. Stuart has always "been there" for family and I make reference to some specific occasions. Several years ago Stuart's sister died suddenly and unexpectedly. Despite his own grief Stuart's attention to our needs then and continuously since has been substantial. Stuart's eulogy at our daughter's funeral was outstanding. Seven years ago my wife had breast cancer surgery and was seriously ill and hospitalised for a very long time. In more recent times Lee has had to cope with bowel cancer surgery. Throughout these times, despite Stuart's own health issues, he could not have been more supportive.

Stuart and I have a passion for fishing and we regularly fish the upper reaches of the Brisbane River together. However, because of Stuart's health these fishing sessions have ceased. In addition to a substantial father/son relationship there exists a genuine mateship.

In recent years I have watched at first hand Stuart's health decline and deteriorate to the level which exists now. I have listened intently to his concerns, anxieties and frustrations and until now I have felt unable to assist directly through intervention. However, a phone conversation which I had with Stuart last night and a subsequent email (Attachment C) also received last night has been the catalyst for this communication to you.

My professional career.

I had a long and successful career in education. In the latter part of that career I was Principal of four non-government independent schools, including two International Schools overseas. I was also Director of Boarding in two non-government schools. I have substantial tertiary qualifications in education and management.

My request for your intervention.

I draw your attention to the last paragraph of Stuart's email to me dated 28th February and copied to you as Attachment C.

"What Shayne needs to understand is that we're simply not capable of putting together a grass roots campaign to advocate for a public enquiry ourselves <u>because we are too ill</u>. We desperately need elected officials like Shayne to do what they are elected to do. We can't do it on our own."

How very sad it is that Stuart and his contemporaries need to reach to the Government and the wider community for support, understanding and acknowledgement when they should have received that support, acknowledgement and understanding from the hierarchy of the Army. The Army which they have served so well for so long.

I have read the speech which you made at The Kings School for White Ribbon Day and draw your attention to several direct quotes from that speech.

".....so much for our pride in looking after our mates. These women had been let down by their leaders and their comrades. They had been robbed of that irreplaceable component of their human and personal identity – their dignity and self respect."

"It requires you to recognise that the standard you walk past is the standard that you accept and that you are judged not just on your actions, but on how you allow others to act."

"This call to arms is daunting. It requires drawing on the most special of human qualities – moral courage."

It is my most sincere belief that there are very plain and unambiguous parallels which can be drawn from the women to whom you refer and to the soldiers to whom Stuart has drawn attention.

The simple question is, do you have the moral courage to take up the issue of Mefloquine in the Army in the same way that you supported the women who were so worthy of that support ?

Soldiers in the Army of which you are so proud deserve and need the same support.

And finally you need to understand the main reason why I have written to you. Stuart has reached out to me in a direct plea for help, emotionally, practically and organisationally because he has come to the absolute end of his tether and his frustration has boiled over almost beyond repair because senior medical Army Officers have scant regard for Stuart's condition and the condition of his contemporaries.

Stuart did not ask me to communicate with you, nor is he aware that I have done so. It will only be in special circumstances that I may confide in him at some future time.

In closing I have attached a piece of writing from Stuart's Facebook page (Attachment D). This is a measure of the man.

I am prepared to travel to Canberra to meet with you.

I look forward to your response.

Sincerely,

Brian McCarthy.

ATTACHMENT "D"

Army Headquarters
R1-4-B003
Russell Offices
PO Box 7902
CANBERRA BC ACT 2610

Telephone: (02) 6265 4311
Facsimile: (02) 6265 5446

OCA/OUT/2015/R21525130

Brian McCarthy
148/102A Moores Pocket Rd
Moores Pocket QLD 4305

Dear Brian,

I refer to your letter of 01 Mar 15 in which you raise concerns that you have for the health of your son Major Stuart McCarthy. I thank you for your correspondence as it enables me to ensure that your son receives the best possible health care.

I appreciate your forwarding a copy of your son's article in which he articulates his concerns in relation to the use of Mefloquine. Appropriate and effectively malarial prophylaxis and treatment remains a major focus for the Australian Defence Force (ADF) as we continue to provide military capability in varied and austere environments.

Mefloquine remains registered with the Australian Therapeutics Goods Administration and is only used by the ADF in accordance with approved product information. It is not the preferred option, and like all malaria treatment and prophylaxis regimes, it may have side effects for some patients. It is available for use within the ADF when it affords the lowest risk to the member. Noting that the consequences of malaria can be as severe as death, it is important that the ADF retain a range of authorised prophylaxis and treatment regimes.

