Ariadne's Thread:
principles for mefloquine toxicity

1. Diagnosing a toxic state should be a physician's first contribution, not a last resort after mental and functional diagnoses have been tried.
2. Diagnosing a toxic state is the most important contribution a physician can make. It organises the history, protects the patient from misdirected treatment, and restores a measure of intelligibility to a confusing illness.
3. Drug-induced toxicities are physical states, not mental or functional disorders.
4. Drug-induced toxicities can endure for years after the triggering drug has been stopped.
5. The persistence of these states in the absence of the drug that triggered them commonly leads doctors to mistaken diagnoses like Functional Neurological Disorder (FND), bipolar disorder, PTSD or depression.
6. FND is commonly based on a range of features that do not co-occur in ordinary neurological syndromes. That range, crossing organic boundaries, is also typical of toxic states contributing to diagnostic confusion.
7. Drug-induced toxicity should be ruled out before FND is assigned. Until that step is routine, referral into an FND service is the wrong response to a veteran with a plausible toxic exposure.
8. Generic referral to a psychiatrist or a community mental health team is not an adequate response to a suspected toxic state, even when there are prominent neuropsychiatric features. If specialist advice is needed, it should come from clinicians prepared to treat the presentation as a toxic injury.
9. Symptomatic treatment with psychotropic drugs, whether for mood, sleep, or other purposes can aggravate a toxic state rather than produce the benefits these drugs can offer in non-dysregulated states.
10. We are not yet aware of any treatment licensed for, or shown in adequate trials to reverse, mefloquine toxicity. Everything tried should be noted, and the consequences recorded in the recipient's own words.
11. A primary care doctor, a generalist, may be safer than a psychiatrist or neurologist working to a standard mental-health or FND pathway.
12. Unless there is an established antidote for a specific problem in a majority of the toxic state being treated, consider avoiding prescribing.
13. Polypharmacy must be avoided.
14. Managing a toxicity has to be predicated on the person in front of the doctor, not on a pathway built from averages that apply to no one.

Mefloquine toxicity needs clinicians who will recognize the injury and follow a thread where there is no map. The challenge as per Hippocrates is to not make things worse.

Ministry of Defence

We sent Ariadne's Thread to the Ministry of Defence, along with other supporting points, some of which are listed below.

The Ministry responded as follows. We would disagree with none of these points and we imagine few colleagues would.

- It is challenging to manage patients with symptomatic presentations whose aetiology is unclear.
- Our patients should be treated as individuals. A good medical history including a good past drug history is essential. The process for differential diagnosis is important.
- In syndromic presentations it is important clinicians acknowledge the patients presenting symptoms and belief about aetiology and work with them to address the symptoms.
- Advocating an approach that does not recognize any potential for comorbidity is problematic.
- NHS England appreciates that mefloquine neurotoxicity does exist and requires clinical management. We look forward to published clinical guidelines from the DHSC/ NICE.

Co-morbidity.

There is no question about the need to treat significant co-morbidity. A significant infection, an emerging diabetic or other disorder, needs management.

These are different scenarios to treating **symptoms of 'depression' or 'anxiety'** where these may be features of enduring mefloquine toxicity rather than a de novo comorbid neuropsychiatric disorder.

1. Depression or anxiety symptoms are often alternate expressions for a host of symptoms such as malaise, asthenia, fatigue, irritability, tension, agitation, stress, etc that arise from the toxic state rather than represent a co-morbid disorder.
2. Depression or anxiety may also represent a temporary demoralization linked to a persisting disability.
3. Neither toxicity nor demoralization are likely to respond to antidepressant treatments and neither should be diagnosed as a functional neurological disorder (FND).
4. High occupational functioning does not rule out significant injury.
5. Prior military culture and sanctuary trauma may militate against reporting problems.
6. A significant (severe) de novo onset depressive disorder warrants treatment with tricyclic antidepressants or ECT. SSRIs have never been shown to treat severe mood

disorders. Less severe mood disorders will clear within 12-16 weeks on average without treatment.

7. A 2022 FDA analysis of over 70,000 patients in antidepressant licensing trials - all done in mild depressions - show only 1 in 6 on active treatment have an unequivocally good response.
8. SSRIs are among the drugs most commonly reported to regulators for disturbed sleep, nightmares, violent dreams, confusional states, balance and vision problems, which overlap with mefloquine toxicity and may compromise future differential diagnoses.
9. There is an increased rate of suicidal (including suicide) and homicidal events on active treatment in SSRI clinical trials.
10. There is an increased rate of suicides along with suicidal and homicidal events in SSRI healthy volunteer studies.
11. Against this background, a prior history of an unequivocally good response to an SSRI may support their safe use.
12. The licensing trials for antipsychotics show higher rates of completed suicides, suicidality and homicidality on treatment than is found for any other drug group. Patients with schizophrenia did not present with an inherently high risk of suicide or homicide before the introduction of antipsychotics.
13. FND is a valid but relatively rare clinical disorder and this diagnosis should only be made where significant drug toxicity has been ruled out.
14. Given there are no recognized treatments for most toxic states, it may take some time before we have treatments for Persistent Mefloquine Toxicity Syndrome and in the absence of treatments, NICE and Guidance issuing bodies are unlikely to issue Guidance.