Clinical Guidelines for providing appropriate care to ADF members and veterans concerned about having been prescribed mefloquine or tafenoquine

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PURPOSE
These clinical guidelines are primarily designed to assist clinicians manage patients who are concerned about having taken mefloquine or tafenoquine and specifically those that are suffering from neuropsychiatric symptoms which they attribute to historical use of these antimalarials (often from the 1999-2002 period). They may also be useful in managing patients with neuropsychiatric symptoms that they attribute to other antimalarials and other medications more generally, or symptoms of unknown cause.

BACKGROUND
In recent years, there has been much publicity in the civilian media and concerns raised by some serving and ex-serving Defence members relating to the use of mefloquine and tafenoquine for malaria 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.”


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 or tafenoquine. Similarly, civilian GPs may encounter ex-serving members with these concerns.
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. In chemoprophylaxis the safety profile of mefloquine is characterised by a predominance of neuropsychiatric adverse reactions. Most of the recent changes in product information relate to the duration that psychiatric or neurological side-effects may last. On occasions, these symptoms have been reported to continue long after mefloquine has been stopped.


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 (21 days on average) it is possible for symptom onset to be weeks after cessation. In rare cases, side-effects may persist for months or longer.

Mefloquine and Post-traumatic Stress Disorder (PTSD) or mild 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 symptoms which can be diagnosed.

Chemically acquired brain injury

Several veterans and people active in the media have suggested that the quinoline class of antimalarials can cause brain injury. In 2017 the Repatriation Medical Authority (RMA) conducted a review of the medical and scientific literature to investigate whether mefloquine, tafenoquine and primaquine can cause chemically acquired brain injury. The RMA found that there is insufficient sound medical-scientific evidence that exposure to these pharmaceuticals causes chronic brain injury.
CYP2D6

CYP2D6 is one of the cytochrome P450 enzymes. It is necessary for the metabolism of primaquine to an active form against malaria. Its role in the metabolism of tafenoquine is less certain. It is not relevant to mefloquine metabolism. The gene that codes for this enzyme is highly polymorphic and individuals can be described as poor, intermediate or normal metabolisers. Several veterans and advocates have stated that people who are poor metabolisers can suffer from tafenoquine or mefloquine toxicity.

There is no evidence linking this enzyme to side effects from these medications. The genetic mutation (for poor or intermediate metabolism) is not predictive of primaquine efficacy. Primaquine may still be effective in someone who has reduced enzyme metabolism. It is reasonable to test individuals who have had a confirmed vivax malaria relapse despite having fully complied with a primaquine course (treatment failure). This testing could be done to inform future malaria treatment options, if this is relevant to their situation. There is no basis for pre-emptive or mass screening.

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 (primarily gastrointestinal upset). It was registered in Australia in 2018 for both prophylaxis (Kodatef™) and radical cure (Kozenis™). It was trialled by the ADF between 1999 and 2001 as an option for prophylaxis, eradication and treatment of malaria.

There is no evidence that tafenoquine causes serious neuropsychiatric effects, either acute or chronic. In patients receiving Kodatef™ in clinical trials, adverse psychiatric reactions included sleep disturbances (2.5%), depression/depressed mood (0.3%), and anxiety (0.2%). Long term use has been 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.

The prescribing information for Kodatef™ advises that it should not be used in people with a history of serious psychosis or current psychotic symptoms, delusions or hallucinations. This is a precaution as there is no data on the safety of tafenoquine in people with a history of psychiatric disorder as these individuals were excluded from clinical trials of tafenoquine for prophylaxis. Serious psychiatric disorders such as psychosis and depression have been associated with some quinoline anti-malarial agents.

Prescribing information and consumer medicine information for tafenoquine is available on the TGA website at www.tga.gov.au and searching the Australian Register of Therapeutic Goods (ARTG).
CLINICAL APPROACH

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

Members presenting who are concerned because they have taken mefloquine or tafenoquine in the past but have no symptoms (the worried well) also 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 or tafenoquine use and the nature of symptoms after ceasing the medication. A comprehensive history is very important, as there are many factors which could be relevant to the presenting symptoms. These include developmental and family history, social history, injury, deployment experiences and other life events. In the ADF, most antimalarial use occurs in the context of deployment.

2. Perform a thorough examination and document any abnormal neurological or other signs as well as relevant negatives. 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. Those 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. Those presenting with psychiatric symptoms should be referred to a psychiatrist, preferably a psychiatrist with experience in military populations, where available.


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, which has already occurred.
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).

9. 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. Be aware that some veterans will not accurately recall whether or not they participated in a trial. They can check if they were a trial participant by contacting adf.malaria@defence.gov.au.


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 to a Defence medical officer with mental health symptoms, psychological distress or increased risk should be assessed and managed in accordance with Defence Health Manual Volume 2 Part 10 Chapter 2 – Assessing and managing 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 Defence Health Manual Volume 2 Part 10 Chapter 1 - 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.

In the civilian sector, acute mental health presentations should be managed according to best practice and local arrangements.

DVA also provides non-liability health care for all mental health conditions and a wide variety of support services, including counselling through Open Arms. Non-liability health care means that the veteran doesn’t have to prove that their mental health condition was caused by their military service.

DVA now has a single free call contact number for all enquiries: 1800 555 254. The DVA website has more information (www.dva.gov.au).

Military Employment Classification and MEC Review Board

For those Defence members still in full time service or in the active Reserves, 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 or tafenoquine 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