



FOB Warhorse Bunker, by Timothy Lawn, watercolor/ink on paper, Iraq, 2005.
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Chapter 19

MEFLOQUINE AND POSTTRAUMATIC STRESS DISORDER

REMINGTON L. NEVIN, MD, MPH*

INTRODUCTION

THE DEVELOPMENT OF MEFLOQUINE

THE HISTORY OF MEFLOQUINE USE IN US MILITARY POPULATIONS

CLINICAL FEATURES OF MEFLOQUINE INTOXICATION

CHRONIC EFFECTS OF MEFLOQUINE TOXICITY

CONFOUNDING OF DIAGNOSTIC AND STATISTICAL MANUAL OF MENTAL DISORDERS-IV POSTTRAUMATIC STRESS DISORDER DIAGNOSTIC CRITERIA

FORENSIC APPLICATIONS

SUMMARY

**Doctoral Student, Johns Hopkins Bloomberg School of Public Health, Department of Mental Health, 624 North Broadway, Room 782, Baltimore, Maryland 21205; formerly Major, Medical Corps, US Army*

INTRODUCTION

Mefloquine (previously marketed in the United States as Lariam [F Hoffmann-LaRoche Ltd, Basel, Switzerland]) is a neurotoxic quinoline-derivative originally developed by the US military for treatment and prophylaxis of malaria.¹ Originally the US military's preferred antimalarial drug, mefloquine has been widely used during overseas operations, but recently lost favor because of its association with severe neuropsychiatric side effects. These side effects are now the subject of a "black box" warning, which must appear on the US product label, accompanied by advisories that psychiatric side effects may last years after dosing, and that neurological side effects may be permanent.² Recent insights suggest that neuropsychiatric side effects may be considered to be symptomatic of a potentially life-threatening intoxication syndrome (or toxidrome) common to other members of the quinoline class.³

Although the drug was originally thought to have few psychiatric effects,³ symptoms of mefloquine intoxication are now known to affect a majority of users when the drug is administered at treatment doses of 1,250 mg,⁴ and at least a sizeable minority when administered at prophylactic doses of 250 mg weekly.⁵ Lariam package inserts now warn that "very common" psychiatric symptoms (including abnormal dreams and insomnia) may affect greater than 10% of prophylactic users, and "common" psychiatric symptoms (including anxiety and depression) may affect 1% to 10% of prophylactic users.^{6,7} Earlier product inserts emphasized that should certain "prodromal" symptoms develop, including anxiety, depression, restlessness, or confusion, the drug must be discontinued to avoid a "more serious event," which is likely a euphemism for fulminant intoxication and neurotoxicity.³ Today's Lariam product information expands on this guidance

to add nightmares to the list of "prodromal" symptoms⁸ and caution that any "change in mental state" is reason to immediately discontinue the medication.⁹

Many of the symptoms of the mefloquine toxidrome, including vivid nightmares, personality and affective change, disordered sleep, irritability, anger, difficulties with concentration, dissociation, and amnesia, may mimic prior *Diagnostic and Statistical Manual of Mental Disorders IV* (DSM-IV) criteria B-D, as well as DSM-5 criteria B-E for posttraumatic stress disorder (PTSD), and may last long after discontinuation of dosing. According to a publication by the Centers for Disease Control and Prevention, these symptoms "may confound the diagnosis and management of posttraumatic stress disorder."¹⁰ As mefloquine has been commonly prescribed to military personnel during combat deployments,¹¹ risk of intoxication may therefore have frequently coexisted with pervasive exposure to DSM-IV and DSM-5 criterion A stressors, particularly confounding the PTSD diagnosis in military and veteran populations exposed to the drug.

In this chapter, the history of mefloquine's development and its use within the US military are reviewed, and then the clinical features of the mefloquine toxidrome are described with its chronic effects. The chapter then highlights how specific psychiatric symptoms caused by mefloquine may readily confound PTSD diagnostic criteria, particularly those of DSM-IV, which unlike DSM-5 did not specify a diagnostic exclusion for symptoms resulting from a medication's effects. This review ends with a discussion of applications of this information to forensic psychiatry and presents a representative case study illustrating challenges in the diagnosis of mefloquine intoxication among military personnel.

THE DEVELOPMENT OF MEFLOQUINE

Mefloquine, known chemically as bis(trifluoromethyl)-(2-piperidyl)-4-quinolinemethanol, is a 4-methanolquinoline structurally related to quinine. Although the first synthesis of mefloquine was reported in 1969,¹² the drug is closely related to the synthetic compound 4-quinolyl- α -piperidylcarbinol first reported 3 decades earlier in 1938.¹³ Mefloquine differs from this previously synthesized compound (later known as SN 2,549)^{14(p1062)} solely by adding two trifluoromethyl groups (CF₃) at the 2 and 8 positions of the quinoline nucleus, which help to impart antimalarial activity and metabolic stability. The antimalarial utility of the trifluoromethyl group was first identified by the Germans,

who in 1938 had synthesized what was considered a less toxic version of chloroquine (then known as resochin) featuring the substituent.^{14(p1236),15} Trifluoromethylated antimalarial compounds were later extensively studied in the US military's World War II antimalarial drug discovery program, during which time more than 13,000 compounds were investigated¹⁶ for their antimalarial activity, of which 103 were subsequently tested in humans.¹⁷ Of these, many quinoline derivatives demonstrated unacceptable toxicity, causing symptoms of "nervousness," "lassitude," or confusional or paranoid psychosis,¹⁷ and extensive neurotoxic lesions throughout the brainstem and limbic system in humans.¹⁸

Although 4-methanolquinolines related to mefloquine were initially the subject of significant human testing during the World War II era program, investigation of these compounds as antimalarials appears to have been abandoned in favor of the 4-aminoquinolines,¹⁹ including chloroquine (previously known as SN 7,618), which despite early German concerns of toxicity became the mainstay antimalarial for the next 20 years.²⁰ By the early 1960s,²¹ owing ostensibly to concerns of rising chloroquine resistance, the US military undertook a second large scale drug discovery program,²² during which time more than 300 4-methanolquinolines were evaluated,¹⁹ including some that had been previously tested from the World War II era program.

