Controversies and Misconceptions in Malaria Chemoprophylaxis for Travelers

Lin H. Chen, MD
Mary E. Wilson, MD
Patricia Schlagenhaft, PhD

Controversies in malaria prevention may arise due to paucity of data or differences between national guidelines and from travelers’ misconceptions perpetuated by rumors, media coverage, and inaccurate advice. Additional sources of controversy include incomplete or inaccessible information, conflicting data, and variation in risk thresholds of individuals and policy-making groups.

These controversies present challenges to clinicians who advise travelers. Travelers may acquire inaccurate beliefs regarding ways to prevent malaria; they may disregard recommendations based on national guidelines, and seek unapproved substitutes for repellents or chemoprophylactic drugs or unconventional ways of taking the medications; or they may discontinue chemoprophylaxis due to fears of adverse events. Discussing controversies with travelers may dispel their misconceptions, enhance their understanding of recommendations, and possibly improve their adherence to recommended preventive strategies.

We examine the following global controversies in malaria prophylaxis: (1) lack of consensus in international recommendations; (2) the neuropsychiatric adverse event profile of mefloquine and the tolerability of this drug in persons involved in activities such as flying, diving, and driving; and (3) failure of currently recommended first-line chemoprophylactic regimens to prevent vivax malaria relapses; potential alternate approaches. First-line chemoprophylaxis refers to the preferred medications that are recommended to prevent or suppress malaria, currently including atovaquone-proguanil, chloroquine, doxycycline, and mefloquine. Relapse refers to peripheral parasitemia and malarial symptoms due to activation of the latent liver forms (hypnozoites) of the parasite.

Context

Controversies in malaria prevention arise from the absence of data, conflicting data between different studies, conflicting recommendations, deviation of local practice from scientific data, and varying risk thresholds. Misconceptions about the seriousness of malaria, the tolerability of chemoprophylaxis drugs, and the efficacy and safety of repellents contribute to the controversies.

Objectives

To compare several national guidelines on malaria chemoprophylaxis to identify variations in recommendations. We reviewed studies on tolerability of mefloquine with particular focus on its neuropsychiatric adverse effects and influence on performance. We also describe why most recommended chemoprophylactic regimens fail to prevent relapses of Plasmodium vivax malaria and review available options.

Evidence Acquisition

We searched scientific publications in MEDLINE via PubMed for relevant articles with a cutoff date of December 2006 using the search terms malaria, chemoprophylaxis, travel, mefloquine, neuropsychiatric adverse events, tolerability, vivax malaria, and primaquine. Additional references were obtained from bibliographies of the selected articles. There were no language restrictions.

Evidence Synthesis

Gaps and conflicts exist among current guidelines. Health authorities vary in the chemoprophylaxis drugs they recommend, the indications for continuous prophylaxis vs no prophylaxis, and the use of standby emergency treatment. Despite widespread reports on the adverse effects of mefloquine, controlled studies found that serious neuropsychiatric adverse events occur at rates comparable with or lower than other chemoprophylaxis drugs. Moreover, mefloquine does not appear to impair performance while driving, flying, or diving. Vivax malaria causes significant illness in travelers, but current first-line chemoprophylaxis agents do not prevent relapses of vivax malaria. Although not licensed in most countries as primary prophylaxis, primaquine effectively prevents relapses of vivax malaria.

Conclusions

Prevention of malaria in travelers requires detailed knowledge of malaria epidemiology and host-vector-parasite interactions. Decisions are complicated by a lack of standardized recommendations, controversies, and misconceptions. Improved international consensus is indicated to minimize conflicting guidelines, clarify controversies, and promote adherence to preventive measures.
MALARIA CHEMOPROPHYLAXIS FOR TRAVELERS

METHODS
We searched the literature in MEDLINE via PubMed with a cutoff date of December 2006 using the search terms malaria, chemoprophylaxis, travel, mefloquine, neuropsychiatric adverse events, tolerability, vivax malaria, primaquine, and obtained additional references from bibliographies of the selected articles. We also reviewed the following journals for relevant reports on malaria in travelers over the past decade: JAMA, New England Journal of Medicine, Lancet, Lancet Infectious Diseases, Clinical Infectious Diseases, American Journal of Tropical Medicine and Hygiene, Journal of Travel Medicine, Transactions of the Royal Society of Tropical Medicine, Morbidity and Mortality Weekly Report, Emerging Infectious Diseases, Bulletin of the World Health Organization, Journal of Infectious Diseases, Annals of Internal Medicine, BMJ, Tropical Medicine and International Health, and Southeast Asian Journal of Tropical Medicine and Public Health. We emphasized the more recent publications, in particular systematic reviews, randomized controlled trials, and travelers' database analyses.

