

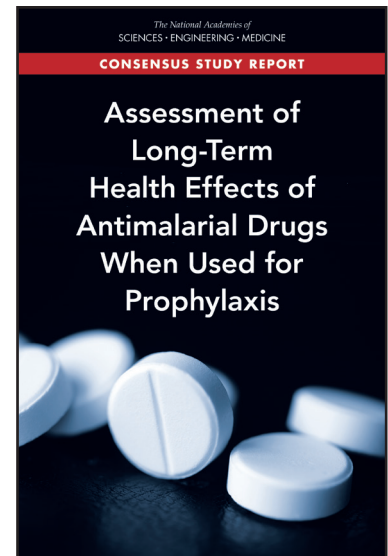


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Assessment of Long-Term Health Effects of Antimalarial Drugs When Used for Prophylaxis

Malaria is a constant threat for nearly half of the world's population. People who travel to highly-affected areas for business, leisure, or military support operations are also at risk. In 2018, the World Health Organization estimated that there were 228 million cases of malaria worldwide, with 405,000 resulting in death. As of 2019 six drugs are approved by the U.S. Food and Drug Administration (FDA) for malaria prophylaxis and are currently available by prescription: chloroquine, primaquine, mefloquine, doxycycline, atovaquone/proguanil (A/P), and tafenoquine. The concurrent and short-term adverse events for users taking these drugs are well documented. However, studies conducted to gain FDA approval are generally limited by small numbers of subjects and short follow-up periods, making it difficult to identify rare but potentially serious adverse events that may persist after the use of the drug has ended, or latent adverse events that do not appear until after use is completed.

Malaria has affected nearly every United States military deployment, and it remains an ongoing threat to those engaged in current conflicts in Southwest Asia and peace-keeping missions to Africa and Southeast Asia. Department of Defense (DoD) policy requires that service members deployed to malaria-endemic areas be issued antimalarial drugs and adhere to the drug-taking regimens. Concern with the potential for persistent adverse events has been raised by veterans, service members, and other users. In response to these concerns, the Department of Veterans Affairs (VA) asked the National Academies of Sciences, Engineering, and Medicine to convene an expert committee to assess the scientific evidence regarding the potential for long-term health effects resulting from the use of the six antimalarial drugs that have been approved by FDA and/or used by U.S. service members for malaria prophylaxis in the past 25 years, or were of interest to VA. VA specified mefloquine and tafenoquine as the two drugs of highest interest and importance and that persistent neurologic and psychiatric outcomes were of particular concern.



“[E]xisting evidence is inadequate or insufficient to conclude whether there is an increased risk of use of a particular antimalarial drug and most health outcomes.”

KEY FINDINGS AND CONCLUSIONS

Following a review of the available published research that was supplemented by information requests, FDA drug labels and package inserts, invited presentations on specific topics, and submissions from the public, the committee concluded that more research is needed to fully and more accurately assess the possibility of persistent and latent adverse health effects following antimalarial use. Even when there were multiple studies of the same drug and same outcome, the characteristics of the study populations and methods were so divergent as to be of questionable relevance to one another. The epidemiologic studies used different designs, populations, and analysis methods; examined disparate adverse events or outcomes; and used diverse methods to collect information. For some studies, the dosage of a particular antimalarial was different from that approved by FDA. Full adherence with the drug regimen was generally assumed, although research has shown this is not always the case.

While the committee recognized the real and serious persistent adverse events for some users of antimalarial drugs, existing evidence is inadequate or insufficient to conclude whether there is an increased risk of use of a particular antimalarial drug and most health outcomes. The committee found that the occurrence of concurrent adverse events enhances the plausibility that problems may persist after use of a drug.

Based on the epidemiologic studies and other supporting information, the existence of some persistent events for certain antimalarial drugs appears to be highly plausible but not sufficiently studied. In a number of instances, studies that found no evidence of an association were of sufficient size and quality that it is unlikely that there are truly large increases in common adverse events, but this did not preclude smaller effects or effects of rarer outcomes. Given the number of people who use antimalarial drugs, even such modest increases in rare events may lead to substantial impairment for the individuals who are affected and result in a large absolute number of adverse events.

