



Clinical Guidelines for providing appropriate care to ADF members concerned about having been prescribed Mefloquine

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PURPOSE

These clinical guidelines are primarily designed to assist clinicians manage patients who are concerned about having been prescribed mefloquine and specifically those that are suffering from neuropsychiatric symptoms which they attribute to historical use of mefloquine (often from the 2000-2002 period). They may also be useful in managing any patients with neuropsychiatric symptoms attributed to other antimalarials and other medications more generally, or symptoms of unknown cause.

BACKGROUND

There has been much publicity in the civilian media and concerns raised by some serving and ex-serving ADF members relating to the use of mefloquine for chemoprophylaxis by the Australian Defence Force. The United Kingdom is experiencing similar concerns and the United States has experienced similar concerns in the past.

On 30 November 2015, Defence released a statement on the use of mefloquine in the ADF that advised if "any ADF member, past or present is concerned that they might be suffering side-effects from the use of mefloquine Defence encourages them to raise their concerns with a medical practitioner so they may receive a proper diagnosis and treatment."

<http://news.defence.gov.au/2015/11/30/statement-on-the-use-of-mefloquine-in-the-ADF/>

It is anticipated that Defence medical officers will encounter ADF members who are concerned that they may be suffering side-effects from historical use of mefloquine.

Mefloquine side-effects

Mefloquine has been registered for malaria chemoprophylaxis in Australia since 1993, and has been prescribed to over 35 million people worldwide. The side-effect profile is well known with most of the recent changes in product information relating to the duration that neurological side-effects may last. It is now acknowledged that in some cases these side-effects may be permanent.

<https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/PICMI?OpenForm&t=PI&q=Lariam&r=/>

The neuropsychiatric side-effects of mefloquine have received the most attention and are best considered as psychiatric – disturbed sleep, anxiety, paranoia, depression, hallucinations and psychosis; and neurological – vertigo, loss of balance, tinnitus, sensorineural hearing loss and neuropathy.

Side-effects from mefloquine usually occur soon after commencing the medication. Side-effects usually resolve within days to weeks after ceasing the medication. Due to mefloquine's long half life it is possible for symptom onset to be weeks after cessation. In rare cases, side-effects may persist for months or longer and more rarely some neurological symptoms become permanent.

Mefloquine and Post-traumatic Stress Disorder (PTSD) or minor traumatic brain injury (mTBI)

There is no evidence that mefloquine causes or triggers PTSD or mTBI. In the acute situation, there is potential for acute mefloquine-related psychiatric symptoms to confound a PTSD or mTBI diagnosis. There is no evidence to suggest that a PTSD diagnosis made months or years after ceasing mefloquine can be attributed to past mefloquine use.

Mefloquine toxicity – CNS toxicity syndrome – mefloquine toxidrome

Dr Remington Nevin, an ex-US Army medical officer has published a number of opinion articles proposing the adoption of diagnoses to describe long term or permanent neurological symptoms related to mefloquine use. None of the terms have been officially accepted and there are no accepted diagnostic criteria, diagnostic tests nor any treatment. Clinicians should understand that members may present seeking one of these diagnoses.

It is important to acknowledge that mefloquine has been associated with long term or permanent neurological side-effects which can be diagnosed.

Tafenoquine

Tafenoquine is a relatively new anti-malarial medication which is chemically closely related to primaquine. As a quinine derivative, it falls into the same broad class of antimalarials as mefloquine however it acts quite differently in the body and its known side-effect profile more closely reflects those of primaquine. It is not yet

registered for use in Australia and is still undergoing Phase 3 clinical trials. It was trialled by the ADF in the late 1990s and early 2000s as an option for prophylaxis, eradication and treatment of malaria.

There is no evidence that tafenoquine causes serious neuropsychiatric effects, either acute or chronic. Long term use is associated with an eye condition, vortex keratopathy (small deposits in the cornea), also seen with long term use of chloroquine. The condition does not affect vision and has no symptoms. It is benign and resolves completely after tafenoquine is stopped.

CLINICAL APPROACH

Persons presenting with neurological or psychiatric symptoms with a history of previous mefloquine use should be thoroughly assessed. It is important to accept that the member has concerns that their symptoms may be related to historical mefloquine use and the concerns should not be summarily dismissed.

Members presenting who are concerned because they have taken mefloquine in the past but have no symptoms (the worried well), need to have their concerns noted and addressed.

What can the general practitioner do?

1. Document any symptoms as part of a comprehensive history. Note the date of symptom onset in relation to mefloquine use and the nature of symptoms after ceasing mefloquine.
2. Examine the patient and document any abnormal neurological or other signs. All patients should receive an audiogram and a Sharpened Romberg test.
3. Assess the patient with readily available psychological screens, if relevant. For example, K-10, DASS-21, DAR or CAPS-5.
4. Arrange further diagnostic investigations or specialist referral as appropriate.
5. Members presenting with neurological symptoms will often require referral to one or more of the following to confirm a diagnosis, quantify symptoms and recommend treatment:
 - a. Neurologist; and /or
 - b. Neuropsychologist (including a request for a battery of tests to baseline neuropsychological function)
6. Members presenting with psychiatric symptoms should be referred to a psychiatrist, where available, preferably a psychiatrist with experience in military populations.

7. Assess and document risk.
8. **Explore useful treatments.** Treatment options will depend on the symptoms being experienced and whether a condition can be diagnosed.
 - a. Where a clinical diagnosis (including a provisional diagnosis) is made, evidence based treatment for the condition should be provided.
 - b. No specific treatment has been proposed for mefloquine related neuropsychiatric problems apart from ceasing the medication.
 - c. Generally, pharmacotherapy or psychotherapy should be withheld until a disorder is diagnosed, however treatment of specific symptoms causing significant distress should be considered even without a provisional or definitive diagnosis (e.g. Prochlorperazine for dizziness).
 - d. Document the claims in the medical record. Include details of deployment location, operation and dates; the antimalarial taken or believed to have been taken and if relating to the 1998-2003 period whether they participated in an Army Malaria Institute trial.
9. Advise the member that there is additional information on anti-malarial use in the ADF available on the Joint Health Command external web site:
<http://www.defence.gov.au/Health/HealthPortal/Malaria/default.asp>

In addition, clinicians may find this article from the September 2015 Australian Family Physician useful: *Managing medically unexplained illness in general practice* <http://www.racgp.org.au/afp/2015/september/managing-medically-unexplained-illness-in-general-practice/>

Risk Assessment and Mental Health Management

Defence members who present with mental health symptoms, psychological distress or increased risk should be assessed and managed in accordance with HD 294 *Risk Assessment and Management of Defence members at Risk of Suicide, Self-Harm or Harm-to-Others*. Defence members who require mental health assessment and treatment are to be managed in accordance with HD 289 *Coordinated Care and Management of Defence members receiving Mental Health Services in Garrison*. The immediate assessment and management of risk, when identified, is the priority.

MEC and MECRB management

MEC considerations will depend on the health status, functional capacity and health support needs of the individual. If a member is not deployable, and the period of non-deployability extends beyond 12 months from onset of illness, MECRB consideration is required.

If the member has raised the possibility of mefloquine being associated with their symptoms, this needs to be documented in the MEC Review.

In summary:

1. Be respectful and acknowledge the concerns
2. Treat when appropriate
3. Offer referral to appropriate specialists for testing/documentation of function and exclusion of other causes
4. Document the member's health record
5. Assess and manage risk