Psychiatric Side Effects of Mefloquine: Applications to Forensic Psychiatry

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Mefloquine (previously marketed in the United States as Lariam®) is an antimalarial medication with potent psychotropic potential. Severe psychiatric side effects due to mefloquine intoxication are well documented, including anxiety, panic attacks, paranoia, persecutory delusions, dissociative psychosis, and anterograde amnesia. Exposure to the drug has been associated with acts of violence and suicide. In this article, we discuss the history of mefloquine use and describe plausible mechanisms of its psychotropic action. Mefloquine intoxication has not yet been successfully advanced in legal proceedings as a defense or as a mitigating factor, but it appears likely that it eventually will be. Considerations for the application of claims of mefloquine intoxication in forensic settings are discussed.

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Mefloquine is a 4-quinolinemethanol antimalarial first synthesized in the early 1970s[1] by researchers affiliated with the United States military's Walter Reed Army Institute of Research (WRAIR).[2] The drug's development was the culmination of a 10-year drug discovery effort, during which time more than 300,000 compounds were screened for their antimalarial properties.[2] Of a handful of compounds active against chloroquine-resistant strains of *Plasmodium falciparum* malaria that demonstrated seemingly favorable toxicity profiles,[2] mefloquine (initially known as WR 142490) was selected for further development and testing in humans.[3]

To secure the drug's commercial manufacture and its continued availability, intellectual property rights and research related to mefloquine were transferred at no cost to F. Hoffman-La Roche Ltd. (Roche).[4] The company pursued regulatory approval and marketed the drug to civilian travelers in the United States under the trade name Lariam® after its initial Food and Drug Administration (FDA) licensure in 1989.[5] Owing to its efficacy, presumed safety, and convenient dose schedule that facilitated prophylactic use, mefloquine was soon identified as the drug of choice[6,7] for use by U.S. travelers to areas of chloroquine-resistant malaria at a dose of one 250-mg tablet weekly.[8,9]

Early prelicensure studies on mefloquine were conducted predominantly among male prisoners,[2,10] military personnel,[5,11,12] and subjects in third-world countries.[11,13,14] Although vertigo and nausea were commonly reported in these early trials, in the absence of sensitive and unbiased prospective reporting[15] the drug was considered to be largely free of the severe psychiatric side effects that had characterized the related antimalarial compounds chloroquine[16,17] and quinacrine.[18,19]

The purported safety of mefloquine was so well established that when reports of severe psychiatric side effects, including amnesia, confusion and psychosis, first emerged in the literature following the drug's early European licensure,[20–23] these symptoms were frequently dismissed as coincidental[24] or were later attributed by influential authors to the stresses of overseas travel, recreational drug use, or pre-existing or latent mental illness.[25–27] Despite

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continued reports in the literature of severe psychiatric side effects following the drug's U.S. licensure, it was only in 2001, after the drug had been in widespread use for over 15 years and the first formal blinded and controlled prospective studies were conducted in a representative civilian population,[28,29] that mefloquine's potent psychotropic capability became more widely appreciated. Results of these and subsequent trials have since demonstrated that the incidence of specific neuropsychiatric symptoms including nightmares, anxiety, and psychosis during prophylactic use are each at least 100 times more common[28,30,31] than has been previously reported.[32–35]

More recent reports of suicide[31,36,37] and suicidal ideation,[38–47] and studies linking the drug to acts of violence[48] have raised additional safety concerns.[49,50] As public awareness of the potential dangers of mefloquine have grown,[51–54] and civil litigation related to the drug has increased,[55,56] mefloquine has lost significant market share in the United States[57] in favor of safer and better tolerated antimalarial medications.[28] Today, mefloquine is no longer considered the drug of choice, either in therapy or in chemoprophylaxis of malaria.[58] Roche recently withdrew Lariam® from the U.S. market, although generic forms remain widely available.[59]

Use of mefloquine had previously been encouraged among United States overseas diplomatic staff[60] and Peace Corps volunteers.[8,25] Mandatory use of the drug was also broadly directed among deployed U.S. military service members.[61,62] Recently, growing awareness of the drug's inappropriate prescribing[33,34,63] to service members with mental health contraindications,[39,62,64] including those with a history of posttraumatic stress disorder and traumatic brain injury,[34,63] and poor documentation of its prescribing[64] has significantly diminished the utility of mefloquine in deployed settings.[65] As a result, today, mefloquine is considered the drug of last resort by U.S. military policy,[66,67] to be used only when doxycycline and the combination drug atovaquone/proguanil (Malarone) cannot be used.[58,65,68,69]

