Australian Government
Repatriation Medical Authority

Senate Standing Committee on Foreign Affairs, Defence and Trade References Committee

The use of the quinoline anti-malarial drugs mefloquine and tafenoquine in the Australian Defence Force

Submission of the Repatriation Medical Authority

July 2018

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1 Summary

The Repatriation Medical Authority (RMA) has found evidence that mefloquine, tafenoquine and related quinoline anti-malarial drugs can have specific adverse effects.

Where use of these drugs can be causally linked to an injury, disease or death the RMA has included an appropriately worded factor in the Statements of Principles (SOPs) concerning the condition.[1]

However, the RMA has not found evidence to provide a scientific basis for the contention that these drugs cause chronic brain damage resulting in a distinctive set of symptoms that would constitute a new disease or injury.

The RMA continues to monitor the medical-scientific literature in respect of these drugs and updates the SOPs accordingly.

2 Background

On 19 June 2018 the Senate referred the use of the quinoline anti-malarial drugs Mefloquine and Tafenoquine in the Australian Defence Force to the Foreign Affairs, Defence and Trade References Committee. The inquiry's terms of reference are:

The use of the quinoline anti-malarial drugs Mefloquine and Tafenoquine in the Australian Defence Force (ADF), with particular reference to:

(a) the current and past policies and practices for:

  (i) prescribing Quinoline anti-malarial drugs to ADF personnel; and

  (ii) identifying and reporting adverse drug reactions from Quinoline anti-malarial drugs among ADF personnel;

(b) the nature and extent of any adverse health effects of those who have taken Mefloquine/Tafenoquine on serving and former ADF personnel;

(c) the support available for partners, carers and families of personnel who experience any adverse health effects of Quinoline anti-malarial drugs;

(d) a comparison of international evidence/literature available on the impact of Quinoline anti-malarials;

(e) how other governments have responded to claims regarding Quinoline anti-malarials; and

(f) any other related matters.

This submission has been prepared by the RMA, specifically addressing (d), the international evidence/literature available on the impact of quinoline anti-malarials. The identification and assessment of such sound medical-scientific evidence (SMSE) is the core function of the RMA[2].

[1] See Table 1 in section 5.
[2] Subsection 196B(1), *Veterans' Entitlements Act 1986*

3 The role of the Repatriation Medical Authority

The RMA is an independent statutory authority responsible to the Minister for Veterans' Affairs. It has five part-time members appointed by the Minister, who are eminent in fields of medical science, including epidemiology, supported by a small full-time Secretariat based in Brisbane.

The primary role of the RMA is to determine SOPs for any disease, injury or death that could be related to military service, based on SMSE. The SOPs state the factors which "must" or "must as a minimum" exist if service is to be accepted as contributing to a particular kind of disease, injury or death.

SOPs cover a wide range of diseases, injuries and kinds of death, including musculoskeletal injuries, cancers, infectious diseases, mental disorders and chronic medical conditions. There are currently 688 SOPs, covering 344 conditions. Two SOPs are determined for each condition, differentiating between the different types of eligible service. Some 92.4% of claims with diagnosable conditions determined by the Department of Veterans' Affairs in 2017 were covered by SOPs.

The SOPs are disallowable instruments which are tabled in both Houses of the Australian Parliament[3]. The SOPs are binding on all decision makers making decisions on claims for compensation (disability pension) under the *Veterans' Entitlements Act 1986* (VEA) or claims for liability for service injuries, diseases and death under the *Military Rehabilitation and Compensation Act 2004* (MRCA)[4].

The RMA's role is limited to determining the SOPs, and it has no involvement in decisions relating to claims by individual veterans, serving members or their dependants. The matters of fact relating to each claim, including the nature of service, the diagnosis of the claimed incapacity (or cause of death) and any connection between eligible service and a factor listed in a SOP, are determined by decision makers including the delegates of the Repatriation Commission and the Military Rehabilitation and Compensation Commission, the Veterans' Review Board and the Administrative Appeals Tribunal.

4 Sound medical-scientific evidence

In determining SOPs, the RMA is required to rely upon SMSE, as defined in subsection 5AB(2) of the VEA. Under this definition, information about a particular kind of injury, disease or death is ***sound medical-scientific evidence*** if:

(a) the information:
  i. is consistent with material relating to medical science that has been published in a medical or scientific publication and has been, in the opinion of the Repatriation Medical Authority, subjected to a peer review process; or
  ii. in accordance with generally accepted medical practice, would serve as the basis for the diagnosis and management of a medical condition; and

(b) in the case of information about how that kind of injury, disease or death may be caused—meets the applicable criteria for assessing causation currently applied in the field of epidemiology[5].

