

Developed by the US Army, the malaria preventative and treatment mefloquine, trade name Lariam, can cause strong psychotic reactions and has been implicated in several military incidents, including the Fort Bragg murder-suicides of 2002. Consulting physician epidemiologist Dr Remington Nevin was motivated by personal experience to research the effects of the drug and call for a comprehensive ban.

By Berenice Baker

Dr Remington Nevin is a man on a mission. He believes that the potential terrifying psychoactive side effects of the widely prescribed anti-malarial drug mefloquine, also known by the trade name Lariam, are so harmful it should never be prescribed in a military context. He's even prepared to suggest the US military-developed drug should never have been licensed in the first place.

Although direct cause-and-effect has yet to be proven in a legal context, mefloquine was implicated in the Fort Bragg murder-suicides of 2002, in which four military wives were killed and two of the partners that killed them then committed suicide. When a Canadian airborne regiment involved in a mid 1990s humanitarian mission in Somalia committed seemingly inexplicable acts of violence, torture and aggression, they had been taking mefloquine. It has also been associated with a number of other stand-alone incidents. What kind of trigger could drive individuals otherwise considered physically and mentally fit – as they must have been to enter military service – into such uncharacteristic behaviour?

A horror film in a pill

“Mefloquine, and many related quinoline anti-malarial drugs, induce an idiosyncratic intoxication reaction that is often preceded by subtle prodromal [indicating the onset of a conditions] symptoms that may be difficult for an individual soldier to identify, particularly in combat settings,” explains Nevin.

“This syndrome can begin with subtle mood or personality change, a sense of unease or foreboding and vivid dreams. With time, and particularly with continued dosing, this can progress to frank anxiety, confusion, restlessness or depression. In certain susceptible individuals, with time or continued dosing, the syndrome can then progress further to frank psychosis, with paranoia, delusions, hallucinations and depersonalisation.

“This psychosis is particularly frightening, and is associated with a risk of particularly grizzly violence and suicide. I often compare this toxic reaction to that illustrated in M. Night Shyamalan’s film *The Happening*. At its worst, mefloquine is a horror film in a pill.”

Even according to the drug pack inserts, these frightening symptoms can occur in up to ten percent of people prescribed mefloquine.

Nevin's involvement began when he was trained by the US military as a preventive medicine physician, which included significant study in the prevention of travel- and deployment-related diseases including malaria. He was taught that the military-developed anti-malarials, including mefloquine, were generally a safe and well-tolerated and that these were ideally suited to military missions owing to their weekly dosing schedule. He says he received very little training, neither in the psychoactive or intoxicating properties of this class of drug, nor in how best to identify these reactions when they occurred.

He was alerted to the US Army's careless prescribing of mefloquine when in 2007 he was deployed with the elite 82nd Airborne Division as the senior public health physician for US forces in Afghanistan and had a role to play in the development of anti-malarial policy and particularly use of this drug.

"When I arrived to Fort Bragg en route to Afghanistan, I was dismayed to be told as I was boarding the plane to reach into a garbage bag, take a box of this medicine and begin taking it," he says. "I didn't receive any

counselling on potential side-effects, there was no proper patient education given, and I wasn't even given a box of medication with my name on it."

As Nevin's training had taught him that the drug was reasonably safe and effective, provided it was carefully prescribed, his initial concern was just that it was being mis-prescribed and sloppily used. But over the course of his deployment, he recognised through first-hand experience that the frequency of side-effects of this drug were much higher than his training had led him to believe.

"Many individuals in my unit suffered very disturbing vivid dreams, changes in personality and mood, very dramatically altered personality," says Nevin. "While it was very easy to attribute these psychological changes in the context of deployment to being in a warzone and being away from home, I recognised that many of these problems could very well be due to the drug."

"This psychosis is particularly frightening, and is associated with a risk of particularly grizzly violence and suicide."

It was the death of a well-liked soldier in Nevin's unit under mysterious circumstances that inspired him to investigate mefloquine in more depth. The otherwise healthy individual was found dead in his quarters with no evidence of suicide. Nevin realised during the course of the investigation he had been mis-prescribed mefloquine.

“He had been diagnosed with a number of health problems in the weeks immediately prior to his deployment, and he should not have been prescribed mefloquine with these medical questions unresolved,” says Nevin. “He was also prescribed a number of other drugs that should not have been taken simultaneously with mefloquine. I began to wonder whether mefloquine had played some role in his death.”

Descent into psychosis

Nevin's investigations uncovered case reports revealing some of the more severe reactions to the drug, the frequency of side-effects from the drug, and the way it had been improperly prescribed. It had been frequently given to soldiers with some contra-indications, such as a history of mental health problems or a simultaneous prescription of an anti-depressant.

“I was very shocked to discover that not only were a sizeable percentage of our soldiers deploying with prevalent mental health conditions, but that a sizeable percentage of them had been issued the drug,” says Nevin. “Even with my limited knowledge at the time I knew that this was very dangerous.”

Adding to the risk was the legalese-heavy language in which the drug inserts was written, seemingly more to protect the drug manufacturers rather than the person taking it. The onus was the person taking mefloquine to recognise developing psychological symptoms as evidence of impending intoxication and know to discontinue the drug on their own. “In practice this just isn’t plausible; it just doesn’t happen. Individuals continue to take the drug beyond the intoxicating threshold and descend into a psychosis that in many cases is life-threatening.”

During his investigations, Nevin also came under pressure from the military to cease his investigations, leading him to believe that this was a topic that the military felt very uncomfortable having explored, not least because it had developed mefloquine.