Because the drug is associated with an increased risk of violence[48] and psychiatric symptoms, users of mefloquine may be likely to be encountered in the civil or criminal legal systems. Current or past users of the drug may claim that exposure has caused physical or mental injury. The psychiatric effects of the drug may be featured in future forensic evaluations, and thus forensic psychiatrists may be called to comment on the drug's effects. In this review, the psychiatric side effects of mefloquine and the putative pathophysiology of these effects are discussed, and specific forensic concerns are considered. This information is anticipated to be useful when forensic psychiatrists are asked to consult on cases involving military personnel and veterans, civilian travelers, and employees on overseas assignment who claim legal implications from their exposure to the drug.

Psychiatric Side Effects

According to the current U.S. mefloquine package insert,[70] psychiatric symptoms associated with prophylactic mefloquine use include abnormal dreams, anxiety, paranoia, agitation, confusion, memory impairment, and hallucinations. Despite over 20 years of licensed use, the underlying pathophysiology of these side effects has been poorly understood.[71] Recent insights[37,40,72] suggest that these side effects result directly from the accumulation of the drug within and acting on specific targets in the brain. In this section, the putative pathophysiology of mefloquine intoxication is described in further detail following a discussion of its typical clinical presentation.

Clinical Presentation

Case reports suggest that mefloquine intoxication may begin with a variable prodrome which may present with personality change,[40] unease,[40] anxiety,[73–75] phobias,[76,77] and a sense of impending doom and restlessness.[76] These prodromal symptoms may progress to outright paranoia,[38,46,73,74,78–81] delusions,[46,47,78,81] magical thinking,[79] persecutory mania,[73,78,81–83] restlessness,[84] aggression,[22] and panic attacks.[44,85,86] Confusion[38,39,87–91] and symptoms of depression[38,39,44,47,92] have also been reported. Such symptoms have been reported after only a single 250-mg tablet[40,93–96] and may progress in severity with subsequent doses.[40,96]

Since the drug's initial licensing in 1989,[97] the U.S. mefloquine package insert has warned that "if signs of unexplained anxiety, depression, restlessness, or confusion are noticed, these may be considered prodromal to a more serious event." The package insert further cautions that should these prodromal symptoms occur, "[i]n these cases, the drug must be discontinued."

Many, but not all,[96] users of mefloquine will correctly discontinue use of the drug at the onset of the unsettling prodromal symptoms of intoxication.[28] However, those with a history of mental illness may erroneously attribute such symptoms to their preexisting condition,[39] or have them obscured or confounded by psychotropic drug use.[39] Since 2002, mefloquine has therefore been contraindicated among those with a current or recent history of psychiatric illness,[61,62,97] as these users may be at greater risk of failing to discontinue mefloquine as directed. The current package insert cautions that mefloquine "should not be prescribed for prophylaxis in patients with active depression, a recent history of depression, generalized anxiety disorder, psychosis, or schizophrenia or other major psychiatric disorders."[70]

It is tempting to speculate that the "more serious event" referenced in the package insert is a euphemism for psychosis. Mefloquine psychosis was characterized as early as 1983,[89] and its early descriptions were consistent with the psychosis caused by related antimalarial compounds.[98–100] Mefloquine psychosis frequently includes auditory[40,73,80] or true visual hallucinations,[22,38,39,80,101] frequently involving religious or morbid themes.[102] Auditory hallucinations typically feature voices that may be incoherent or mumbling.[40,102] Some individuals report a sense of the presence of a nearby nondescript figure.[40] Olfactory hallucinations[103] have also been reported. The often vivid and terrifying nature of the hallucinations produced by mefloquine are illustrated by an early unindexed case report, similar to at least one other published report,[41] describing a man who jumped from his hotel room in the false belief that his room was on fire. Of note, vivid dreams or horrific, terrifying nightmares,[39,104] also frequently reported by users of mefloquine, are characterized as having "Technicolor clarity" and being "vividly remembered days later,"[5] suggesting that these may also be prodromal to or inform later symptoms of psychosis. Hypnopompic hallucinations and sleep paralysis have also been reported.[39]

Mefloquine psychosis may be distinguished from schizophrenia and certain other forms of psychiatric illness in that it may feature prominent characteristics of dissociation.[105] Symptoms of derealization[40,103] and depersonalization,[40,93,101] compulsions toward dangerous objects,[106] and morbid curiosity about death[43] may accordingly underlie reports of seemingly spectacular and impulsive[36] suicide, suicide attempt,[41] and parasuicidal behavior[40] associated with the use of mefloquine.