[3] Section 42, *Legislation Act 2003*
[4] Subsections 120A(3) and 120B(3), *Veterans' Entitlements Act 1986*
[5] Subsection 5AB(2), *Veterans' Entitlements Act 1986*

4.1 Critical appraisal

In assessing SMSE to determine whether or not a specific factor should be included in a SOP, the RMA considers both the quantity and quality of the evidence. Higher quality evidence has more weight than lower quality evidence. There are well established epidemiological principles which are used to distinguish between higher and lower quality evidence, the process being called "critical appraisal". Further detail about the way in which the RMA assesses the SMSE is available in its *Practices and Procedures* document, published on the RMA website (**Attachment 1**).

Important features which are considered in the critical appraisal process include:

- the study design,
- the method of selection of study subjects,
- the way in which the factors of interest and outcomes are measured,
- the assessment and control for potential confounders (alternative causes),
- the statistical significance of the results,
- the strength of the association, consistency of the evidence, temporality (cause before effect), dose-response effects and biological plausibility.

The critical appraisal process helps determine the degree to which the evidence supports a particular hypothesis, or leaves open the possibility that alternative factors could account for the phenomenon or the association.

Case reports

In terms of study design, case reports are considered low quality evidence because they generally leave open the possibility that symptoms could be caused by other risk factors or other diseases. This is especially so when symptoms are common in the general community, which is the case with many of the symptoms reported after taking mefloquine (vomiting, diarrhoea, dizziness, vertigo, sleepiness, sleep disturbances, headache, anxiety, depression and forgetfulness).[6] This increases the possibility that an association in any one individual has occurred by chance or that there is another explanation for the association.

Controlled studies

Studies which have a control or comparator group are able to account for background rates of symptoms. They can also account for alternative explanations for symptoms, such as having a psychiatric illness, and being exposed to other medications or risk factors. Studies carried out prospectively or longitudinally also take account of bias in the results caused by the natural tendency of people to recall exposures more frequently if they are unwell than if they are well (termed recall bias).

Animal studies

Evidence of pathology based on animal studies needs to be confirmed by pathological and epidemiological studies in humans because of interspecies differences, the high doses which tend to be used in animal studies, and the difficulty of relating animal behaviours to human symptoms.

[6] Australian Medicines Handbook (2018). Mefloquine. Available at https://amhonline.amh.net.au/chapters/anti-infectives/antiprotozoals/antimalarials/mefloquine. Accessed 12 July 2018.

5 Acute health effects of quinoline anti-malarials and Statements of Principles

Anti-malarials are among a wide range of drugs that the RMA considers routinely when undertaking investigations, where there is SMSE showing a potential link between a drug and the condition under investigation. Under its legislation, the RMA is required to exclude the temporary and reversible acute effects of exposure to pharmaceutical agents from consideration, but does consider long term effects and long term consequences of acute effects.[7]

SOPs are updated regularly, so any new evidence in relation to mefloquine, tafenoquine or other anti-malarials can be taken into account during these investigations. As a result of concerns that have been raised more recently in relation to mefloquine and tafenoquine, the RMA has reviewed the evidence and undertaken a number of additional investigations.

There is considerable experience and a body of literature concerning mefloquine because it is approved for use in several countries (including the USA, Canada, the UK, Europe, Japan and Australia) and has been used by international travellers since the 1990s.

Experience with tafenoquine has been limited to clinical trials in the Australian Defence Force and in civilian populations in a number of countries. These trials support the safety and efficacy of tafenoquine for malaria prevention and prevention of relapse. In January 2018, tafenoquine was listed by the Therapeutic Goods Administration for use under the Special Access Scheme.[8] In July 2018, the US Food and Drug Administration approved the use of tafenoquine for the prevention of relapse of *Plasmodium vivax* malaria.[9]

Mefloquine is currently included as a factor in SOPs for 15 conditions and tafenoquine is included as a factor in SOPs for six conditions (see Table 1 below). The wording of the mefloquine- or tafenoquine-related factors in these SOPs requires a close temporal link between the taking of the drug and the onset of the condition (for example, within the two days before, or at the time of), reflecting the well-accepted evidence that these agents can have acute neuropsychiatric effects.