THE HISTORY OF MEFLOQUINE USE IN US MILITARY POPULATIONS

Although many of the early Phase I and Phase II trials of mefloquine were conducted among prisoners,^{31–33} contract employees,³¹ and residents of Third World countries,³⁴ the drug was also tested on US military personnel at various times during the 1980s before its licensure by the Food and Drug Administration (FDA) in 1989.³⁵ Although details of many of these experimental uses are not available, in one published study from 1988 not listed in the Lariam New Drug Application,³⁴ 134 soldiers were administered 250 mg of the drug weekly for 4 weeks while on exercises in Thailand.³⁶

In the very early years following the drug's FDA licensure in 1989, mefloquine appears to have been used infrequently by the US military, possibly because of concerns for its initially complex and potentially confusing dosing regimen, which recommended every-other-week dosing after the fourth week.³⁷ For example, there was little mefloquine used among US personnel during the 1990–1991 Persian Gulf War.³⁸ However, in 1991, mefloquine was the subject of a large randomized trial to assess tolerability during simplified dosing regimens,³⁷ during which time 203 US Marines were administered the drug.³⁵ This study noted a high prevalence of prodromal symptoms among subjects. Vivid dreams, described as often “terrifying nightmares with technicolor clarity,” occurred in 7% of mefloquine users; irritability in 4%; concentration problems in 5%; anger and moodiness each in an additional 1%; and insomnia in 25%.³⁵ At the time, the US package insert cautioned to discontinue use of the medication if “anxiety, depression, restlessness, or confusion” developed, but the incidence of these specific symptoms was not assessed, and it appears that this guidance was not consistently communicated or enforced during the trial.³⁵ For example, 2 of the 203 participants, after failing to discontinue the drug at the

mefloquine (known as WR 142,490) quickly emerged as the favored of these drugs based on the results of limited human testing,^{23,24} which indicated the drug was free of the serious psychiatric side effects, including suicide and psychosis, that had characterized related quinoline antimalarials,²⁵ including chloroquine.^{26–28} Soon after its reported first synthesis, mefloquine had been singled out by the US Army for larger scale commercial synthesis, first by the Aerojet Solid Propulsion corporation,¹² and then in anticipation of commercialization, by F Hoffmann-La Roche Ltd.²⁹ So rapid was the testing of the drug in field settings that one researcher noted, “Phase II clinical trials threatened to outstrip needed Phase I testing.”³⁰

onset of severe insomnia, were ultimately hospitalized for severe depression and suicidal thoughts, which were later deemed due to “preexisting” conditions. Despite these findings, the drug was deemed “well tolerated” and recommended for expanded use.³⁵

With the seemingly favorable results of these trials and following a change in the package label to recommend once-a-week dosing,^{39,40} documented large-scale military use of mefloquine began in earnest in 1992–1993 during Operation Restore Hope in Somalia,⁴¹ where mefloquine sensitivity had been demonstrated in prior field studies.^{42,43} Although precise usage figures are uncertain⁴⁴ during much of the estimated 163,000 person weeks of deployment time in Somalia,⁴⁵ published reports⁴⁶ suggest a majority of more than 30,000 US personnel ultimately stationed there^{44,47} received mefloquine under command-supervised weekly administration,⁴⁴ with some initial users of the alternative drug—doxycycline—switching to mefloquine⁴⁸ on command directive.⁴⁹ Based on published reports³⁵ the incidence of discontinuation of mefloquine resulting from prodromal symptoms was exceptionally rare; in one study, only 1 in 344 soldiers discontinued mefloquine.⁵⁰ Contrary to today's guidance, soldiers in Somalia reporting vivid dreams or “lightheadedness” (which should be taken to indicate confusion or difficulties in concentration⁵¹) do not appear to have been directed to discontinue the drug.⁵⁰ Although “more serious events” including psychosis or hospitalization were not reported in the definitive published study of mefloquine use among US personnel in Somalia,⁴⁴ postmarketing surveillance reports describe a US military member on mefloquine who was hospitalized and experiencing psychosis, confusion, depression, fatigue, hostility, agitation, and paranoia⁵²; more than 120 Somalia era veterans later complained of psychiatric symptoms, including flashbacks, night-

mares, paranoia, and suicide attempts,⁵³ linked to their use of the drug. One soldier later described the effects of the drug as “so much darkness in your brain and so much violence,” and reported suffering lasting confusion, paranoia, and suicidal and homicidal ideation.⁵²

Despite early concerns for its safety,⁵⁴ mefloquine nevertheless became the drug of choice for most US military operations,⁵⁵ but its regular use soon attracted further concern. In 1996 officials were informed that family members of US Special Forces soldiers had noted “drastic” changes in mood, impulsivity, and irritability linked to their spouses’ use of the drug.⁵⁶ Soon after the start of the Afghanistan war in 2001, where the drug was also used frequently,⁵⁷ one veteran of early operations in Pakistan complained of hallucinations and delusions while taking the drug and of subsequently suffering “frightening flashes” of anger. Another family member reported his son was hospitalized with hallucinations, anxiety, and depression.⁵²

By the summer of 2002, after a rash of homicides and suicides at Fort Bragg had been committed by soldiers returning from Afghanistan, concerns of behavioral toxicity had attracted national media attention.^{52,58} Two soldiers murdered their wives and then immediately committed suicide⁵⁹; another soldier murdered his wife and subsequently killed himself in prison the following year.⁶⁰ According to family members and acquaintances, the soldier had been experiencing delusions, paranoia, strange behavior, and uncharacteristic fits of rage after returning home.^{52,56,61} All three soldiers had taken mefloquine; two had documentation of taking the drug on deployment before the killings⁶²; while the third had also been taking the drug,⁶³ according to unit members, but had stopped some months prior.