The Therapeutics Goods Administration updated its Mefloquine product information in 2014. The Repatriation Medical Authority, as an independent statutory body, last reviewed the Statement of Principles relating to Mefloquine in 2009. In light of the updated product information, the Surgeon General of the ADF will request the Repatriation Medical Authority complete a further review.

The welfare and health of Army personnel remains my highest priority. Noting that your son has recently posted to Sydney, I have ensured that there is a new team of medical and command personnel in place to ensure the best possible management of his health and welfare.

D.L. Morrison, AO
Lieutenant General
Chief of Army

17 March 2015

ATTACHMENT "E"

The Hon Stuart Robert MP
Assistant Minister for Defence

MC15-000373

01 APR 2015

The Hon Shayne Neumann MP
Member for Blair
PO Box 5117
BRASSALL QLD 4305

Dear Mr Shayne Neumann

Thank you for your representation to the Minister for Defence, the Hon Kevin Andrews MP, on behalf of Major Stuart McCarthy, regarding his paper on the history of the anti-malarial drug Mefloquine. I understand that Major McCarthy submitted a very similar paper to the Australian Army Journal for publication in 2014.

I am advised that Major McCarthy's paper, while raising valid concerns, significantly overstates the risks of long term or permanent side-effects associated with Mefloquine use. The paper would be improved by reframing the discussion based on a wider assessment of available literature and a consideration of all scientific views on this topic. Major McCarthy was advised to utilise the expertise of the Army Malaria Institute to improve his paper, which he has declined.

Mefloquine remains registered with the Therapeutics Goods Administration and is used by the Australian Defence Force in accordance with approved product information. None of the leading drug regulatory authorities in the world have recommended a proactive engagement of past recipients of Mefloquine as suggested by Major McCarthy in his paper. It is Defence's assessment that engagement as recommended by Major McCarthy would cause unnecessary distress to the vast majority of recipients. This distress outweighs any potential benefit to the potentially very small number of members with unrecognised long term or permanent side-effects.

Aside from Major McCarthy's paper, the Therapeutic Goods Administration updated its Mefloquine product information in 2014. The Repatriation Medical Authority, as an independent statutory body, last reviewed the Statement of Principles relating to Mefloquine in 2006 and 2009. In light of the updated product information the Repatriation Medical Authority will be requested by the Surgeon General Australian Defence Force to review Mefloquine as a factor in its Statements of Principles on neurological and psychiatric conditions. Major McCarthy's paper will be included as part of the request.

The Army Malaria Institute has a standing brief to monitor international literature and the malaria policies of our coalition partners. It is well placed to identify any requirement to change Australian Defence Force malaria policies going forward.

I trust this information is of assistance to you and Major McCarthy.

Yours sincerely

Stuart Robert

ATTACHMENT "F"

The Hon Stuart Robert
Assistance Minister for Defence
Parliament House
Canberra ACT 2600

Brian McCarthy
148/102A Moores Pocket Rd
Moores Pocket Qld 4305
brianandlee2@bigpond.com
13th May 2015.

Dear Assistant Minister,
I have a copy of your letter of April 1st in reply to a letter from Shayne Neumann MP, Member for Blair, of 4th Feb.

My son, Major Stuart McCarthy, and I are constituents of the electorate of Blair. My son has confided in me completely about the health issues which he is facing as a serving officer in the Australian Army and I continue to act in his best interest. Stuart and I have met with Shayne Neumann in his electoral office.

Your response to Shayne Neumann's letter is nothing more than a white wash to what is a serious health issue in the Army and the ADF.

You stated,
"It is Defence's assessment that engagement as recommended by Major McCarthy would cause unnecessary distress to the vast majority of recipients. This distress outweighs any potential benefit to the potentially very small number of members with unrecognised long term or permanent side effects."
This statement is beyond belief and carries no credibility whatsoever for the following reasons.

- ***What research has been completed to substantiate "very small number" ? Who authorised this research and where is it published ?***
- ***Do you know what is unrecognised ? If you do, please advise me.***
- ***Any member with unrecognised long term or permanent side effects from Mefloquine deserves to be given full consideration. Or, is Defence intending to just throw those members away ?***

These questions are the very reason why Major McCarthy has recommended an Outreach Programme.

