U.S. Department of Veterans Affairs

VA's Charge to the Committee

Presentation for: NASEM Committee to Review Long-Term Health Effects of Antimalarial Drugs:

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BOTTOM LINE UP FRONT

- VA charges this committee to conduct a study to look at the side-effects (persistent or latent) of anti-malarial drugs.
- Concern about these drugs, and in-particular mefloquine (Lariam™) has been raised to VA by Veterans, Veteran Service Organizations, Congress, media and advocacy organizations.
  - Veterans allege devastating side effects from anti-malaria drug they were ordered to take. WUSA9 May 3, 2018
  - Lawyers claim anti-malarial drug to blame for soldier who killed 16 in Afghanistan massacre. Military Times May 18, 2018
  - The Quinism Foundation Calls on the Peace Corps to Deprioritize Use of Mefloquine and Investigate Claims of Misuse. Dec 2018
  - There has been Congressional interest, e.g. Senator Robert Menendez, NJ, Dec 2016 letter with response by former VA Secretary, Dr. David Shulkin.
  - Letters to VA, DoD and CDC leaders - Quinism Foundation.

BACKGROUND: MEFLOQUINE

- The World Health Organization estimates that in 2015, malaria caused 214 million clinical episodes and 438,000 deaths. https://www.cdc.gov/malaria/about/facts.html
- Many anti-malarials have been developed and tested. Lariam was discovered at the Experimental Therapeutics Division of the Walter Reed Army Institute of Research (WRAIR), Washington, DC in the 1970s. (Trenholme GN, Science 1975)
- In 2013 the US Food and Drug Administration added a boxed warning to mefloquine regarding the potential for neuropsychiatric side effects. The neurologic side effects can include dizziness, loss of balance, or ringing in the ears. The psychiatric side effects can include feeling anxious, mistrustful, depressed, or hallucinations. https://www.fda.gov/downloads/Drugs/DrugSafety/UCM362232.pdf
- Usage of mefloquine has decreased in the military in response to DoD Defense Health Agency memorandums in 2009 and 2013 that provided guidance on prescribing the drug.

CENTERS FOR DISEASE CONTROL AND PREVENTION

- Mefloquine is one of several options that can be used for the prevention and treatment of malaria. Mefloquine remains an important component of CDC's strategy to prevent malaria in travelers, especially those who are unable to take doxycycline and atovaquone-proguanil. https://www.cdc.gov/malaria/features/mefloquinelabeling.html

- Considerations when choosing a drug for malaria prophylaxis:
  - Recommendations for drugs to prevent malaria differ by country of travel and can be found in the country-specific tables of the Yellow Book.
  - No antimalarial drug is 100% protective and must be combined with the use of personal protective measures, (i.e., insect repellent, long sleeves, long pants, sleeping in a mosquito-free setting or using an insecticide-treated bed-net).
  - Considerations include the possibility of drug-drug interactions with other medicines that the person might be taking as well as contraindications, such as drug allergies. https://www.cdc.gov/malaria/travelers/drugs.html

CONCLUSIONS FROM RECENT PEER-REVIEWED LITERATURE

- DoD - Eick-Cost et al. Neuropsychiatric Outcomes after Mefloquine Exposure among U.S. Military Service Members Am. J. Trop. Med. Hyg. 2017.
  - "In summary, on a population level, this study did not find an association between mefloquine and NPOs [neuro-psychiatric outcomes] among U.S. military service members, with the exception of anxiety, tinnitus, and PTSD for some sub-cohorts."
- CDC-Tan et al. Long term health outcomes among Returned Peace Corps Volunteers after malaria prophylaxis,
  - "When excluding those with prior psychiatric illness, there were no differences in psychiatric diagnosis rates."
- Nevin et al. Identification of a Syndrome Class of Neuropsychiatric Adverse Reactions to Mefloquine from Latent Class Modeling of FDA Adverse Event Reporting System Data. Drugs R D 2017
  - "A distinct neuropsychiatric syndrome class was identified that was strongly and significantly associated with reports of mefloquine" using latency modeling of FDA Adverse Event Reporting System Data."
- VA-Schneiderman AI et al. Associations between Use of Antimalarial Medications and Health among U.S. Veterans of the Wars in Iraq and Afghanistan Am. J. of. Trop. Med. and Hyg. 2018
  - "No significant associations were found between mefloquine and MH measures. These data suggest that the poor physical and MH outcomes reported in this study population are largely because of combat deployment exposure."

TAFENOQUINE- NEWEST DRUG

- The prophylactic drug was originally discovered by researchers at the Walter Reed Army Institute of Research (WRAIR) in 1978 and the drug was developed jointly between the US Army and 60 Degrees Pharmaceuticals (60P) starting in 2014. It is the first FDA approved anti-malarial in 18 years. The drug was approved in July as GSK's Krintafel, a single-dose treatment for the prevention of relapse of Plasmodium vivax malaria in patients aged 16 years and older. https://www.mdmag.com/medical-news/fda-approves-tafenoquine-for-malaria-prevention

- Psychiatric adverse reactions including anxiety (<1%), abnormal dreams (<1%), and insomnia (3%) have been reported in clinical trials of the drug. https://www.rxlist.com/krintafel-drug.htm#warnings

- *Concerns over new anti-malaria drug fast-tracked by FDA.* WUSA 9 updated 5/13/18 discusses concerns raised primarily in Australian Veterans.

CHARGE TO COMMITTEE

- An ad hoc committee of the National Academies of Sciences, Engineering, and Medicine will conduct a study to assess the long-term health effects that might result from the use of antimalarial drugs by adults, in particular mefloquine, for the prophylaxis of malaria.

- The committee will examine the currently available medications, as approved by Food and Drug Administration and/or used by the Department of Defense, and of interest to the Department of Veterans Affairs. The long-term health effects are those that might occur in any organ system.

CHARGE (CONTINUED)

- These include latent effects that might be expected from their use by service members during deployment to areas with endemic malaria, such as Afghanistan. Special attention will be given to possible long-term neurologic effects, long-term psychiatric effects and the potential development of Posttraumatic Stress Disorder (PTSD).

- Additionally, the committee will consider approaches for identifying short-term, long-term, and persistent adverse health effects of anti-malarials. The committee will develop findings and conclusions based on its review of the evidence; the report will not include recommendations.

LIST OF MEDICATIONS (NOT TO BE EXCLUSIVE)

- Mefloquine
- Atovaquone-proguanil
- Chloroquine
- Doxycycline
- Primaquine
- Quinine Sulfate
- Hydroxychloroquine
- Halofantrine
- Mepacrine
- Tetracycline
- Sulfadoxine Pyrimethamine
- Tafenoquine - https://www.mdmag.com/medical-news/fda-approves-tafenoquine-for-malaria-prevention

SUMMATION

- This issue is of international importance.
- Involvement of multiple federal agencies.
- Thank you for serving on this NASEM committee.

- Questions?