In all three cases, there were marital issues; at least one case was suspected of being exacerbated by the drug’s behavioral effects.⁵⁶ In two cases, the soldiers “returned early from Afghanistan specifically in response to their requests for emergency leave to address perceived marital distress.”⁶² Numerous barriers to marital counseling and behavioral care at Fort Bragg were identified in the final report of the formal Army investigation, which concluded that “marital discord” was a “major factor” in the killings.⁶²

Although the formal Army investigation failed to rule out mefloquine as the cause of violence in at least two cases where unambiguous records of prescribing existed,⁵² as a result of no history of mefloquine use in a fourth unrelated case who did not deploy, the report concluded the drug was “unlikely to be the cause of this clustering.”⁶²

When military operations began in Iraq in 2003, medical intelligence reports had suggested the possibility of chloroquine-resistant malaria.⁶⁴ To “err on

the side of caution,” widespread use of mefloquine was directed throughout the theater.^{64,65} Although recordkeeping of prescribing was poor⁶⁶ and many prescriptions⁶⁷—particularly those in theater⁶⁸—were never documented,⁶⁹ electronic records revealed a sharp increase of documented prescribing to active duty personnel—from 18,704 in 2002 to 36,451 in 2003.⁶⁵ Representing a conservative lower estimate of use, for the 12 months ending October 2003⁷⁰ electronic records documented approximately 45,000⁷¹ to 49,000 mefloquine prescriptions, comprising more than 1 million 250 mg tablets.⁷²

In the summer of 2003, FDA implemented new requirements that all mefloquine prescriptions be accompanied by written warnings specifying that users seek medical attention if prodromal symptoms of intoxication develop.⁶⁹ However, surveys indicated that few deploying service members received written or even verbal warnings,^{63,65,67} whereas public statements by senior military physicians⁷³ and formal policy guidance served to undermine awareness of the drug’s frequent intoxicating effects. An Army memorandum issued the previous year in 2002 erroneously stated psychiatric symptoms from mefloquine occurred only “at a rate of one per 2,000 to 13,000 persons.”⁷⁴ This memorandum understated the risk by at least a factor of 100: a randomized clinical trial the year before had demonstrated that prodromal symptoms of anxiety and depression each occurred in 4% of users,⁷⁵ whereas the mefloquine package insert continued to make clear that should these prodromal symptoms develop, the drug “must be discontinued.”

The awareness was so poor among US forces of mefloquine’s written warnings that even fulminant cases of intoxication were misattributed to other causes. One soldier, who received no warnings of the mefloquine’s intoxicating effects,⁷⁶ suffered panic attacks and hallucinations while taking the drug. On demanding medical attention for his concerns, he was charged with cowardice and later with dereliction of duty for failing to obey orders.⁷⁷ Only months later did physicians suspect mefloquine in the etiology of his disorder.

A case report, whose publication was delayed by nearly a decade,⁷⁸ described an airman who continued to take mefloquine despite experiencing restlessness, depression, and severe emotional lability. With continued dosing his condition progressed and he was subsequently hospitalized with hallucinations and suicidal ideation.⁷⁹ Other media reports highlighted similar cases of hallucination, impulsive aggression, and paranoia in one returned soldier⁸⁰; and anxiety, depression, and paranoia in other soldiers taking the drug.⁶⁵ In subsequent congressional testimony, one

soldier who had experienced 3 weeks of nightmares before discontinuing the drug testified that “every soldier I know has problems with it.”⁷³ Military leaders were quick to dismiss such testimony as “perception,” cautioning “that perceptions can become realities” should it become “widely held that this medication is widely problematic.”⁷³

In a prior report, military leaders had been warned that “[a] possible consequence of continued use of mefloquine . . . is that the negative publicity surrounding the drug may lower compliance among deployed personnel.”⁸¹ Despite evidence of such lowered adherence,⁷³ military leaders favored the drug because of its perceived efficacy, weekly dosing schedule, and lower cost relative to better tolerated⁷⁵ daily drugs.⁸¹ In August 2003 a group of 225 Marines sent ashore in Liberia were instructed to take mefloquine. Earlier that year, these Marines had served briefly in Iraq and Djibouti where they had also been directed to take mefloquine. Following 10 days ashore in Liberia, an outbreak of febrile illness subsequently affected 80 of the 225 Marines; 36 remained shipboard to be managed empirically, while 44 were medically evacuated for presumed malaria. On epidemiological investigation, 21 of the 44 (45%) endorsed poor medication adherence.⁸² Although military physicians had claimed anonymous surveys showed that forgetfulness, not prodromal symptoms, was “overwhelmingly” the cause of poor adherence,⁸³ later published reports revealed that surveys were not anonymous, raising questions regarding the validity of these responses. The report also speculated that compliance “may have been even lower than reported because some Marines may have overestimated their adherence for fear of administrative sanctions.”⁸²