An additional distinguishing feature reported with mefloquine psychosis is impairment of short-term memory. Consistent with prodromal symptoms of confusion, this deficit may be marked by initial attentional disturbances, with later insufficiencies in short-term working and spatial memory,[40] verbal memory,[38] and temporospatial disorientation.[39,40,101,106–108] With preserved implicit memory, those affected by mefloquine intoxication may take part in highly complex and directed actions[74] and may even demonstrate improved psychomotor performance[109] during learned tasks, but may later experience profound anterograde amnesia to actions and events.[20,106,107]

Pathophysiology

These diverse psychiatric side effects may now be understood as manifestations of a single underlying pathophysiological process best characterized as a toxic limbic encephalopathy. The limbic system, which includes the hippocampus and amygdala, is one of the oldest portions of the brain phylogenetically and is considered the system responsible for preservation of the self and the species via the generation of emotions, reward mechanisms, sexual drive, and the formation of long-term memories, including fear memory.[110]

The current U.S. package insert for mefloquine warns of a risk of "encephalopathy of unknown etiology." However, unlike the more generalized toxic encephalopathies, including hepatic encephalopathy,[111,112] the acute effects of mefloquine appear to affect limbic and related structures predominantly, while relatively sparing much of the cortex.[58] As a result, clinically, the symptoms of limbic encephalopathy resulting from mefloquine intoxication appear very similar to those observed with the various forms of limbic encephalitis[113] and limbic epilepsy.[114] Although the underlying molecular targets are distinct and while the etiology of limbic encephalitis and epilepsy are variable, a pathophysiological mechanism shared in common among these conditions appears to be a dysfunction of limbic inhibitory interneurons, which contributes, among other effects, to dysregulated limbic dopaminergic neurotransmission.[58,115]

Mefloquine is highly lipophilic[116] and may accumulate in the limbic system[117] relative to other areas

of the brain,[118,119] where it acts to disrupt a form of direct intercellular electrical communication[120] that is essential for coordinated inhibitory control. Gap junction channels, composed of proteins called connexins, are involved in coordinated synchronization of neuronal activity, particularly of inhibitory interneurons[121] found throughout the limbic system.[122] At concentrations consistent with limbic accumulation, mefloquine has been demonstrated to inhibit electrical coupling of neurons with effects on limbic inhibition[123,124] and resultant mesolimbic dopaminergic tone.[125,126] In dysregulating limbic inhibition, this mechanism may mimic to some degree what is also seen with intoxication by phencyclidine (PCP),[127] ketamine,[128] and other dissociative amnestics and hallucinogens,[129–131] whose effects share many schizomimetic properties in common with those of mefloquine intoxication and limbic encephalitis.

In addition to a dose-dependent progression, symptoms of mefloquine intoxication may exhibit a waxing and waning presentation. It is tempting to speculate that in some cases, this presentation may reflect the clinical course of an underlying limbic status epilepticus[114] or limbic seizure[132–134] kindled by the drug.[135] In this regard, it is reasonable to speculate further that simultaneous use of alcohol or certain other drugs together with mefloquine could lower limbic seizure threshold or cause a further dysregulation of limbic inhibitory interneurons,[125] contributing to a risk of sudden potentiation. Reports describing seizures and psychotic reactions immediately following alcohol ingestion are well represented in the literature,[42,136,137] and alcohol use is frequently raised as a potential confounding factor in cases of severe reactions to the drug.[27,138]

Careful neuropsychological testing reveals that mefloquine intoxication may induce very specific deficits, including in word finding, processing speed, verbal learning, and auditory and visual memory[38,39,40] broadly suggestive of dysfunction of the hippocampus, as is observed to be caused by mefloquine in experimental studies.[139–141]

While characteristically affecting limbic centers, the effects of mefloquine intoxication may extend beyond the limbic system. As is frequently reported with limbic encephalitis,[142,143] limbic brain injury,[144] and intoxication from PCP and ketamine,[127,128] mefloquine intoxication may also result in complex behavioral changes, including social and behavioral disinhibition,[78,101] irritability,[39] heightened or altered sexual libido,[81,144] and impaired judgment,[40] suggestive of involvement of the frontal lobe or the prefrontal cortex. Similarly, reports of very complex visual illusions distinct from hallucinations[40,80,85] suggest extralimbic involvement encompassing the visual pathways. Reports of multifocal myoclonus[145,146] and deficits in motor speed[38,39,40] and motor learning[147] are suggestive of further involvement of the basal ganglia and inferior olive.