GUIDELINES ISSUES
Recommendations for malaria chemoprophylaxis involve complex decision making and must consider the destination, the host, the activities, and the duration of exposure. Many national health authorities issue recommendations on malaria chemoprophylaxis for commonly encountered situations; however, these broad guidelines miss some itineraries and types of travelers. In addition, conflicting recommendations by authorities in different countries can lead to confusion for travelers and clinicians.

Common controversies include continuous prophylaxis vs no prophylaxis and choice of agent for prophylaxis and for specific risk groups. Most health authorities (with the exception of the Advisory Committee on Malaria Prevention for UK Travelers and Canadian Advisors on Tropical Medicine and Travel, Public Health Agency of Canada) do not address malaria prevention for long-term travelers in detail.\(^1\)\(^2\) We reviewed this subject recently\(^3\) and will not discuss it herein. Most guidelines provide general areas of risk; however, malaria transmission data by specific destination would aid in assessing the potential benefit from chemoprophylaxis. Additionally, health authorities seldom address travelers with frequent, brief visits to malaria-endemic areas. Yet occupational travelers may have a higher incidence of malaria than tourists\(^4\) and should receive more focused attention. Most recommendations do not explicitly describe how risk-benefit-cost analyses influence the considerations for chemoprophylaxis.

Differences exist among the chemoprophylaxis regimens that are licensed, recommended, and distributed in each country. Table 1 lists the key medications recommended for malaria chemoprophylaxis in the United States,\(^5\)\(^6\) Canada,\(^7\) United Kingdom,\(^7\) France,\(^8\) Germany,\(^9\) Switzerland,\(^10\) Ja-

### Table 1. Medications Licensed and Recommended for Malaria Chemoprophylaxis by Various Countries\(^*\)

<table>
<thead>
<tr>
<th>Medication Approved and Available for Malaria Chemoprophylaxis</th>
<th>United States(^5,6)</th>
<th>Canada(^7)</th>
<th>United Kingdom(^7)</th>
<th>France(^8)</th>
<th>Germany(^9)</th>
<th>Switzerland(^10)</th>
<th>Japan(^11)</th>
<th>Australia(^12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chloroquine</td>
<td>Licensed</td>
<td>Licensed</td>
<td>Licensed</td>
<td>Licensed</td>
<td>Licensed</td>
<td>Licensed</td>
<td>Not licensed</td>
<td>Licensed</td>
</tr>
<tr>
<td>Hydroxychloroquine</td>
<td>Licensed</td>
<td>Not licensed</td>
<td>Not licensed</td>
<td>Not licensed</td>
<td>Not licensed</td>
<td>Licensed but not to be used alone</td>
<td>Not licensed</td>
<td>Not licensed</td>
</tr>
<tr>
<td>Proguanil</td>
<td>Not licensed</td>
<td>Not licensed</td>
<td>Licensed</td>
<td>Licensed</td>
<td>Licensed</td>
<td>Licensed but not to be used alone</td>
<td>Not licensed</td>
<td>Licensed</td>
</tr>
<tr>
<td>Mefloquine</td>
<td>Licensed</td>
<td>Licensed</td>
<td>Licensed</td>
<td>Licensed</td>
<td>Licensed</td>
<td>Licensed but not approved for use in children</td>
<td>Licensed</td>
<td>Licensed</td>
</tr>
<tr>
<td>Doxycycline†</td>
<td>Licensed for ≥8 y</td>
<td>Licensed for ≥8 y</td>
<td>Licensed for ≥8 y</td>
<td>Not licensed</td>
<td>Not licensed</td>
<td>Licensed for ≥8 y</td>
<td>Not licensed</td>
<td>Licensed for ≥8 y</td>
</tr>
<tr>
<td>Atovaquone-proguanil</td>
<td>Licensed</td>
<td>Licensed</td>
<td>Licensed</td>
<td>Licensed</td>
<td>Licensed</td>
<td>Licensed</td>
<td>Not licensed</td>
<td>Licensed</td>
</tr>
<tr>
<td>Primaquine</td>
<td>Licensed only for radical cure but not recommended as primary prophylaxis in CDC guideline</td>
<td>Licensed</td>
<td>Not licensed and not recommended for primary prophylaxis</td>
<td>Not licensed</td>
<td>Not licensed</td>
<td>Not licensed and not registered for primary prophylaxis</td>
<td>Not licensed</td>
<td>Not licensed</td>
</tr>
<tr>
<td>Proguanil in combination with chloroquine</td>
<td>Not licensed</td>
<td>Not licensed</td>
<td>Licensed</td>
<td>Licensed</td>
<td>Licensed‡</td>
<td>Licensed</td>
<td>Not licensed</td>
<td>Licensed</td>
</tr>
</tbody>
</table>