[7] Subsection 5D(1), *Veterans' Entitlements Act 1986 ("Disease" does not include… "the temporary effects of extraneous agents")*
[8] Therapeutic Goods Administration (2018). 1.19 Tafenoquine succinate. Available at. https://www.tga.gov.au/book-page/119-tafenoquine-succinate. Accessed 23 July 2018.
[9] US Food and Drug Administration (2018). FDA Approved Drug Products. Available at https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&applno=210795. Accessed 23 July 2018.

A table with the full wording of mefloquine- or tafenoquine-related factors in each SOP is also attached (**Attachment 2**). An example of how the SMSE concerning mefloquine and tafenoquine was examined is provided in relation to anxiety disorder (**Attachment 3**).

Table 1 SOPs with factors relating to mefloquine or tafenoquine, as at July 2018

Condition	Instrument Numbers	Drug
acquired cataract	87 of 2016	mefloquine and tafenoquine
anxiety disorder	102 & 103 of 2014, amended by 99 &100 of 2016	mefloquine
bipolar disorder	53 & 54 of 2018	mefloquine
depressive disorder	83 & 84 of 2015	mefloquine
epileptic seizure	77 & 78 of 2013	mefloquine and tafenoquine
heart block	1 & 2 of 2014	mefloquine
methaemoglobinaemia	47 & 48 of 2010	tafenoquine
myasthenia gravis	75 & 76 of 2015	mefloquine
peripheral neuropathy	74 of 2014	mefloquine
psoriasis	31 & 32 of 2012	mefloquine and tafenoquine
sensorineural hearing loss	5 & 6 of 2011	mefloquine and tafenoquine
schizophrenia	83 & 84 of 2016	mefloquine
suicide and attempted suicide	65 & 66 of 2016	mefloquine
tinnitus	33 & 34 of 2012	mefloquine and tafenoquine
toxic retinopathy	19 of 2018	mefloquine
trigeminal neuropathy	79 of 2015	mefloquine

6 Consideration of the evidence relating to mefloquine, tafenoquine or primaquine as possible causes of chronic brain injury

In 2017 the RMA conducted an investigation of the hypothesis that mefloquine causes a form of chronic brain injury, variously termed "chronic, mefloquine-induced toxic encephalopathy", "chronic mefloquine toxicity syndrome" or "chemically-acquired brain injury".

It had been postulated that mefloquine and related quinoline drugs cause permanent brain injury, resulting in a range of symptoms that persist over the long term. The RMA examined the evidence relating to tafenoquine and primaquine as well as the evidence relating to mefloquine, on the basis that these drugs all belong to the quinoline chemical class.

The RMA declared in August 2017 that it did not propose to determine SOPs concerning chemically-acquired brain injury caused by mefloquine, tafenoquine or primaquine. In its declaration, the RMA stated that the decision had two bases:

(1) there is insufficient SMSE that exposure to mefloquine, tafenoquine or primaquine causes chronic brain injury; and
(2) the SMSE does not show that there is a characteristic and persisting pattern of signs and symptoms following exposure to mefloquine, tafenoquine or primaquine that could be determined to be a particular kind of disease of, or injury to, the brain.

The RMA determination concerning the contended condition is in accordance with its statutory role, provided under subsection 5D(1) of the VEA, to determine whether or not there exists a particular kind of injury or disease which is the subject of a request.

6.1 *Relevance of the totality of the evidence and consideration of the quality of evidence*

In respect of both of the above conclusions, critical appraisal of the quality and quantity of the available evidence was an important consideration. More detail about the range and quality of the available evidence concerning the possible existence of chemically-acquired chronic brain injury is provided in the briefing paper (**Attachment 4**), and summarised in a statement of reasons issued at the time of the RMA decision not to determine a SOP for the postulated condition (**Attachment 5**).

The hypothesis that mefloquine causes permanent brain damage is based on proposed causal mechanisms and pathology identified in high dose animal studies mostly conducted shortly after World War II. There is no direct evidence that it causes permanent brain damage in humans given therapeutic doses.

The claim that there are persistent symptoms that are due to mefloquine is based on a small number of case reports and adverse event reports of a variety of commonly experienced symptoms in a widely prescribed medication. These same animal studies and human case reports are cited repeatedly as the basis for the contention of a syndrome resulting from permanent brain injury.

Animal studies and case reports are considered "hypothesis generating", since the associations they suggest need to be evaluated in well-conducted comparative studies in humans. Human studies of this type are considered higher quality evidence. Because of the lack of supporting evidence from such studies, the RMA found that the evidence was not persuasive when critical appraisal of the total body of SMSE was taken into account.