As with certain forms of limbic encephalitis,[142,148,149] limbic encephalopathy resulting from mefloquine intoxication may also progress to involve the brainstem,[40] and consequently users of mefloquine may experience numerous physical symptoms, including nausea and emesis, which are broadly referable to interconnected limbic and brainstem centers.[150] Additional probable brainstem symptoms reported with mefloquine use include vertigo, disequilibrium, nystagmus, photophobia, and accommodative dysfunction suggestive of involvement of the vestibuloocular nuclei[40,70,151]; paresthesias of the extremities and face,[43,45,70,152] suggestive of posterior column[153] or trigeminal nerve nuclei involvement; autonomic dysfunction including temperature sensitivity,[39] bradycardia, bradypnea, and postural orthostatic tachycardia syndrome[45,154,155]; and gastrointestinal complaints including abdominal pain,[156] esophageal dysmotility, anorexia,[45] and diarrhea, signaling possible involvement of the vagus nerve dorsal motor nuclei. Rare reports of anticholinergic syndrome[157] may indicate further brainstem involvement.

As is observed in cases of limbic encephalitis,[158] PCP toxicity,[159] and limbic seizure,[160] limbic and associated brainstem encephalopathy may also cause chronic symptoms arising from permanent neurotoxicity[40,158] and neurodegeneration of limbic and brainstem centers.[160] While long-term follow up of mefloquine intoxication is only rarely documented in the literature,[45] vertigo lasting as long as 18 months has been reported.[94] Supporting experimental findings of mefloquine neurotoxicity[153,161–163] are observations that related antimalarial compounds[99,164–168] cause a multifocal pattern of microscopic lesions, visible on careful histopathologic study, that affect numerous brain and brainstem regions, but are typically too small to be visualized with conventional magnetic resonance imaging (MRI).[40]

Mefloquine has itself recently been demonstrated to induce similar microscopic lesions in the brainstem of animal models.[153]

Forensic Applications

Mefloquine has been implicated in many cases of aggressive violence[169–172] and in cases of behavior change linked to nonviolent criminal conduct,[173,174] but we know of no case in which exposure to the drug has been successfully used as a defense or raised to mitigate criminal responsibility at trial. Similarly, mefloquine has been frequently linked to suicide and self-harm,[30,169,175–177] but to the authors' knowledge this association has never been a factor in any successful and publicly documented legal action. In addition, both military and civilian users of mefloquine have advanced claims of harm and damages in civil courts,[55,56,178] but the outcomes of many of these cases have not been made publicly available.

Historically, the forensic application of a claim of mefloquine intoxication has been made challenging by missed diagnosis and the attribution of psychiatric effects to other causes.[178] These problems may now be ameliorated by an improved understanding of the unique clinical presentation of mefloquine intoxication and by insight into the pathophysiology of related neurotoxic effects.[40] Successful forensic application of a claim of mefloquine intoxication today rests on establishing that plausible exposure to the drug has occurred and in demonstrating the onset of characteristic or pathognomonic signs or symptoms of intoxication and subsequent neurotoxicity, in temporal association to exposure and to the reasonable exclusion of other plausible etiologies, by record review, careful clinical history, or neuropsychiatric evaluation and in consultation with other medical specialists.

Exposure

The forensic application of a claim of mefloquine intoxication begins with establishing plausible evidence of exposure. In cases where clear documentation of individual prescribing exists in the medical record or if an individual has retained individually labeled medication, exposure may be readily proven or conceded. However, as mefloquine is commonly mass prescribed as a public health measure,[65] often without individualized documentation or labeling, unequivocal evidence of exposure may frequently be unavailable. In U.S. military settings, where individualized documentation may be poor[64] and widespread experimental use before licensure is known to have occurred,[2,5,12] presumptive evidence of exposure may rest on the individual's reporting a reliable history of taking the drug and of being assigned to a military unit to which the drug was issued by policy or procedure,[62] evidence of which may on occasion be publicly available or may be found in individual service records.