- ***Your statement implies very clearly that Defence is not at all concerned in righting a wrong which has long been perpetuated by Defence since Mefloquine was first prescribed to Defence personnel.***
- ***Your statement also implies very clearly that Defence is not the least bit concerned for the health welfare of Defence Personnel (past and present) impacted by Mefloquine.***

Your statement,

> ***"The Army Malaria Institute has a standing brief to monitor international literature and the malaria policies of our coalition partners. It is well placed to identify any requirement to change Australian Defence Force malaria policies going forward."***

requires challenge.

Major McCarthy and I, and many others worldwide, have monitored the same literature independently and we have come to the same conclusion which is,

Mefloquine is neurotoxic and does cause major, long term serious side effects to some for whom it is prescribed.

Worldwide there is massive condemnation of Mefloquine and outstanding evidence that those military personnel impacted should be identified and provided with an appropriate diagnosis, treatment and management. This is the second element of Major McCarthy's proposal.

How could your advisors have ignored this in the preparation of the letter to Shayne Neumann which you initiated and signed ?

In signing and forwarding that letter you have made a very serious error in judgement. Your platitudinous response was completely inappropriate and without significant substance.

You now have the opportunity to retract your original letter and to replace it with another document which acknowledges the impact of Mefloquine and which outlines, in detail, how Defence intends to identify those impacted and what processes will be implemented to remedy the substantial health issues caused to Defence personnel.

You, the Minister for Defence and Defence Leadership must act now. You must be open, factual and honest, no matter what, in the interest of so many men and women who are ill because of the actions and failures of the Defence Health Command.

I have correspondence on file with the Chief of Army in relation to the Mefloquine issue. I have not copied that correspondence here, but it would be very appropriate for you to obtain copies from his office so that you and your advisors can determine a much better understanding of the Mefloquine issues than you currently display.

I have copied this correspondence to the Minister for Defence as I am not confident that he would have been consulted/advised about the matters which have been raised by my son and I re' Mefloquine.

Finally, I am staggered that with your Army background you are not prepared to take up the Mefloquine issue on behalf of your previous contemporaries, some of whom you may have served with, who have been impacted seriously. Did you take Mefloquine in Bougainville ?

I look forward to your prompt response.

Sincerely,

Brian McCarthy.

cc. The Minister for Defence.

ATTACHMENT "G"

The Hon Stuart Robert MP
Assistant Minister for Defence

MC15-001213

Senator Peter Whish-Wilson
Senator for Tasmania
PO Box 5194
LAUNCESTON TAS 7250

24 MAY 2015

Dear Senator Whish-Wilson

Thank you for your representation to the Minister for Veterans' Affairs, Senator the Hon Michael Ronaldson, on behalf of Mr Brian McCarthy regarding the use of mefloquine by the Australian Defence Force (ADF). As this matter falls within my portfolio responsibilities, your correspondence has been passed to me for response.

You may care to note that I responded to a similar representation from the Member for Blair, the Hon Shayne Neumann MP, on behalf of Mr McCarthy's son, Major Stuart McCarthy in April 2015.

I am advised that mefloquine is a very effective anti-malarial medication and remains registered with the Therapeutic Goods Administration. The side-effects of mefloquine are well known to the Therapeutic Goods Administration and Defence, including the neurotoxic side-effects as referred to by Mr McCarthy.

While significant side-effects are uncommon, most resolve fully once the medication is ceased with long term or permanent side-effects being rare. In Defence use, mefloquine is a third line agent. Over the last five years, of the 20,000 ADF members deployed to malarious areas, only an average of 25 members have been prescribed mefloquine each year.

Mr McCarthy should be assured by ADF policy which requires the member to be advised to contact their medical officer if they develop symptoms while taking mefloquine. It is also ADF policy that all ADF members are to have a post deployment examination three months after their return to Australia. This examination is targeted at looking for any residual deployment related health issues, including any which may be related to anti-malarial medication.

Defence also conducts a formal comprehensive periodic health examination on all ADF members, which includes the completion of a broad health questionnaire by the ADF member. Any positive responses or abnormal finding on a clinical examination are explored to make an appropriate diagnosis and if there is any incapacity, to consider referral to the ADF Rehabilitation Program. At this stage, the member will have ceased the use of mefloquine and there is generally no requirement to establish mefloquine as a cause, in order to appropriately diagnose, manage and rehabilitate a member with a potential long-term mefloquine side-effects.

Parliament House, CANBERRA ACT 2600

Defence considered Major McCarthy's proposal for a proactive outreach program to all serving and ex-serving members who have been prescribed mefloquine. I am advised that this course of action is not recommended by the Therapeutic Goods Administration or any other leading drug regulatory agency in the world. Further, it was assessed that this approach would cause undue distress to the vast majority of recipients who currently have no enduring mefloquine related side-effects.