Formal meetings were soon convened to discuss rising concerns about the drug, including the problem of low adherence.⁸⁴ In prior meetings, leadership had been encouraged to be more “up front about the side effects”⁴⁹ to counter low adherence, but better enforcement of directly observed therapy was also proposed. Although expanded use of better tolerated⁷⁵ daily drugs had been recommended, concern was expressed at their cost and convenience in directly observed therapy.⁴⁹ One presenter, arguing the merits of its weekly dosing, predicted that “[m]ilitary personnel will die of malaria if [mefloquine is] not available.”⁷²

In spite of continued leadership’s support for the drug, these meetings failed to counter overwhelming public and congressional⁸⁵ concerns; despite claims of continued safety and efficacy, most first-line use of mefloquine was subsequently discontinued by 2004. Having learned in July 2003 that what little malaria there was in Iraq was sensitive to chloroquine, the

US military switched briefly from mefloquine to chloroquine by early 2004⁸⁶ before discontinuing chemoprophylaxis altogether by late 2004.^{65,84,87} In Afghanistan, forces gradually switched to doxycycline following an official report linking mefloquine to a soldier’s suicide.⁸⁸ Subsequent US Army policy made doxycycline the drug of choice in Afghanistan, with mefloquine remaining only in limited use, notably in operations in Djibouti and throughout the Horn of Africa.⁸⁹

By 2006, public and congressional focus on the drug had lessened, and partially in response to rising rates of malaria,⁹⁰ widespread use of mefloquine in Afghanistan was subsequently resumed. Later analyses of electronic records suggested that nearly 40% of those deployed that year had been prescribed mefloquine before deployment.¹¹ However, these analyses also revealed widespread problems with prescribing. As preexisting behavioral health conditions, such as anxiety and depression, had been known to confound recognition of developing prodromal symptoms of intoxication, the mefloquine product insert had long noted that the drug should be used with caution in such patients. In subsequent years, this language was strengthened and the drug was formally contraindicated in such patients.⁹¹ Amidst earlier concerns that soldiers with such behavioral health conditions were on occasion being inappropriately deployed,⁶⁷ in congressional testimony, military leaders had promised such soldiers would not be prescribed mefloquine⁶⁷ and would be offered an alternate medication⁹² as previously formalized in Army policy.⁷⁴ By 2007, analysis suggested that 1 in 10 deploying soldiers had behavioral health conditions that contraindicated taking the drug; of these, later analysis revealed that 1 in 7 with such behavioral health conditions had been erroneously prescribed the drug, contrary to existing policy and package insert guidance.¹¹

With rising recognition of the difficulties in ensuring the drug’s proper prescribing, military authors writing for the Centers for Disease Control and Prevention would later note that the “continued routine use of mefloquine” had become “less desirable.”¹⁰ A 2009 Army policy memorandum prioritized the use of daily medications and stated that “[m]efloquine should only be used for personnel with contraindications to doxycycline.”⁹³ This policy was extended throughout the Department of Defense later in the year.⁹⁴ Although these policies led to widespread prescribing changes in Afghanistan,^{95,96} mefloquine was briefly reprioritized for continued use in Africa⁹⁷ after the death from malaria of a sailor deployed to Liberia revived concerns about the effectiveness of daily medi-

cations.⁹⁸ However, counterbalancing concerns for the risks of mefloquine, particularly when administered under conditions of directly observed therapy,⁹⁹ soon also arose after a sailor experienced significant toxicity from the drug.¹⁰⁰ By late 2011, following a meeting of key military stakeholders,¹⁰¹ deployment guidance even for sub-Saharan Africa had prioritized the use of safer daily medications, including the combination drug atovaquone-proguanil and the broad-spectrum antibiotic doxycycline, and emphasized that mefloquine use “should be restricted to individuals unable to receive either of the other regimens.”¹⁰² In early 2012, after concerns arose that some service members were continuing to be prescribed the drug contrary to policy, senior military health officials ordered an additional review of mefloquine prescribing practices,¹⁰³ and a prominent editorial called for military officials to better explore “possible alternatives.”¹⁰⁴ Further restrictions were formalized in 2013, when mefloquine was declared the “drug of last resort”¹⁰⁵ and reserved only for those “with intolerance or contraindications to both first-line medications” atovaquone-proguanil and doxycycline.¹⁰⁶

Although falling short of a complete prohibition, policy changes beginning in 2009 served to “casually sideline”¹⁰⁷ what was the last remaining product of the largest drug discovery effort of its time,^{107,108} replacing its use in part with a drug that was the military’s antimalarial drug of choice 20 years earlier and before mefloquine’s 1989 introduction.⁵⁰ In the 3 years from 2007–2009, electronic pharmacy records indicate US military facilities issued 48,538 mefloquine prescriptions to active duty personnel; but in the 2 years from 2010–2011 following the policy changes, only 11,494 prescriptions were issued.¹⁰⁹ Popular news reports that cited purchase figures confirmed the substantial decline in the drug’s use and concluded that the US Army had effectively pushed mefloquine “to the back of its medicine cabinet.”⁹⁵ Intriguingly, almost 4 decades earlier, influential authors had cautioned that mefloquine “promises to be broadly useful” to the US military, but noted presciently that “[i]f this promise is not realized, it will doubtless not be for lack of antimalarial activity, but rather because of toxicological attributes not identified in the small-scale studies pursued to date.”¹⁹