In cases of individual travelers for whom records have been misplaced or are not available, presumptive evidence of exposure may be established by a process of ruling out the prescribing of alternative drugs as plausible options. For example, mefloquine exposure should be considered highly probable among U.S. travelers who report a reliable history of taking a single tablet weekly[9] for malaria prophylaxis during travel to malaria-endemic areas with documented chloroquine resistance,[3,35] where use of weekly chloroquine would have been inappropriate according to prevailing recommendations[65] and published standards of care.[179–181]

In cases of more recent use where exposure remains in contention, demonstration of the drug or its metabolite in body fluids may be required. Owing to the drug's exceptionally long excretion half-life of approximately one month,[182,183] sensitive testing may provide direct evidence of exposure, even many months after final use. Because of its lipophilicity[116] and its recycling within the enterohepatic circulation, mefloquine may be excreted unchanged in the feces[12] and also may be found in the gastric juices and bile. As a result of the drug's accumulation in tissue,[12] it also may remain readily detectable at low concentrations in serum.[183] The various hydrophilic metabolites of mefloquine[182] may also be found at low concentrations in urine, bile, feces, and serum.[12] Testing for such compounds is readily available at analytic reference laboratories using established techniques.[12,184]

Mefloquine may also be occasionally detected in the cerebrospinal fluid,[21,185] although cerebrospinal fluid concentrations correlate poorly with concentrations in other compartments,[21,24,186] and cerebrospinal fluid[186] and serum concentrations themselves correlate poorly with brain accumulation[119,187] and with propensity to psychiatric effects.[24,188,189] Owing to the marked heterogeneity of mefloquine neuropharmacokinetics,[190] which remain poorly understood but are most likely subject to multifactorial

genetic[191,192] and pharmacologic influences,[193,194] any demonstration of mefloquine or its metabolite in any compartment of body fluid should be considered sufficient evidence of exposure and hence of potential brain accumulation and plausible intoxication.

Forensic Evaluation

While the unique presentation of mefloquine intoxication has been clinically well characterized in the present review, where exposure to mefloquine has been established, it is appropriate for the forensic psychiatrist to consider the diagnosis only when other psychiatric, medical, and substance-induced etiologies can be reasonably excluded as more probable causes. Advancing a defensible claim of mefloquine intoxication may therefore require the collaborative involvement of other medical specialists in addition to conventional neuropsychiatric evaluation, so as to rule out confidently other plausible etiologies, including those caused by other intoxicants and disease states. Careful record review, clinical history, and appropriate consultation, are essential for improving the specificity and sensitivity of the diagnosis.

As the characteristic limbic symptoms of mefloquine intoxication may closely mimic those caused by PCP, ketamine, and other dissociative amnestics and hallucinogens, the forensic psychiatrist considering a claim of mefloquine intoxication should address the possibility of voluntary or involuntary intoxication by these substances. Similarly, consultation with neurology should be considered to rule out closely related conditions such as limbic encephalitis or prior clinical history of limbic seizure, which in certain cases may also confound the diagnosis of mefloquine intoxication. While EEG is typically normal after both asymptomatic administration of mefloquine[195] and after some cases of mefloquine intoxication,[41,101] the presence of deep epileptiform or other abnormal activity,[20,84,107,137,186,196,197] in the absence of a clinical history of limbic seizure disorder, strongly supports the diagnosis of mefloquine intoxication or neurotoxicity.

In the absence of a clinical history of central injury or neurologic disorder, certain brain or brainstem findings, including persistent vertigo or disequilibrium,[40] or certain visual disorders[85] that develop subsequent to mefloquine exposure should be considered pathognomonic of mefloquine neurotoxicity. With appropriate history, these symptoms strongly support a claim of preceding intoxication. Specialty consultation with neuro-optometry, neuro-otology, or ear, nose, and throat specialists, with a particular focus on identifying central nervous system injury, should therefore be considered an invaluable component of the forensic evaluation, particularly in individuals previously considered for a diagnosis of somatoform, conversion, malingering, or personality disorder, which the complex signs and symptoms of mefloquine neurotoxicity may mimic or be mistaken for on casual evaluation.[40]

Routine brain imaging, including MRI, would be expected to be normal in most cases of mefloquine intoxication and neurotoxicity[40] and should not be considered essential for diagnosis, although such studies are useful, in that they may help to rule out potential confounding etiologies such as mass effect and stroke. Similarly, limited reports of positron emission tomography (PET) studies in cases of mefloquine intoxication have shown normal results,[137] but both PET and other functional imaging modalities may hold promise as additional experience is gained. Similarly, as the resolution of MRI improves to encompass the visualization of submillimeter lesions, conventional imaging may also hold promise. In this manner, histopathological findings at autopsy of characteristic multifocal brain or brainstem lesions, in the absence of other plausible etiologies, would also be pathognomonic of mefloquine neurotoxicity.