Notwithstanding this, the Surgeon General Australian Defence Force has made a formal request for the Repatriation Medical Authority to review mefloquine as a factor in their Statement of Principles for neurological and psychiatric conditions, noting that it is already accepted as a factor for a number of conditions.

I acknowledge that Mr McCarthy may still wish to make a submission to the Foreign Affairs, Defence and Trade Senate Committee's inquiry into mental health of serving ADF personnel. As you know, the Parliament of Australia website contains details about the inquiry's Terms of Reference, guidance on preparing a submission and the process for making a submission. The following link may assist Mr McCarthy find this information at:

www.aph.gov.au/Parliamentary_Business/Committees/Senate/Foreign_Affairs_Defence_and_Trade/ADF_Mental_Health

I trust this information is of assistance to you and Mr McCarthy.

Yours sincerely

Stuart Robert

ATTACHMENT "H"

Criminal Negligence[1] s289
(In Charge of Dangerous Things)

It is the duty of every person who has [in his charge or] under his control[2] anything ... of such a nature that, in the absence of care or precaution in its use or management, the life, safety or health of any person may be endangered, to use reasonable care and take reasonable precautions to avoid that danger; and he is held to have caused any consequences which result to the life or health of any person by reason of any omission to perform that duty.

To establish that the defendant is guilty of [manslaughter or other offence] through criminal negligence, the prosecution must therefore prove, beyond reasonable doubt, that the defendant

i) **owed the prescribed duty of care;**

ii) **omitted to perform that duty; and**

iii) **thereby caused the** [death or other event]**.**

These three matters require elaboration.

First, was the duty owed by the defendant?

You may be satisfied beyond reasonable doubt that the defendant had such a thing, namely (insert description) **[in his charge or] under his control when** (viz insert material time)**, and that it was of such a nature that,[3] in the absence of care or precaution in its use or management, the life, safety or health of a person may be endangered. If so, turn to consider the second issue: whether the defendant is shown beyond reasonable doubt to have omitted to perform his duty to use reasonable care to avoid danger to life, safety or health. And in**

---

1 *R v Hodgetts & Jackson* [1990] 1 Qd R 456; *MacKenzie* (2001) 11 A Crim R 534 [53]; cf *Attorney-General's Reference (No 2 of 1999)* [2000] 3 WLR 195, 206-207. As to the directions required where there might be criminal responsibility under s 289 or else in circumstances where s 23(1)(a) or (b) might be germane, see *Stott & Van Embden* [2001] QCA 313 [20], [22]; *Kidd* [2001] QCA 536.

2 *Stott & Van Embden* [2001] QCA 313 [20], [22].

3 As to what constitutes a dangerous thing for this purpose see *Stott & Van Embden* at [23].

Mental health of ADF serving personnel
Submission 20

ATTACHMENT "I"

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Mefloquine Toxicity and PTSD, or How the Cure is Worse than the Disease

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By Denise Williams, *June 26, 2014 at 4:03 pm*

No one will dispute that malaria is a killer. Millions have died from the raging and uncontrollable fevers that accompany the parasitic infection. Millions more are left with life-long and life altering symptoms. There are regions of the world where the disease is so resistant to drugs to be nearly impervious to all antibiotics and medical interventions. The need for an effective prophylactic is critical, particularly for troops attempting to achieve military objectives in places where the disease is endemic.

In the 1970's, a very interesting precedence was set. Scientists and a pharmaceutical company partnered with the Federal government on the development of the next-generation anti-malaria drug. This was the first time such a partnership, termed a Public-Private Venture was undertaken. The results of what some have termed this unholy alliance have been chilling.

The developed drug was mefloquine. Of all the anti-malarial drugs, it showed the lowest potential for liver or kidney side-effects. More importantly, it was designed to be effective with weekly dosing. Because it is based on that old standby quinine, it would not contribute to the development of drug resistant strains of malaria; it is a prophylactic that prevents the symptoms, not an antibiotic that treated the disease.

There are levels of testing that drugs must go through to ensure both their efficacy and safety. In short, once a drug has been developed and has passed preclinical (animal) trials, it is moved to Phase I testing. At this stage, healthy volunteers are dosed to determine the most common side-effects, how a drug is metabolized and how it is excreted.