CLINICAL FEATURES OF MEFLOQUINE INTOXICATION

As is now understood, the “toxicological attributes” of mefloquine include potent effects on the limbic system and brainstem,^{3,99} where the drug may accumulate¹¹⁰ relative to other areas of the brain.^{55,111} Experiments in animal models have demonstrated that at physiological concentrations, mefloquine may induce disruptions in electrical activity in the amygdala¹¹² and hippocampus,^{113,114} with effects on fear conditioning¹¹⁵ and memory.¹¹⁶ Mefloquine may also induce disruptions in limbic inhibition^{117,118} with resultant effects on mesolimbic dopaminergic tone.^{119,120} Mefloquine disrupts autonomic responses in the brainstem¹²¹ and affects electrical activity in the pedunculopontine nucleus,^{122,123} striatum,¹²⁴ and inferior olive.^{125,126} These effects and others may explain the predominance of disturbances in emotion, memory, and sleep, and symptoms of complex neurologic dysfunction commonly observed in cases of mefloquine intoxication.³

As noted in the original product insert, certain symptoms, including “anxiety, depression, restlessness, and confusion,” should be considered prodromal to a “more serious event,” likely a euphemism for fulminant intoxication and neurotoxicity.³ Such intoxication may manifest with predominant features of restlessness and anxiety^{127–129} and may begin with a prodrome of insomnia,¹³⁰ nightmares,⁷⁹ unease,⁹⁹ phobias,^{131,132} and a sense of impending doom and restlessness¹³¹; and it may progress quickly to include

outright paranoia,^{130,133} persecutory mania,¹³⁴ panic attacks,¹³⁵ and impulsive aggression.¹³⁶ Intoxication may also include features of confusion^{133,137} and psychosis, and may begin with a prodrome of vivid dreams⁷⁹ and progress quickly to include delusions,¹³⁸ magical thinking,¹³⁹ dissociation,¹⁴⁰ derealization,¹⁴¹ and auditory,¹⁴² olfactory,¹⁴¹ and visual hallucinations⁵¹ and illusions.¹⁴³ Hypnopompic states,^{77,79} spatiotemporal disorientation,⁹⁹ and anterograde amnesia may also occur.^{144,145} Significant personality change⁹⁹ and depression,^{79,133,146} morbid curiosity toward dangerous objects¹⁴⁷ and death,⁵⁴ suicidal ideation and attempt,¹⁴⁸ completed suicide,^{107,149} and acts of violence¹⁵⁰ are not uncommon.

Many of the symptoms of the mefloquine toxidrome are best understood as a manifestation of an underlying toxic limbic encephalopathy.⁹⁹ Toxic encephalopathy (or “acute brain syndrome”¹⁵¹) was first noted before the drug’s US licensure,^{145,152} and a risk of “encephalopathy of unknown etiology” was noted on the original US product inserts. Similar to what is observed with various forms of limbic encephalitis,³ this toxidrome may also be accompanied by neurological effects including seizures^{153–156} and symptoms referable to the midbrain or brainstem nuclei, including paraesthesias,^{54,157,158} disequilibrium,⁹⁹ parkinsonism¹⁵⁹ and other movement disorders,¹²⁸ vertigo,^{99,160} visual disturbances,¹⁶⁰ and autonomic dysfunction.^{161,162}

CHRONIC EFFECTS OF MEFLOQUINE TOXICITY

Although early product labeling failed to warn of the possibility of chronic effects, by the summer of 2002, after numerous published reports^{160,163,164} of chronic symptoms lasting 1 year or more, the US package insert was updated to note that “anxiety, paranoia and depression . . . hallucinations and psychotic behavior” on occasion “have been reported to continue long after mefloquine has been stopped.”⁵⁸ By 2004 a Veterans Health Administration’s informational letter cautioned that use of the drug could be associated with symptoms “that persist for weeks, months, and even years after the drug is stopped.”^{38,165} Today’s US mefloquine product labeling warns that psychiatric side effects may last years after dosing and that neurological side effects may be permanent.² The Lariam product information acknowledges a risk of “long lasting serious mental health problems” and warns of a risk of an “irreversible” condition should the medication not be stopped at the onset of certain prodromal symptoms.⁸

Although the chronic effects of mefloquine toxicity had previously been attributed to the long half-life of

the drug, as would be expected of a highly lipophilic compound¹⁶⁶ that concentrates in brain and is subject to complex and heterogeneous neuropharmacokinetics,¹⁶⁷ psychiatric effects show little correlation with measurable serum levels.^{168,169} With the benefit of current knowledge, many of the chronic effects of mefloquine are best understood as reflecting central nervous system toxicity resulting from the drug’s heterogeneous accumulation in the brain,¹⁷⁰ which remains poorly understood but appears subject to multifactorial genetic^{171,172} and pharmacologic influences.^{173,174}

Evidence of the central nervous system toxicity of mefloquine was noted as early as 1996,¹⁷⁵ and by 2003 the drug had been clearly demonstrated to cause neurotoxic lesions in the brainstem of animal models at physiological concentrations.¹⁷⁶ Authors noted that mefloquine’s psychiatric effects could be plausibly due to “[i]mpairment or loss of neurons in specific regions of the brain” and that “[m]efloquine-induced neurotoxicity in the limbic system might be responsible for reported disturbances in emotion.”¹⁷⁶

CONFOUNDING OF DIAGNOSTIC AND STATISTICAL MANUAL OF MENTAL DISORDERS-IV POSTTRAUMATIC STRESS DISORDER DIAGNOSTIC CRITERIA

Given the relatively high prevalence of psychiatric symptoms including nightmares, anxiety, and memory and sleep problems caused by mefloquine, military authors writing for the Centers for Disease Control and Prevention have noted that use of the drug may “confound the diagnosis and management” of PTSD.¹⁰ Unlike many other *DSM-IV* disorders, the diagnostic criteria for PTSD provided no exclusion for symptoms resulting from a medication’s direct effects. It is therefore conceivable that patients experiencing mefloquine’s toxic effects may have appeared to meet formal PTSD diagnostic criteria, even if the etiology of the symptoms was distinct from the effects of traumatic stress.