Abbreviation: CDC, Centers for Disease Control and Prevention.

*Licensed indicates that the medication is licensed for malaria chemoprophylaxis and available in the country. Not licensed indicates that it is not approved for malaria chemoprophylaxis or is not available.
†In some countries, doxycycline is licensed for specific indications but not malaria chemoprophylaxis. In Germany it is often used for this indication but not licensed for malaria prophylaxis off-label use.
‡A fixed combination of chloroquine (100-mg base) and proguanil (200 mg) is available as Savarine in France.
chemoprophylaxis for travelers to
differences among the guidelines: (1)
United States. Similarly, the drug pro-
travel to areas with unreliable or poor
Island, the Amazon region—and for
recommend chemoprophylaxis only for
prophylaxis with SBET, unconfirmed di-
revised recommenda-
tions will reflect the limited malaria risk
for most travelers to Mexico and che-
prophylaxis will only be indicated in
rare situations (Paul Arquin, MD, Ma-
laria US travelers returning from
and found the incidence to be ex-
tremely low and primarily due to P vivax.
Therefore, the revised recommenda-
tions will limit the recommended malaria risk
for most travelers to Mexico and che-
malaria and (2) standby chemoprophylaxis.

TABLE 2

<table>
<thead>
<tr>
<th>Indications</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Certain travel destinations</td>
<td>Continuous chemoprophylaxis</td>
</tr>
<tr>
<td>Low-risk areas</td>
<td>Seasonal chemoprophylaxis</td>
</tr>
<tr>
<td>Unreliable or poor medical care</td>
<td>SBET</td>
</tr>
</tbody>
</table>

Two additional areas highlight the
differences among the guidelines: (1)
chemoprophylaxis for travelers to Plas-
moodium vivax—predominant areas or
areas with low risk and (2) standby
emergency self-treatment (SBET).

For high-risk regions such as Kenya,
the World Health Organization13,14 and
all national health authorities consis-
tently recommend chemoprophyl-
xis.2,5,7-12 Recommendations vary more
for lower-risk areas, such as India and
border areas of Thailand. For these loca-
tions, some authorities recommend
continuous chemoprophylaxis while
others recommend seasonal chem-
 prophylaxis or SBET.2,5,7-12

For travelers to P vivax—predomi-
nant areas, such as Mexico, recommen-
dations differ further still and include
no chemoprophylaxis, different medica-
tions, and different regimens (continu-
ous chemoprophylaxis and SBET).2,5,7-12

Of note, the Centers for Disease Preven-
tion and Control recently evaluated ma-
laria in US travelers returning from
Mexico and found the incidence to be ex-
tremely low and primarily due to P vivax.
Therefore, the revised recommenda-
tions will reflect the limited malaria risk
for most travelers to Mexico and che-
prophylaxis. The misuse of SBET and
associated errors added to the debate
(trendy travelers to replace chemo-
 prophylaxis with SBET, unconfirmed di-
agnosis after initiating SBET, delay or lack
of medical evaluation, and mistakes with
medication).3,17,18

Standby emergency self-treatment clearly carries potential
 dangers of serious morbidity and rare
mortality and requires careful selection
of patients and detailed instructions.