If toxicity is determined to be at acceptable levels, the drug is moved on to Phase II where effectiveness is determined by a controlled trial. Some

people are given the drug, others are given a placebo and the results prove the drug's efficacy.

The next step is Phase III. Now the drug is given to a larger population to further study safety and effectiveness. Again, once those studies prove the efficacy and safety of the drug, it can then be prescribed to the general public. It is important to note that even once a drug is released, doctors and clinicians still report any adverse events, information which is continuously collected and determines if additional warnings will be required by the FDA to be added to the label.

In the case of mefloquine, this step was never taken. Phase III clinical testing did not occur. The significance of skipping this crucial step cannot be overstated. Instead, all of the data collected during preclinical, Phase I and Phase II was turned over to the manufacturer, and with FDA approval Mefloquine was rolled out to our troops.

It is very important to note the sample sizes typically used in Phase I and Phase II will generally total less than 500 individuals. Yet, even with that small sampling, a significant percentage of side effects were reported. Because of the speed at which the drug was moved along the testing pipeline, only the immediate and shortest of the short term effects could be noted, but they included reports of adverse reactions rates of 70% or more of the participants. But, those reactions were deemed both brief and insignificant and the drug itself held such promise, so those adverse events were ignored, dismissed or considered inconsequential.

Anyone who has taken mefloquine will recognize those immediate reactions, as they are still experienced; changes in mood, depression, anxiety, sleeplessness, irritability and ringing in the ears. Bear in mind that none of these reactions can be medically or scientifically quantified – they are all subjective. A doctor cannot look in your ear canal and see the ringing you hear any more than they can run a blood test for irritability.

What became apparent was that many of these symptoms persisted beyond the 4-6 hour expected window after dosing. With each subsequent dose, the side-effects were more pronounced but because they were expected by the patient, were often better self-managed. The most important factor to bear in mind is that in the 1980's and 1990's, very few of our troops dosed with mefloquine encountered combat. There were no large scale wars involving hundreds of thousands of personnel.

This bears repeating. Mefloquine was developed as a Public-Private Venture between a pharmaceutical company and the Department of Defense. Without Phase III testing, it was approved by the FDA for use, though it was not made available to the general public as a prophylactic until 1989. The first randomized, controlled study was not conducted until 2001 at which point more than two-thirds of study participants reported adverse events. Had this data been available previously, the FDA would not have approved the drug.

Yet, for all practical purposes the data was available because testing had been done on thousands of members of the U.S. military, though not according to any clinical protocols. Phase III testing requires the drug be given to a large and diverse, healthy population, an apt description of our troops. But contraindications were not studied and adverse reactions were dismissed and/or ignored. Because the drug worked as intended – it prevented most cases of malaria with minimal concurrent renal and hepatic side-effects with a single weekly dose.

MEET THE BLOGGER

Denise Williams

Born and bred in Chicago, now living in the wilds of far suburbia. I'm a Gold Star Mom, a wife and step-mom to two terrific boys. My views are generally politically and socially conservative, though I am far from a Party line Republican. I believe in this country, our Constitution and above all, in the right of life, liberty and the pursuit of happiness. I believe our government is supposed to serve the people, not tell them how to live. To me, this is just common sense, but since it seems to be a minority opinion, it has become "Uncommon Sense".

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Due to a combination of randomized trials conducted as late as the early 2000's, alarming reports from doctors and medical practitioners who prescribed the drug to the traveling public, and some U.S. Army researchers, mefloquine was finally acknowledged as a neurotoxin with significant incidents of neuropsychiatric side effects. But it wasn't until the end of the decade that action was finally taken by the Army.

In 2009, the Army Surgeon General Lt.General Eric Schoomaker issued a directive stating in part that mefloquine should not be given to soldiers who have experienced a Traumatic Brain Injury, or TBI or who exhibited symptoms of a TBI. Later that year, doxycycline, an antibiotic, was made the antimalarial prophylactic of choice for our military. Still, it wasn't until September of 2013 that Special Forces Operations in Ft. Bragg issued a ban on mefloquine for those, our most elite troops. Perhaps it was finally understood that if those who have proven themselves the most physically and mentally tough are being diagnosed with severe PTSD and succumbing to suicide, there is something other than combat as a causative factor.

Mefloquine was not prescribed only to US military personnel. Troops in other countries were also dosed, but those neuropsychiatric adverse events were acknowledged and taken seriously. In Ireland, for example, the manufacturer of mefloquine under the name brand Lariam has added warnings that the drug can cause suicide. Since the drug was released to the general public in 1989, the U.S. product label has carried the warning that the drug can cause anxiety, depression, hallucinations and other psychotic reactions, but the addition of suicide, suicidal ideation and self-harm is significant.