How commonly the symptoms of mefloquine intoxication might have complicated the PTSD diagnosis in military settings is unclear. An underpowered¹⁷⁷ retrospective study of US military personnel found an increased risk of hospitalization for diagnosed anxiety disorders and PTSD among those with prior mefloquine exposure as compared to those deployed without mefloquine exposure,¹⁷⁸ but the results of this study were not statistically significant. Despite formal recommendations, no similar study of outpatient encounters has been published,⁸⁴ and no long-term studies of veterans have been performed to rule out a higher incidence of such disorders after mefloquine

exposure. Anecdotal reports, however, suggest that symptoms caused by mefloquine may be highly comparable to those of PTSD and may have plausibly confounded or complicated diagnosis.^{38,165} In one documented case, a soldier prescribed antidepressants and mefloquine on the same day was diagnosed within 5 weeks with anxiety disorder and organic brain disease suggestive of the toxic encephalopathy of mefloquine intoxication. The soldier was subsequently diagnosed with depression, suicide attempt, and PTSD by week 10.¹⁷⁹ Although the actual number of those potentially receiving a PTSD diagnosis under similar circumstances is far from certain, the possibility that at least some diagnosed cases may represent missed diagnoses of mefloquine intoxication seems apparent.

In deployed settings where US military personnel may have been exposed to mefloquine, the ubiquity of potentially traumatic experiences may have had the effect of significantly reducing the specificity of *DSM-IV* diagnostic criteria. For example, in an early study of returning service members from Afghanistan and Iraq, encompassing the period of widespread mefloquine use, between one-quarter and one-half of subjects reported feeling “in great danger of being killed;” more than one-third to one-half reported witnessing individuals wounded or killed,¹⁸⁰ consistent with *DSM-IV* criteria of experiencing, witnessing, or being

confronted by events involving “actual or threatened death or serious injury” (criterion A1). Similarly, intense fear, helplessness, or horror (criterion A2), while seemingly specific to external traumatic stressors, may be readily confounded by the onset of panic attacks or certain symptoms of psychosis,¹⁸¹ which may solely result from mefloquine’s effects but whose specific symptoms may reflect fearful or horrific content that may risk being attributed to an external stressor in the context of military deployment.⁷⁷

Other symptoms of mefloquine intoxication may also closely mimic many criteria B (re-experiencing) and C (avoidant/numbing) symptoms. For example, intrusive recollections (criterion B1), possibly reflecting the effects of daytime or hypnopompal hallucinations,⁷⁹ are a common feature of case reports.⁷⁷ Similarly, distressing nightmares (criterion B2), frequently described as “vivid” and “terrifying,”³⁵ are a pervasive feature of intoxication, affecting more than one-third of military users during prophylactic dosing.⁵ Similarly, again possibly reflecting the effects of hallucinations, symptoms consistent with flashbacks (criterion B3) are commonly reported with reports of directed actions in response to perceived threats.⁶⁵

As the symptoms of mefloquine intoxication may present independent of a specific external traumatic stressor, individuals suffering from its effects may not exhibit psychological distress or physiological reactivity specifically in response to traumatic reminders (criteria B4 and B5), but instead may experience such reactions unpredictably and without obvious triggers.⁷⁹ In certain environments, where traumatic reminders are prevalent or where ascertainment or recall bias may identify these preferentially on examination, such symptoms may be erroneously attributed to traumatic reminders, which confounds diagnosis. Similarly, while the effects of mefloquine intoxication may result in nonspecific avoidance behaviors, these may risk being similarly misattributed to an external traumatic stressor (criteria C1 and C2) on examination. Conversely, because of the lasting effect of mefloquine on memory and its association with anterograde amnesia,¹⁴⁵ the inability of those suffering intoxication to recall specific aspects of a presumed trauma (criterion C3) coincident with dosing may—in some contexts—be erroneously deemed as meeting diagnostic criteria.

Because of the effects of mefloquine on mood and its association with personality change and symptoms of depression,^{79,133,146} those suffering from intoxica-

tion may exhibit diminished interest in significant activities (criterion C4) or show detachment from others (criterion C5).⁷⁹ Similarly, a restricted range of affect (criterion C6) may reflect the direct effects of the drug on affect or be confounded by mild symptoms of confusion,^{133,137} dissociation,¹⁴⁰ or derealization.¹⁴¹ Since those experiencing intoxication from mefloquine may also experience numerous poorly understood somatic and psychiatric complaints, they may experience a sense of foreshortened future (criteria C7).⁷⁹

Criterion D (hyperarousal) symptoms resulting solely from mefloquine may also be problematic to distinguish from those from a specific traumatic etiology and may be highly prevalent in cases of mefloquine intoxication. Sleep problems (criterion D1), a prominent feature, may affect a sizeable minority of prophylactic users,³⁵ with severe cases of insomnia and “restlessness” commonly reported.⁹⁹ Irritability (criterion D2), also a commonly reported symptom,⁵⁶ may have multiple etiologies, including reflecting an effect of mefloquine-induced vestibular dysfunction or cognitive impairment.⁹⁹ Concentration problems (criterion D3) are also commonly reported in cases of mefloquine intoxication, including problems with executive, visuospatial, and verbal memory, and deficits in orientation and attention.¹³³ Similarly, symptoms of sensory overload, described as “a whole rush of stuff going into your brain at one time,”⁷⁹ may be taken as symptoms of hypervigilance (criterion D4). Lastly, exaggerated startle response (criterion D5), while not commonly reported in the literature, is consistent with persistent heightened anxiety and autonomic dysfunction, and may be expected to co-occur with other lasting symptoms of mefloquine intoxication.