TOLERABILITY OF MEfloQUINE

Mefloquine is one of the most widely
used malaria chemoprophylactic drugs
with more than 30 million global users.
It has been available in Europe since
Mefloquine adverse event case reports
are plentiful and most scientific reports on
the tolerability of mefloquine highlight
the drug’s neuropsychiatric profile. The
more recent studies on mefloquine’s tol-
erability have sought to clarify the cli-
nical spectrum of less severe but poten-
tially incapacitating neurological and
psychiatric events and to elucidate the
risk factors for such events.

This section aims to review the lit-

MALARIA CHEMOPROPHYLAXIS FOR TRAVELERS

©2007 American Medical Association. All rights reserved.
moprophylactic studies that detail the neuropsychiatric adverse event profile of mefloquine and (2) clinical toxicity studies that evaluate the impact of mefloquine use on activities such as driving, flying, and diving.

**MAIN AREAS OF CONTROVERSITY**

Experts disagree over the tolerability of mefloquine prophylaxis vs alternatives, such as doxycycline, atovaquone-proguanil and chloroquine-proguanil, mainly with regard to neuropsychiatric events. Neuropsychiatric disorders include 2 broad categories of symptoms: central and peripheral nervous system disorders (headache, dizziness, vertigo, seizures) and psychiatric disorders (major psychiatric disorders, affective disorders, anxiety, and sleep disturbances). Studies conducted in travelers during the selected period show disparate results due to differing designs, definitions, method, and study populations.

Many studies included in Table 3 are observational or interview-based studies in which potential confounders can distort the association between the risk of developing neuropsychiatric adverse events and the use of the drug. The controlled, double-blind studies comparing mefloquine-associated adverse events with that of the comparator regimens provide more objective data. Some studies use objective, validated psychomotor tests and specialized mood questionnaires, such as the “Profile of Moods States” to quantify moods and feelings. Whereas, many prospective studies on mefloquine’s adverse events may not identify relatively rare severe adverse events partly because of the small number of participants, the database analyses are essential in having a sample size large enough to analyze serious adverse events and in drawing significant conclusions.

Studies from the early 1990s did not identify any significant excess of neuropsychiatric adverse events in mefloquine users. Peace Corps volunteers using mefloquine prophylaxis up to 2½ years experienced strange dreams (25%), insomnia (9%), and dizziness (8.4%), similar to those using chloroquine (corresponding incidence 26%, 6.5%, and 10%); no severe neuropsychiatric reactions were causally associated with mefloquine. Results were similar in tourists returning from East Africa (n=139,164); headache occurred in 6.2% mefloquine users vs 7.6% of chloroquine-proguanil users with no excess