The single most upsetting fact to note is that prior to dosing our troops, there were no studies done on drug interactions. But, there were clinically noted contraindications for mefloquine long before the drug was released to the general public in 1989. By the early 1990's, it was clear that adverse reactions were so common and significant in concurrent dosing of mefloquine and opiates, anti-anxieties, anti-depressants, anti-psychotics and sleep-aids, warnings were attached to the label. Each of those drugs cause symptoms that are identical to PTSD. Mefloquine causes symptoms that are identical to PTSD. Now, we are sending our troops into combat with compromised nervous systems from mefloquine toxicity, exposing them to the stressors assumed to be the prime cause of PTSD, then treating those symptoms with more drugs that also cause symptoms of PTSD. And the Deparment of Defense and the Army in particular are surprised and baffled at the skyrocketing rates of PTSD and suicide among our military and veterans.

The U.S. military has been strongly encouraged to study the causal relationship between mefloquine and suicide, yet those studies have yet to be done. Instead, statements by the Department of Defense, including statements made to Congress, are still blaming suicide among our troops and veterans on pre-existing mental health issues and personal relationship failings as the prime causative factors.

Worst of all is how our military institutions still refer to PTSD as a mental illness when it has been known for all these years that PTSD can be caused by the neurotoxin mefloquine. At the very least, every member of the military and every veteran who presents with PTSD symptoms should have their history checked for mefloquine dosing. If they took the little pill even once, their diagnosis should read "Mefloquine Toxicity", not "PTSD". There is no cure for mefloquine toxicity. That said, we do know how to make it worse - by adding other drugs to the already compromised nervous

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system, specifically drugs intended to treat symptoms of PTSD. Considering this, proper diagnosing is critical; this intentional misdiagnosis is criminal.

This is one of those things that just baffle the mind. There is a drug that was prescribed to our troops, that everyone was ordered to take, that has known and admitted significant psychological adverse reactions. Concurrent or subsequent administration of anti-psychotics, anti-depressants, anti-anxiety and sleep aids is contraindicated. Those with a TBI or symptoms of a TBI are also contraindicated for this drug. The U.S. military has violated, by standard operating procedure, all of these contraindications, but doesn't believe this drug is a factor and therefore refuses to even conduct studies based on the mountains of data already collected. Instead, their stance is the suicide epidemic is a mystery but most probably related to individual, personal or pre-existing issues.

Each post in this series will be added to the Post Traumatic Stress page and will be accessible by clicking the button at the top of the post. You can also type your email address in the box and click the "create subscription" button. My list is completely spam free, and you can opt out at any time.

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Filed under: Mefloquine, Post Traumatic Stress, Post-Traumatic Stress Disorder
Tags: mefloquine, PTSD, PTSD causes

by Taboola

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Leslie Lakatos Kane · Follow · Argosy University

Interesting read. Are you able to provide citations on this information because I would like to read much more about possible correlation of this drug and symptomology of PTSD. Thank you! Leslie

Reply · Like · 1 · Follow Post · June 27, 2014 at 9:22am

Denise Williams · Follow · Top Commenter · Freelance Writer at Self-Employed

Leslie, this and the other posts in the series are the result of more than two years research. I've used scores of sources, which is why I've chosen not to cite these posts. Everything in this piece can be found with a simple google search of "mefloquine + ptsd". I wrote this because the information is so widely available but so few seem to know.

Reply · Like · 1 · June 28, 2014 at 12:01am

Leslie Lakatos Kane · Follow · Argosy University

thanks for replying

Reply · Like · June 28, 2014 at 12:14am

Michael Tosser · Works at Aquatica Tropicals Ruskin

For those looking for more details on Mefloquine, and asking for sources, here's the US Military's Deployment Health Clinical Center's page regarding Mefloquine:

http://www.pdhealth.mil/mefloquine.asp#va

Specific links ot PTSD may or may not exist - But a lot of my brothers and sisters have potentially been misdiagnosed with PTSD due to the complications of Mefloquine - Many of which are nearly identical to PTSD's effects.

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Jeanne Lese · Carlow University

Mefloquine is used on civilians as well as the military. Please visit Mefloquine (Lariam) Action for more :
http://www.lariaminfo.org

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This is a very clearly written review.

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https://www.facebook.com/groups/mefloquine/

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