Many symptoms of mefloquine intoxication have been reported to last at least 1 month (criterion E), and case reports describing persistent symptoms lasting a year or more after dosing have been reported.^{160,163,164} In some cases, certain psychiatric symptoms, such as irritability, may become relatively more prominent following resolution of acute intoxication.⁹⁹ Cases of fulminant intoxication, particularly those featuring panic attacks or symptoms of psychosis, will be likely to cause significant acute distress and functional impairment (criterion F).⁷⁹ However, even chronic symptoms, such as memory impairment and irritability, may be significantly functionally impairing, particularly if accompanied by vestibulopathy or disequilibrium or other chronic neurological sequelae.⁹⁹

FORENSIC APPLICATIONS

As a result of the significant similarities among conditions, the forensic psychiatrist may be asked to evaluate a prior PTSD diagnosis for the possible con-

founding effects of mefloquine intoxication. Such an evaluation may be critical in determining eligibility for disability and adjudicating claims of harm, or in

legal cases where ascertaining the possible effects of the drug may be relevant.³

Although this chapter has established that many of the psychiatric symptoms caused by mefloquine may be indistinguishable from those resulting from traumatic exposures, the frequent association of mefloquine intoxication with chronic neurological symptoms—including vertigo, disequilibrium, and certain visual disorders including accommodative dysfunction and photophobia—may permit the effects of mefloquine to be disentangled in forensic evaluation from those resulting from the effects of combat stress.³

In particular, mefloquine's previously demonstrated brainstem neurotoxicity, together with the known class effects of related quinoline antimalarials in inducing multifocal neurotoxic lesions throughout the midbrain and brainstem nuclei, may—in some cases where these are clinically significant—provide an opportunity for objective demonstration of injury. Although the neurotoxic lesions produced by the quinolines are typically too small to be visualized on conventional imaging studies, and although routine neurological evaluation is typically nonspecific in such cases, specialty consultation with neuro-optometry, neuro-otology, or ear, nose, and throat specialists with a focus on identifying central nervous system injury may document objective evidence of subtle brainstem dysfunction, and thus prove a valuable component of the forensic psychiatric evaluation. Similarly, as the complex signs and symptoms of mefloquine neurotoxicity may mimic or be mistaken for a malingering diagnosis, or of somatoform, conversion, or personality disorder, such specialty evaluation should be considered essential when these additional diagnoses are under consideration.³

Establishing a diagnosis of mefloquine intoxication with or in place of a PTSD diagnosis ultimately requires establishing plausible evidence of mefloquine exposure. However, as mefloquine has been commonly mass prescribed in US military settings¹⁰ without individualized documentation, traditional methods of establishing evidence of exposure may be unavailable. For example, research in Afghanistan in 2006 suggested 30% of soldiers had begun their malaria prophylaxis in theater,¹⁷⁹ where prescribing has traditionally been beyond the capture of electronic medical records systems.⁶⁸ Among Army personnel, who comprised the majority of personnel deployed in the period, there were only 6,514 mefloquine prescriptions electronically documented between October 2007 and September 2008 to active duty personnel¹⁷⁹; and in 2008 there were 8,574 such prescriptions among Army personnel overall.⁹⁵ In contrast, during an approximately equal period, a total of 32,404 bottles of 25 mefloquine tablets was delivered to supporting

logistics bases overseas in Europe and Southwest Asia, comprising sufficient mefloquine for 16,000 year-long prescriptions or 32,000 6-month refills.¹⁷⁹ A comparison of these figures suggests a significant proportion of these were electronically undocumented. As a result, in US military settings, where individualized documentation is acknowledged to have been poor,¹⁰³ presumptive evidence of exposure to mefloquine may rest on the service member demonstrating possession of remaining prescribed mefloquine tablets, or if these are unavailable, reporting a reliable history of taking the drug and being assigned to a military unit to which the drug was issued by policy or procedure. Evidence of this may on occasion be found in individual service records, or in other cases this may be attested to by other unit members or by knowledgeable medical or command authorities.

For illustrative purposes, a representative case of mefloquine intoxication is presented in the accompanying case study. This case demonstrates the characteristic features of intoxication mimicking acute stress reaction and subsequently being diagnosed as PTSD, while demonstrating some of the pathognomonic features of subsequent neurotoxicity. These features permitted a plausible claim of causality to be established despite potentially confounding factors including alcohol use and brain injury. This case illustrates the utility of being able to demonstrate plausible mefloquine exposure and the value of diagnostic insights gleaned from appropriate specialty consultation.

Case Study 19-1: In September 2003, a previously healthy 33-year-old male soldier newly deployed to Iraq presented to a combat stress control unit complaining of the acute onset 4 days earlier of severe anxiety, paranoia, visual and auditory hallucinations, persecutory delusions, and confusion, with worsening physical complaints of dizziness and photophobia. The soldier was a member of a US Army Special Forces unit located at a small team house in the city of Samarra. The night his symptoms began, he reported being jolted awake by a “hyperrealistic” and terrifying nightmare in which his room was exploding in a giant fireball. Believing the team house was under attack and believing he saw the enemy bursting into his room,⁶⁴ he grabbed his weapon and quickly donned his combat gear and proceeded to conduct a tactical room-to-room search of the house's sleeping quarters. He was horrified to perceive the sleeping members of his unit as mangled corpses, vividly reminiscent of the corpse of an insurgent he had seen the evening before in conjunction with a mission. With insight that he was hallucinating, he returned to his room anxious, paranoid, and unable to sleep.