The use of mefloquine declined sharply during the Iraq War that started in 2003. Rather than representing recognition of the dangers it posed, the military claimed the decision to discontinue its use was due to the fact that there was a mefloquine-resistant strain of malaria. But over time, the military realised there was very little to no malaria in Iraq at all, and use of the drug subsided.

Unfortunately, this wasn't the end of the mefloquine story. The military medical community that had developed the drug and had been a strong advocate of its use was still very much of the opinion that this is a safe and effective drug in 2004 and into 2005. It is reported that mefloquine is given to inmates at Guantanamo Bay, and the British Ministry of Defence still issues it to 2,500 soldiers a year.

“They claimed the concerns in the press were being overblown and congressional interest in the drug was being misdirected,” says Nevin. “I believe the military capitulated to tremendous public and congressional concern in curtailing but not

prohibiting use of the drug outright. In Iraq the decision to continue was straightforward because there was no indication to use the drug in the first place.”

Nevin still hears reliable reports from some soldiers that the drug had been erroneously prescribed throughout the war to individual units or to individual deployments by physicians who simply weren't aware of current guidance. The drug was certainly widely used in Afghanistan while the war in Iraq was taking place.

Stress of deployment

It could be argued that the military environment exposes individuals to conditions that cause symptoms similar to the worst side-effects of mefloquine. Couldn't they be attributed to the like of post-traumatic stress disorder or traumatic brain injury?

“TBI has been relatively uncommon until relatively recently, and it would be unusual for a military to be deploying a large number of individuals who are symptomatic of a prior TBI or PTSD at time of deployment,” says Nevin. “The assumption is we deploy healthy individuals without symptoms and without prior medical problems.”

“The military is an unsafe environment to use drugs that require an individual to self-identify as having mental problems.”

The problem comes from the fact that during the deployment, individuals may be mildly anxious, have difficulty sleeping and may be suffering nightmares related to the stress of deployment. These may make it difficult for the individual to recognise the developing intoxication.

“Unfortunately there has been so little education within the military community into how to recognise an intoxication reaction to the drug that when they do occur, even in the early

weeks of a war, they are often erroneously attributed to things like combat stress or to a traumatic brain injury when they should more accurately be attributed to the effects of the drug,” says Nevin.

Nevin cites the case of Georg-Andreas “Andrew” Pogany, a Green Beret with a previously unsullied record who in 2003 became the first American soldier to face a court-martial for cowardice. Two years later, he received an honourable discharge for medical reasons related to PTSD – he was haunted by horrific incidents he witnessed during his service, including seeing an Iraqi cut in half by machine-gun fire. Pogany maintains his panic attacks may have been attributable to taking mefloquine.

“Pogany’s story is a perfect example of how even frank psychotic reactions are mis-attributed,” says Nevin.

Too dangerous for use

As the evidence against mefloquine mounts up, what would Nevin's ideal outcome be?

“Mefloquine is clearly too dangerous for continued use,” he says. “And future antiviral [drugs] which share these properties should be banned. The military is an unsafe environment to use drugs that require an individual to self-identify as having mental problems. The military has long had a stigma against identifying mental health problems. I suspect many of the early subjects on whom these drugs were tested, many of whom were military members, did not report the hallucinations, nightmares or anxiety and depression that occur as a result of using this drug.”

Safe alternatives are available. Doxycycline is a well-tolerated wide-spectrum antibiotic that is used to treat chronic conditions such as rosacea and acne and is well-tolerated in military environments. It is a current drug of choice with the US military in Afghanistan and no problems with it have been identified.

“In fact compliance with anti-malarial medication [taking the pills] has increased since we switched from mefloquine to doxycycline,” says Nevin. “I think that’s because soldiers recognise that mefloquine is a dangerous drug and doxycycline is more broadly accepted by soldiers now, because they know it doesn’t have the same dangerous psychiatric effects.”

Another effective anti-malarial with the trade name Malarone is available, but costs thousands of dollars, making it unattractive for military use. However, given the current cost of deploying a soldier to Afghanistan is roughly a million dollars a year, it would be a small price to pay to avoid the effects of mefloquine.

“But the lesson from mefloquine teaches us that many decades may pass before the dangerous toxic effects of a drug are realised,” warns Nevin. “So although I have hopes that Malarone will prove to be a generally safe medication, I do worry that in time we may learn it has dangerous properties too.”

An end to mefloquine? With many armed forces, including those of the UK, dragging their feet over withdrawing mefloquine, does it have a future in the military at all?

“I continue to question whether military forces, including those of the MOD, can use mefloquine safely in accordance with the package leaflet,” says Nevin.

“For example, the current UK package leaflet informs patients to ‘talk to your doctor’ if they experience ‘unusual behaviour’, ‘feeling restless’, ‘agitation’, ‘new or worsening feelings of anger or aggression’, and ‘disturbance of attention’. Owing to the difficulty of disentangling symptoms of drug toxicity from those due to deployment stress, in military settings, safe use of mefloquine would require the drug to be discontinued in a sizable minority, if not a majority, of its users. This makes its continued safe use in military settings impracticable,” says Nevin.

Mefloquine represents the perfect storm of a drug developed by the military, which is then forced to defend it years beyond when, based on the reported evidence, it should have been withdrawn.

Due to its military development and backing, this particular drug may quietly disappear off the radar rather than face an outright ban. But hopefully future generations of anti-malarials destined for military use will learn from the mefloquine nightmare.

<https://www.army-technology.com/features/featuremefloquine-the-militarys-deadly-malaria-treatment-4402886/>