A Clinician’s Guide to Screening for Symptomatic Mefloquine Exposure and Evaluating Claims of Chronic Neuropsychiatric Effects from Mefloquine Poisoning

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Disclosures

• The presenters have the following interests to disclose:
  • Dr. Nevin serves as consultant and expert witness in criminal and civil cases involving claims of adverse effects from mefloquine
  • Dr. Ritchie serves as consultant in criminal cases involving claims of adverse effects from mefloquine
  • The views expressed are those of the presenters and are not necessarily those of the Department of Defence (DoD) or the Department of Veterans Affairs (VA)

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Learning Objectives

At the conclusion of this activity, the participant will be able to:

1. Demonstrate methods for screening veterans for symptomatic mefloquine exposure
2. Identify neuropsychiatric effects associated with symptomatic exposure to mefloquine
3. Describe plausible pathophysiologic mechanisms of mefloquine's chronic neuropsychiatric effects
4. Assess the relevance of mefloquine’s chronic neuropsychiatric effects in the diagnosis and management of various psychiatric and neurologic disorders
CE/CME Credit

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Background

• Mefloquine developed by the U.S. military as an antimalarial drug
  – Origins in the Vietnam War

• Widespread use during deployments beginning in the 1990s (e.g. Somalia, OIF/OEF)
  – Hundreds of thousands exposed

• Recently deprioritized for use
  – Followed FDA boxed warning and recognition of chronic neuropsychiatric effects
2013 FDA Boxed Warning

WARNING
Mefloquine may cause neuropsychiatric adverse reactions that can persist after mefloquine has been discontinued.

Mefloquine should not be prescribed for prophylaxis in patients with major psychiatric disorders. During prophylactic use, if psychiatric or neurologic symptoms occur, the drug should be discontinued and an alternative medication should be substituted (see WARNINGS).

The most frequently reported adverse reactions are nausea, vomiting, loose stools or diarrhea, abdominal pain, dizziness or vertigo, loss of balance, and neuropsychiatric events such as headache, somnolence, and sleep disorders (insomnia, abnormal dreams). These adverse reactions may occur early in the course of mefloquine use. It has been reported that dizziness or vertigo, tinnitus and hearing impairment, and loss of balance may continue for months or years after discontinuation of the drug and may be permanent in some cases.

More severe neuropsychiatric disorders have been reported such as: sensory and motor neuropathies (including paresthesia, tremor and ataxia), convulsions, agitation or restlessness, anxiety, depression, mood swings, panic attacks, memory impairment, confusion, hallucinations, aggression, psychotic or paranoid reactions and encephalopathy. Cases of suicidal ideation and suicide have been reported.
Mefloquine Neurotoxicity

• Chronic effects are most parsimoniously explained by *idiosyncratic* neurotoxicity
  – *In vitro* and *in vivo* evidence
  – Evidence from structurally-related quinoline drugs

• Focal effects within specific *brainstem* and *limbic* structures

• Symptomatic mefloquine exposure as a risk factor for chronic effects

On his first day in Iraq with the Special Forces, Staff Sergeant Georg-Andreas Pogany saw something so horrific, he suffered a panic attack. The U.S. military responded by humiliating and berating him, taking away his weapon, sending him home, and charging him with cowardice, a crime punishable by death. For the past year, he's been fighting to explain what happened—and to clear his name.

The Coward

By Jeanne Marie Laskas

Photographs by Dan Winters

Date July 2004
Vignette #1

- 33 year old male, Army intelligence officer, TS clearance
- PMH: None
- Deployed to Iraq in 2003
- Presented acutely in theater to combat stress control after suffering vivid nightmares, visual hallucinations, panic, persecutory delusions, confusion, and dizziness
• Initially diagnosed with combat stress reaction vs. panic attack, attributed to his observing a dead body the day prior
• Charged with cowardice and returned to the U.S.
• Evaluated by ENT and found to have objective evidence of central vestibular dysfunction
• Charges dropped
• Medically separated from service for PTSD and vestibular disorder
• Awarded 30% rating for service-connected “vestibular dysfunction secondary to adverse reaction” to mefloquine
• Awarded 30% rating for service-connected PTSD “with toxic psychosis secondary” to mefloquine
• Additional ratings for tinnitus, GERD, and IBS