The next day, he informed his supervisor of his psychotic symptoms and his fears that he was having a “nervous breakdown.” That day, as he interacted with team members, he perceived them as horrific “talking skeletal remains,” and he heard nearby muffled voices plotting his death. His persecutory delusions worsened the following day when, after insisting on medical care for his symptoms and fearing for

their safety, his unit members disarmed and confined him while they awaited his transport to a nearby combat stress control unit. Over the next 2 days, as he awaited evaluation, he was repeatedly advised that he had a choice to return to his duties or face legal repercussions for what appeared to be cowardly behavior.

His medical history was significant only for a sports concussion in his mid-teens, for which he was briefly hospitalized and had made a complete recovery. He had no personal or family history of mental illness. He was serving as a human intelligence collector and interrogator, had passed a full background investigation, and had been granted a top secret security clearance.

His only medication was mefloquine, which he had begun approximately 2 weeks before his departure to Iraq. He had taken his third 250 mg weekly dose 2 days before the onset of his symptoms. In the days before his arrival in Iraq he had consumed a modest amount of alcohol with meals while awaiting air transport. Before the acute onset of his psychosis, he had experienced no prodromal symptoms, including vivid dreams, personality change, anxiety, restlessness, depression, or confusion.

At the time of initial evaluation, his psychiatric symptoms were attributed to a combat stress reaction or to a panic attack stemming from his initial encounter with the deceased Iraqi insurgent.¹⁷³ An adverse reaction to mefloquine was not suspected. The soldier had been issued the drug months after the FDA first required issuance of the mefloquine medication guide “wallet card,” but despite this requirement, he did not receive either the wallet card or the verbal or other written instructions on under what conditions to discontinue the drug. Unaware of the information contained in this documentation, he continued to take mefloquine for 2 additional weeks after the onset of his symptoms of anxiety and confusion for a total of five doses.

Although combat stress control had recommended local treatment, his unit had elected to initiate legal proceedings. He was swiftly returned to the United States and subsequently charged by the US Army under Article 99 of the Uniformed Code of Military Justice with cowardice, a crime that carries a maximum penalty of death.

On seeking civilian counsel, and based on intense media interest in his case, his legal team became informed that his symptoms might be related to mefloquine and proposed exposure as a defense. The soldier’s use of mefloquine was initially challenged by the US Army, owing to lack of documentation of a prescription. However, exposure was conceded when the soldier demonstrated possession of his remaining tablets.

In October 2003, the charge of cowardice was dismissed without explanation and immediately replaced with a charge of willful dereliction of duty. This charge was dismissed in December 2003, after which the soldier spent months while additional charges were considered and his medical concerns were evaluated. During this period, a PTSD diagnosis was assigned. Although his psychiatric symptoms gradually improved, his physical symptoms including vertigo, disequilibrium, photophobia, and accommodative dysfunction became relatively more prominent.

In March 2004, following an independent medical evaluation arranged through his counsel, a military physician concurred that “[b]ased on the [soldier’s] historical account of the anxiety symptoms that occurred in Iraq, it is very plausible that the symptoms that he experienced could be related to his use of mefloquine.”¹⁷³ On subsequent evaluation, an ear, nose, and throat specialist documented nystagmus, and he was diagnosed with a vestibular injury and “likely [mefloquine] toxicity.” Brainstem injury was suspected.¹⁷³

Upon being informed of this diagnosis, in June 2004 the US Army terminated all legal action against the soldier, explaining that “[a]dditional information became available over time that indicates that [the soldier] may have medical problems that require treatment.”¹⁷⁴

Although the US Army never formally acknowledged causal attribution to mefloquine, the soldier was temporarily medically retired in April 2005, and he was formally medically retired for his vestibular disorder and a PTSD diagnosis in August 2006. In subsequent years, many of his chronic symptoms of disequilibrium gradually improved following physical and vestibular rehabilitation, but a decade after onset he complains of being occasionally short tempered and irritable and experiencing intermittent vertigo and photophobia.

SUMMARY

In settings where use of the drug cannot be ruled out, symptoms of the mefloquine toxidrome—including nightmares, anxiety, and memory and sleep problems—may plausibly confound a PTSD diagnosis and other stress disorders related to military service. With this chapter, it should be evident that the mefloquine toxidrome—long and previously overlooked—may have significant relevance in military forensic psychiatry, particularly in the evaluation of soldiers and veterans with prior service in Somalia, Iraq, Afghanistan, and other areas of the world where the drug is likely to have been used since its development more than 40 years ago.¹⁸²

In addition to aiding and informing current practice, the observations in this chapter may also suggest the intriguing historical question of whether lasting effects similar to those now attributable to mefloquine may also have occurred from the administration of other closely related quinoline antimalarial drugs, including quinacrine during World War II and chloroquine during the Vietnam War. In this respect, it is intriguing that PTSD evolved considerably as a diagnostic entity in the years following the Vietnam War, mirroring in some ways the greater understanding of stress disorders in the years following World War II.^{183,184} The potential for significant confounding of

the effects of intoxication from antimalarial quinolines with those caused by war-related traumatic exposures provides a fascinating glimpse into the complexities

and challenges of military forensic psychiatry and points to untapped opportunities for more important research.

DISCLOSURES

Dr Nevin receives consulting fees from attorneys representing clients alleging harm from their exposure to mefloquine, and he has been retained as an expert witness in criminal and civil cases involving civilians and military personnel exposed to the drug.

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