<table>
<thead>
<tr>
<th>Health Authority or Country</th>
<th>Guidelines for SBET</th>
<th>Recommended and Available SBET</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHO (United Kingdom)</td>
<td>Consider for travel to remote areas and may have to self-diagnose malaria, frequent brief stays in endemic areas over a long period, or travel remote rural areas where risk of malaria is low and adverse effects from medication outweigh the risk of infection; the drug for SBET must be different from the drug used for prophylaxis, and the area should not have known resistance to the chosen drug</td>
<td>Chloroquine, only for Plasmodium vivax areas Mefloquine Quinine Quinine + doxycycline Artemether-lumefantrine Atovaquone-proguanil</td>
</tr>
<tr>
<td>United States</td>
<td>Consider for remote travel, travelers who elect not to take chemoprophylaxis, who choose a suboptimal regimen, or who only tolerate a suboptimal regimen</td>
<td>Atovaquone-proguanil</td>
</tr>
<tr>
<td>Canada</td>
<td>Consider for long-term travelers and expatriates living in areas with significant transmission of malaria and where medical care may be unreliable, in particular travelers to sub-Saharan Africa</td>
<td>Atovaquone-proguanil Quinine + doxycycline</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>Consider for remote travel; travel to any remote location within 3 mo of possible malaria exposure; unable to obtain medical advice within 24 h of illness</td>
<td>Chloroquine, only for areas without resistance Artemether-lumefantrine Atovaquone-proguanil Quinine + doxycycline Quinine + clindamycin, for pregnancy</td>
</tr>
<tr>
<td>France</td>
<td>Should be limited to infrequent situations where it is not possible to get medical evaluation within 12 h, trips &gt;7 d in remote endemic areas, travelers who cannot take the recommended chemoprophylaxis or stopped taking chemoprophylaxis, such as a frequent traveler or expatriates staying for &gt;6 mo</td>
<td>Mefloquine Quinine Atovaquone-proguanil</td>
</tr>
<tr>
<td>Germany</td>
<td>For regions with low risk of malaria infection, SBET is recommended instead of chemoprophylaxis to minimize the risk of complications from chemoprophylaxis regimens</td>
<td>Chloroquine, only for areas without resistance Artemether-lumefantrine Atovaquone-proguanil Mefloquine</td>
</tr>
<tr>
<td>Switzerland</td>
<td>For regions with low risk of malaria infection, SBET is recommended instead of chemoprophylaxis to minimize the risk of complications from chemoprophylaxis regimens</td>
<td>Chloroquine, only for areas without resistance Artemether-lumefantrine Atovaquone-proguanil Mefloquine</td>
</tr>
<tr>
<td>Japan</td>
<td>For malaria-endemic areas that do not fit into the absolute indications for chemoprophylaxis, SBET can be considered. General practitioners should not prescribe these medications; specialists should be consulted</td>
<td>Mefloquine Quinine Sulfadoxine-pyrimethamine</td>
</tr>
<tr>
<td>Australia</td>
<td>Consider SBET for travelers who elect not to take chemoprophylaxis or who take chloroquine for areas with chloroquine resistance</td>
<td>Artemether-lumefantrine Atovaquone-proguanil Mefloquine</td>
</tr>
</tbody>
</table>

Abbreviations: SBET, standby emergency self-treatment.

*This information is provided for comparison and not to be used as a guide for prescribing.
### Table 3. Chemoprophylactic Studies or Analyses Describing Some Aspect of the Neuropsychiatric Adverse Event Profile of Mefloquine*