Screening for Symptomatic Mefloquine Exposure

• Screen *all* Gulf War era and post-9/11 era veterans

• White River Mefloquine Instrument - 2 Question (WRMI-2)
  – Designed to have high sensitivity

• **Assessment of relevant exposure**, not a clinical instrument

• A positive exposure screen should prompt taking a focused mefloquine history

“Have you ever taken the weekly drug mefloquine (also known as Lariam®) to prevent malaria?"

If yes, “At any time while taking the drug, did you experience abnormal dreams or nightmares, insomnia, anxiety, depression, restlessness, or confusion?”
“Psychiatric symptoms such as insomnia, abnormal dreams/nightmares, acute anxiety, depression, restlessness or confusion have to be regarded as prodromal for a more serious event [emphasis added]”
Focused Mefloquine History

• Pre-exposure symptomatology
• Confirmed or suspected exposure
• Prodromal symptoms
• Circumstances of any continued use
• Evolution of symptoms
• Temporal relation of symptoms to other exposures (e.g. concussive events and traumatic stressors)
Vignette #2

- 32 year old male naval officer
- PMH: None
- Deployed to seas off East Africa in 2009
- Experienced intense nightmares and anxiety early during deployment
- Subsequently developed disequilibrium and confusion
- Experienced a traumatic event (i.e. enemy gun fire) towards the end of his deployment
• Diagnosed with PTSD following his return home

• Subsequently evaluated for persistent vertigo; found to have normal MRI of the IACs, hyperactive VOR gains and low VOR phase on RCT, deemed consistent with central vestibulopathy

• Suffers persistent insomnia, nightmares, depression, anxiety, dizziness, and poor short-term memory

“In the oculomotor, trochlear, an abducent nuclei there was considerable dropping out of nerve cells, degenerative changes in many that remained, and moderate proliferation of microglia and oligodendroglia. A representative field from the oculomotor nucleus is illustrated in Fig. 4. 

Somewhat slighter changes were observed in the vestibular nuclei, especially in the medial vestibular nucleus.”

“...in doses well below the lethal level [these drugs] produced striking symptoms of central nervous system injury associated with severe lesions in the principal nuclei of the proprioceptive, visual-reflex, and vestibulo cerebellar pathways....”

NEUROTOXICITY OF THE 8-AMINOQUINOLINES

III. The Effects of Pentaquine, Isopentaquine, Primaquine, and Pamaquine on the Central Nervous System of the Rhesus Monkey

The basic experiments (4), which assisted in establishing the position of the above 8-aminoquinolines in the treatment of relapsing malaria in man, included studies of the reactions of the rhesus monkey to these drugs with special reference to effects on the central nervous system. Interest in the latter effects rested on the observation that the closely related compound, Plasmocid, when administered to rhesus monkeys, evoked a complex group of neurological symptoms, associated with severe and widespread degenerative lesions in various cell groups of the spinal cord, brain stem, and cerebellum (1, 5–7). Whereas intoxication with even multilethal doses of pentaquine, isopentaquine, or primaquine did not evoke similar symptoms, the close structural relations of these compounds to Plasmocid (fig. 1), their high inherent toxicity and capacity to evoke reactions which might mask symptoms of low grade neuronal injury, plus the likelihood of their widespread use in malaria therapy made a detailed search for central nervous system lesions highly desirable.