The committee presents 31 conclusions regarding the level of association between exposure to a drug of interest and persistent or latent adverse events by body system (see the conclusions insert for a full list of all persistent or latent adverse events studied). Because veterans and active-duty military are the VA's popula-

tion of interest, studies of these groups were accorded considerable weight in the committee's deliberations. Other populations that use antimalarial drugs were also considered because these populations do not have some of the potentially confounding stressors, such as combat, typically found in military populations.

The committee concluded that there is sufficient evidence of an association between the use of tafenoquine and vortex keratopathy, a buildup of deposits in the eye that does not result in any clinical implications, such as loss of vision. However, all cases resolved within 3 to 12 months post-tafenoquine use. Associations for all other persistent or latent adverse events and use of the six antimalarials of interest were determined to be inadequate or insufficient. However, the committee also concluded that based on the existing epidemiologic evidence or supporting information, seven of the drug–outcome associations have a basis for further research.

Committee members considered the most plausible persistent adverse effects to be those that result from enduring concurrent events and thus gave additional weight to evidence for concurrent events in determining whether there is a basis for further research.

NEUROLOGIC AND PSYCHIATRIC OUTCOMES

Of the six drugs, concerns were greatest for mefloquine. Concurrent adverse neurologic and psychiatric events associated with the use of mefloquine are well recognized; however, epidemiologic studies that examined these outcomes at least 28 days post-drug-cessation do not indicate an increase of persistent neurologic or psychiatric events relative to other antimalarial drugs or no use of antimalarial drugs. The committee examined the results from three high-quality studies—all conducted using active-duty U.S. military or veteran populations—that reported PTSD diagnoses or PTSD symptoms and accounted for deployment and combat exposure. Following its review, the committee concluded that there is insufficient or inadequate evidence of an association between the use of mefloquine for malaria prophylaxis and persistent or latent psychiatric events, including PTSD. However, the committee concluded that there is a basis for further study of mefloquine use and associations of neurologic and psychiatric events.

“There is a sharp contrast between the amount of evidence concerning adverse events experienced while using antimalarial drugs and the effects experienced after the course has ended.”

Tafenoquine is a newly approved antimalarial drug and, like mefloquine, is contraindicated in persons with a history of psychotic disorders or current psychotic symptoms. None of the epidemiologic studies on tafenoquine included data on psychiatric adverse events for which the timing post-cessation was specified. In clinical trials the most common concurrent psychiatric adverse reactions for tafenoquine were reported to be sleep disturbances, depression or depressed mood, and anxiety. As such, the committee concluded that there was a basis for further study of persistent or latent psychiatric events.

ADVANCING RESEARCH ON ANTIMALARIAL DRUGS

Given the serious health consequences of malaria and the billions of people at risk of contracting it, antimalarial drugs will continue to be a necessary front-line defense for both active-duty military and other populations that travel to malaria-endemic areas. Studying the persistent and latent effects of exposures is challenging, and it is important to recognize that a perfect or complete understanding is likely unrealistic. However, that does not mean this research should not be done. To establish more definitive associations between use of antimalarial drugs and persistent adverse health impacts, the committee recognized the need for more studies that are designed to examine potential persistent outcomes and overcome the considerable weaknesses noted in the existing research. Such studies should include: explicit documentation of the antimalarial dosage used; the timing of both antimalarial drug use and symptom or event occurrence; extended follow-up of users that includes assessments at multiple time points; and validated documentation of potential confounders and health outcomes, including a careful collection of neurologic and psychiatric outcomes using validated instruments.

Study samples need to be of sufficient size to detect associations of rare events if they do exist. Using standardized definitions and making exposure, outcome, and variable conditions as compatible as possible would allow for a better synthesis of the evidence across studies. In the report, the committee presents several strategies and approaches that would advance the evidence base on persistent or latent adverse events associated with the use of antimalarial drugs. It also outlines examples of approaches that are unlikely

to provide much additional insight regarding the persistent adverse events of antimalarial drugs.

There is a sharp contrast between the extensive evidence concerning adverse events experienced while using antimalarial drugs and the limited high-quality information available concerning adverse experiences that are present after their use has ended. Although conducting high-quality research on the persistent and latent effects of taking antimalarial drugs is challenging, this should not prevent it from being done.

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