<table>
<thead>
<tr>
<th>Source</th>
<th>Study</th>
<th>No. of Participants Using Mefloquine</th>
<th>Neuropsychiatric Adverse Events</th>
<th>Reported Serious Neuropsychiatric Adverse Events</th>
<th>Information on Latency, Duration, and Outcome of Neuropsychiatric Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controlled trials</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schlagenhauf et al.37 2003</td>
<td>RC, DB, 4-group Comparator: doxycycline, atovaquone-proguanil, chloroquine-proguanil POMS questionnaire</td>
<td>153</td>
<td>The mefloquine group had the highest proportion of moderate neuropsychiatric events particularly in women (P = .0003)</td>
<td>No serious AE reported</td>
<td>No details on latency and duration of AE provided</td>
</tr>
<tr>
<td>Van Rems djik et al.36 2002</td>
<td>RC and DB Comparator: atovaquone-proguanil</td>
<td>119</td>
<td>Mefloquine was associated with a significant increase in depression, anger, fatigue, vigor, and total mood disturbance in the POMS questionnaire</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overbosch et al.40 2001</td>
<td>RC and DB Comparator: atovaquone-proguanil</td>
<td>483</td>
<td>Participants who took atovaquone-proguanil had fewer treatment-related neuropsychiatric AEs than those using mefloquine (14% vs 29%; (P = .001))</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ohr et al.45 1997</td>
<td>RC and DB Comparator: doxycycline</td>
<td>204</td>
<td>More mefloquine users reported neurologic symptoms, dizziness, and headache than doxycycline users, but both were better tolerated than placebo Dizziness was reported significantly more frequently with mefloquine than with placebo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boudreau et al.32 1993</td>
<td>DB and RC Comparator: chloroquine</td>
<td>203</td>
<td>Sleep disturbance, increased dream activity, and depressive feeling were more frequent in mefloquine users vs chloroquine users</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other studies</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wells et al.30 2006</td>
<td>Military database analysis of mefloquine prescriptions and hospitalizations</td>
<td>8858</td>
<td>Mefloquine prescribed service members were at a significantly decreased risk of any-cause hospitalization</td>
<td>All events were serious as a hospitalization was required</td>
<td></td>
</tr>
<tr>
<td>Kitchener et al.34 2006</td>
<td>Open-label, prospective military study using comparator: doxycycline</td>
<td>1157</td>
<td>57% of mefloquine users vs 56% of doxycycline users reported ≥1 AEs—most commonly sleep disturbance, headache, tiredness, and nausea 94% of mefloquine users said they would use it again</td>
<td>3 Serious AEs of a neuropsychiatric nature possibly related to mefloquine; 2 of the 3 individuals had an undisclosed history of neuropsychiatric disorders</td>
<td></td>
</tr>
<tr>
<td>Van Rems djik et al.35 2005</td>
<td>Nationwide case-control study from 4 alarm centers in the Netherlands</td>
<td>111</td>
<td>Use of mefloquine was associated with an increased risk of psychiatric events in women and in patients with a history of psychiatric diseases</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meier et al.36 2004</td>
<td>United Kingdom–based general practice research database person-time, nested case-control analysis</td>
<td>35370</td>
<td>No evidence was found that mefloquine increased the risk of first-time diagnosis of depression but may have increased the risk of acute psychosis or panic attack</td>
<td>The absolute risk of such serious events during mefloquine use is low and is estimated at 1-3 cases during 6500 treatment courses</td>
<td></td>
</tr>
<tr>
<td>van Rems djik et al.36 2002</td>
<td>Prospective POMS</td>
<td>179</td>
<td>Use of mefloquine was associated with neuropsychiatric type AE particularly in women The profile was shown by validated psychological tests POMS These events were more common in first-time mefloquine users</td>
<td>Mild short-term neuropsychiatric AE occurred in 32% of young travelers during the first 3 wk</td>
<td></td>
</tr>
<tr>
<td>Schwartz et al.42 2001</td>
<td>Case-control study of persons presenting to emergency departments with possible serious AE</td>
<td>17</td>
<td>Report describes 17 suspected serious AEs mainly associated with the central nervous system Women (76%) predominate in this series of severe/serious events</td>
<td>Most of the patients reported that their AE began early in prophylaxis after the first 1-3 tablets</td>
<td></td>
</tr>
<tr>
<td>Lobel et al.43 2001</td>
<td>Cross-sectional airport study Comparators: doxycycline, chloroquine-proguanil</td>
<td>3866</td>
<td>Neuropsychiatric AEs were reported by 7.8% of mefloquine users vs 1.9% of atovaquone-proguanil users</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Croft and Garner,41 2000</td>
<td>Systematic Cochrane review</td>
<td>2750</td>
<td>Mefloquine more likely to cause insomnia and fatigue than other regimens</td>
<td>(continued)</td>
<td></td>
</tr>
</tbody>
</table>
MALARIA CHEMOPROPHYLAXIS FOR TRAVELERS

Table 3. Chemoprophylactic Studies or Analyses Describing Some Aspect of the Neuropsychiatric Adverse Event Profile of Mefloquine® (cont)