“The brain stem structure that we observed to be primarily targeted by mefloquine was the n. gracilis. The n. gracilis is a component of the dorsal column system which transfers proprioceptive signals... Simple clinical neurological exams of humans might also reveal whether the loss of proprioceptive function underpins the vertigo/dizziness seen with some mefloquine-treated patients. **It is also important to point out that the mefloquine-induced brain stem injury revealed by silver staining is permanent in nature.**

Vignette #3

- 24 year old male sailor
- No past medical history
- Deployed to Spain in 2012 on mefloquine
- Experienced unease, anxiety, and foreboding, followed by auditory hallucinations, paranoia, and insomnia
- Subsequently developed cognitive impairment, tinnitus, disequilibrium, and “wavy” and rotational vertigo
• Normal rotary chair testing, enhanced right-sided VEMP, falls on CDP SOTs 5 and 6 that were considered aphysiologic.

• On specialist referral to ENT, ageotropic torsion then brief rightbeat nystagmus on right DH; geotropic then downbeat nystagmus on left DH; pure downbeat positional nystagmus without fixation in supine head-hanging position, not reversing on sitting, suspicious for brainstem lesion near vestibular nuclei.

Vignette #4

• 47 year old male with nightmares, anxiety, dizziness, and episodic “cliff edge” vertigo after mefloquine

• Spontaneous upbeating nystagmus suppressed on fixation; borderline slow vertical saccade velocities

• Normal MRI and CDP, normal VNG, DH, & calorics; on RCT, VOR borderline low gains, fast nystagmus decay on bidirectional step testing

• Considered consistent with a central process
Vignette #5

- 37 year old male with nightmares, anxiety, paranoia, panic, photophobia, tinnitus, dizziness, and vertigo after mefloquine in 2002
- On VNG, slow saccade velocities, low gain in counterclockwise OPK, non-fatiguing left beating nystagmus, not stopping with fixation on right DH; on RCT, fast nystagmus decay on counterclockwise testing
- Considered consistent with a central process, possibly in the velocity storage mechanism
“Confounding” of PTSD and TBI Diagnosis

- According to military authors writing for the CDC, mefloquine “confounds the diagnosis and management” of PTSD and TBI

- Confounding
  - Separate causal pathway to outcome
  - Correlation between exposure and confounder
Confounding

Exposure to Stressors

- Insomnia
- Nightmares
- Depression
- Anxiety
Confounding

Exposure to Stressors

Other Exposure

Insomnia
Nightmares
Depression
Anxiety
Confounding

Exposure to Stressors

Confounder

assumed causation

independent causation

correlation

Insomnia
Nightmares
Depression
Anxiety
Confounding

Exposure to Stressors 

Mefloquine 

assumed causation 

actual causation?

Insomnia 
Nightmares 
Depression 
Anxiety 
Dizziness 
Vertigo

DSM-5 PTSD Criterion H

- The 2013 revision to the DSM added a diagnostic exclusion
- Per Criterion H, the symptoms that would otherwise contribute to a PTSD diagnosis cannot be due to the effects of a medication
- In practice, symptoms such as nightmares or insomnia that first began with mefloquine use, prior to any trauma, should not contribute towards PTSD diagnostic criteria
“Quinism”

• Evidence of common signs and symptoms caused by quinoline drugs
  – Quinine, quinacrine, primaquine, chloroquine, mefloquine, tafenoquine

• Evidence of a common etiology and pathophysiology
  – Focal brainstem and limbic neurotoxic injury

• An emerging disorder with significant potential relevance to epidemiology, treatment, and disability compensation
Some Quinism “Red Flags”

- Sleep disturbances: severe insomnia, nightmare disorder, central and obstructive apnea
- Vestibular symptoms: dizziness, disequilibrium, vertigo, paresthesias
- Central visual symptoms: photophobia, accommodative disorder, binocular dysfunction
- Panic, agoraphobia, “supermarket syndrome”
- Cognitive dysfunction, personality changes, paranoia, psychosis
- Esophageal and GI conditions
- Neuroendocrine conditions
Where to Refer?

• Neurology
• ENT / Neuro-otology (*rotary chair testing*)
• Neuro-ophthalmology / Neuro-optometry
• Sleep Medicine
• Neuropsychological testing
• Speech-Language Pathology
• WRIISCs and NICoEs