6.2 *Limitations of the available animal studies and case reports*

A key limitation of the post-World War II studies of various experimental quinoline compounds was the very high or lethal doses of the drugs used. In the study of rhesus monkeys the authors state that "the results of the present study indicate little likelihood that significant neuronal injury would result from clinical use of either pentaquine, isopentanquine, primaquine or pamaquine in doses such as are employed for malaria therapy".[10] This study did not demonstrate that the brain area responsible for balance (the vestibular system) was a site of injury, even at high doses of the specified drugs. Another

[10] Schmidt IG, Schmidt LH (1951). Neurotoxicity of the 8-aminoquinolines. III. The effects of pentaquine, isopentaquine, primaquine, and pamaquine on the central nervous system of the rhesus monkey. J Neuropathol Exp Neurol, 10(3): 254.

experimental drug, plasmocid, only produced significant involvement of the vestibular system of rhesus monkeys with fatal or very high doses.[11]

A key limitation of the case reports is there is no unexposed comparison groups, so that they cannot take into account background rates of common symptoms and other potential reasons for symptoms. For example, if a symptom is present in 1% of the community, then even if it is not caused by the drug, it would still be expected to be present in 1% of people taking the drug. That is the reason why longitudinal studies with comparison groups are critical to determining whether the symptom is caused by the drug.

In fact, the higher quality evidence from longitudinal studies shows overall findings of similar or decreased risk of neuropsychiatric outcomes, including vertigo, in those taking mefloquine compared to those who were not taking mefloquine.

In order to define a disease based on symptomology alone, it is necessary to be able to specify, at least in broad terms, the frequency, duration and pattern of symptoms that are typically representative of the condition. Although a range of symptoms has been reported following use of mefloquine, the timing, duration, severity and set of essential individual symptoms which would define the condition have not been established in any consistent manner. One study attempted to define a syndrome using statistical analysis of symptoms[12] but did not address this problem because it did not specify the timing or duration of symptoms in relation to taking mefloquine.

6.3 Lack of evidence of harm despite widespread, long term use

Given that mefloquine has been used by more than 35 million travellers for chemoprophylaxis worldwide since 1985 in Europe and since 1990 in the USA[13], it would be expected that even rare effects would be able to be detected with reasonable frequency if a causal relationship existed. Instead, there are only five case reports of people with some long term symptoms (especially vertigo or dizziness), together with reports of persistence of a range of commonly experienced symptoms amongst some of the cases reported to adverse event databases.

Of note, the World Health Organisation has included mefloquine in its Model List of Essential Medicines. This document is an expert assessment of the minimum medicine needs for a basic health-care system, listing the most efficacious, safe and cost-effective medicines for priority conditions.[14]

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[11] Schmidt I, Schmidt L (1948). Neurotoxicity of the 8-aminoquinolines; lesions in the central nervous system of the rhesus monkey induced by administration of plasmocid. J Neuropathol Exp Neurol, 7(4): 368-98.
[12] Nevin RL, Leoutsakos JM (2017). Identification of a syndrome class of neuropsychiatric adverse reactions to mefloquine from latent class modeling of FDA Adverse Event Reporting System Data. Drugs R D, 17(1): 199-210.
[13] Schlagenhauf P, Adamcova M, Regep L, Schaerer MT, Rhein HG (2010). The position of mefloquine as a 21st century malaria chemoprophylaxis. Malar J, 9: 357.
[14] WHO Model List of Essential Medicines, 20th list (2017). Available at http://www.who.int/medicines/publications/essentialmedicines/20th_EML2017_FINAL_amendedAug2017.pdf?ua=1 Accessed 31 July 2018.

6.4 Conclusion

The contention that chronic brain injury occurs as a result of having taken mefloquine or other quinoline drugs has been advanced on the basis of some case reports and adverse event reports of persistence of symptoms that are common in the general population, and some pathology identified from high-dose animal studies of experimental quinoline compounds.

The evidence from these studies is limited for the reasons outlined above. Taken together with other higher quality studies, and in the context of a drug in common use over the last 30 years, the evidence is insufficient to support the contention that these drugs cause chronic brain damage resulting in a distinctive set of symptoms that would constitute a new disease.

7 Attachments

Attachment 1	**RMA Practices and Procedures**
Attachment 2	**Table of Statements of Principles with factors relating to mefloquine or tafenoquine**
Attachment 3	**Briefing paper for focussed review of anxiety disorders**
Attachment 4	**Briefing paper for investigation into chemically-acquired brain injury due to mefloquine, tafenoquine or primaquine**
Attachment 5	**Declaration and Statement of Reasons for investigation into chemically-acquired brain injury due to mefloquine, tafenoquine or primaquine**