Among the challenges faced by the forensic psychiatrist in advancing a claim of mefloquine intoxication, even when other plausible conditions have been confidently excluded, is that many of its characteristic or pathognomonic signs and symptoms may remit with time.[40] Delays inherent to the legal system may therefore rob the traditional neuropsychiatric examination of much of its utility and sensitivity when conducting a forensic evaluation on an individual with mefloquine exposure. Detailed record review or the taking of a very careful clinical history may overcome some of these limitations by helping to identify the characteristic or pathognomonic signs and symptoms of intoxication or of subsequent neurotoxicity, in temporal association with exposure. As short-term memory loss and anterograde amnesia may limit the sensitivity of self-reported history,[101] obtaining collateral information from friends and family members[40,46,101] and from

fellow travelers[24,46] or service members[39] may be very helpful in this regard.

The presence of comorbid conditions may create a challenge for the forensic psychiatrist in evaluating a claim of mefloquine intoxication. For example, it is now well established that symptoms of mefloquine intoxication may confound the diagnosis of posttraumatic stress disorder and traumatic brain injury.[65] In certain cases, particularly those involving U.S. service members or veterans in whom these conditions may be common or may not be ruled out, the combination of certain symptoms on careful history, including auditory, visual, or olfactory hallucinations; confusion; and anterograde amnesia, developing in proper temporal relation to exposure, may aid in establishing the diagnosis of mefloquine intoxication to a reasonable degree of certainty, even in the presence of these comorbid conditions.

For illustrative purposes, we refer readers to a representative case of mefloquine intoxication published by United Press International.[173,174]

Conclusions

After 40 years of experimental and licensed use where the intoxicating properties of mefloquine were poorly appreciated, the drug now appears to have significant forensic importance. As public and professional awareness and understanding grows of the drug's significant psychotropic and neurotoxic potential, the prior use of mefloquine is nearly certain to get increasing attention within criminal, civil, and military courts. In cases involving suicide, homicide, and other acts of violence or criminal conduct associated with mefloquine exposure, or in cases where a litigant alleges that exposure to mefloquine caused harm, the forensic psychiatrist may be called on to provide expert testimony at trial. In all cases, the relationship between the drug's administration and the symptoms in question must be carefully evaluated and the temporal relationship adequately established,[198] to assign causation confidently. The pathophysiological insights presented in this review will aid the forensic psychiatrist in conducting an evaluation and in securing appropriate consultation in support of this goal.

As evidence is increasingly clear that use of mefloquine is associated with a risk of long-term injury and harm, as well as death of self or others, so long as the drug remains licensed for use, physicians who continue to prescribe it must exercise caution to minimize potential liability. Such care includes implementing careful screening for contraindications and ensuring consideration of alternative medications. The insights of the present review also emphasize the critical importance of thoroughly documenting patient education should mefloquine be prescribed, including informing patients of those prodromal symptoms that should compel them to discontinue the medication immediately and seek medical assistance.[96] However, as mefloquine intoxication that adversely affects decision-making may occur after only a single 250-mg tablet,[40] and as the onset of psychosis may take place suddenly and even without prodromal symptoms, such education may minimize, but will clearly not eliminate,[96] the risk of acute harm and subsequent neurotoxicity associated with the drug.

Our evolving experience with mefloquine raises questions about the potential for lasting behavioral effects from other antimalarial medications, including those presently under development,[199] as well as from those long assumed to be benign. Our experience with mefloquine reemphasizes that many decades may pass before the dangers of a drug are widely appreciated.[10,186] In the particular case of mefloquine, the reasons for this delay, including those related to the unusual circumstances of its development and initial testing[200] and its frequent use among individuals with limited personal autonomy and within highly regimented organizations, would clearly benefit from further exploration.

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