<table>
<thead>
<tr>
<th>Source</th>
<th>Study</th>
<th>No. of Participants Using Mefloquine</th>
<th>Neuropsychiatric Adverse Events</th>
<th>Reported Serious Neuropsychiatric Adverse Events</th>
<th>Information on Latency, Duration, and Outcome of Neuropsychiatric Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observational</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Potasman et al.54, 2000</td>
<td>Postal and telephone survey of 2500 travelers</td>
<td></td>
<td>11.3% Of all travelers regardless of whether they used antimalarials reported neuropsychiatric-type events Mefloquine was used significantly more often by those who had neuropsychiatric AEs than by the entire cohort</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hoelbe et al.46, 1997</td>
<td>Telephone Interview</td>
<td>104</td>
<td>Mefloquine users showed an excess risk of depression (excessive risk, 7.2 per 100 users) and dizziness (excessive risk, 9.3)</td>
<td>2 Of the 3 women experienced serious AEs and were admitted to hospital and 1 woman had a seizure</td>
<td>Most of the mild AEs occurred after the first or second dose 2 Of the serious neuropsychiatric AEs occurred after the initial mefloquine dose The seizure occurred after the fourth mefloquine dose in combination with excess alcohol</td>
</tr>
<tr>
<td>Phillips and Klass,54, 1996</td>
<td>Prospective questionnaire study Comparator: doxycycline</td>
<td>285</td>
<td>Rate of disabling neuropsychiatric events in women was 1.8% (9/171)</td>
<td>1 Severe neuropsychiatric reaction, a visual hallucination, described in detail</td>
<td>The event occurred 2 d after taking the sixth mefloquine dose Event lasted 15 min and resolved spontaneously</td>
</tr>
<tr>
<td>Corbett et al.55, 1996</td>
<td>Questionnaire survey Comparator: chloroquine</td>
<td>117</td>
<td>Probable symptoms of depression/anxiety were reported by 21% of mefloquine users vs 10% of chloroquine users</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schlagenhauf et al.41, 1996</td>
<td>Longitudinal study with psychomotor tests, POMS, and plasma sampling</td>
<td>420</td>
<td>7.9% Mefloquine users reported neurological/psychiatric-type symptoms Women were more likely to report AE (P = .02). Those reporting AE had no significant performance deficit in computerized psychomotor tests</td>
<td></td>
<td>Most of these AEs occurred after the first or second mefloquine dose and resolved spontaneously</td>
</tr>
<tr>
<td>Lobel et al.54, 1993</td>
<td>Evaluation of the use of mefloquine by US Peace Corps</td>
<td>802</td>
<td>No serious AE observed</td>
<td></td>
<td>Frequency of the incidence of mild AE declined with increasing duration of mefloquine use</td>
</tr>
<tr>
<td>Bem et al.46, 1992</td>
<td>Retrospective evaluation of 59 spontaneous reports up to May 1991</td>
<td></td>
<td>Identified persons with a history of seizures or manic-depressive illness as being particularly at risk of neuropsychiatric AE Concluded that mefloquine should be contraindicated in such persons More women reported neuropsychiatric disorders than men did</td>
<td></td>
<td>26 Convulsions were reported 7 Cases occurred after first mefloquine dose with a mean of 4.5 tablets Recovery took from 2 d to 1 mo For the other serious neuropsychiatric AEs, onset was after a mean of 3 doses Recovery took from 5 d to 7 mo</td>
</tr>
<tr>
<td>Weinke et al.46, 1991</td>
<td>Retrospective review of patient records</td>
<td>12</td>
<td>Moderate to severe neuropsychiatric AE occurred in an estimated 1/13,000 prophylactic users based on the estimated number of mefloquine users in Germany</td>
<td>Risk is 1/13,000</td>
<td>Latency ranged from 2.5-20 d Toxic reactions persisted for 2-10 d</td>
</tr>
<tr>
<td>Sturchler et al.47, 1990</td>
<td>Spontaneous reports to Roche up to September 1989</td>
<td></td>
<td>31% Of the neurologic AE and 61% of the psychiatric-type AE appeared after the first dose of mefloquine</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: AE, adverse event; DB, double-blind; PC, placebo-controlled; POMS, profile of moods states; RC, randomized controlled; SAE, serious adverse event.

*Serious as defined by the Council for International Organisations of Medical Sciences as "fatal, life-threatening, leading to or prolonging a stay in hospital or resulting in severe disability."
of dizziness, depression, and insomnia in mefloquine users.\textsuperscript{31}

A meta-analysis found that rates of withdrawal and overall incidence of adverse events with mefloquine were not significantly higher than those observed with comparator regimens.\textsuperscript{41} However, mefloquine was more likely to cause insomnia and fatigue (odds ratio, 1.64; 95% confidence interval, 1.18-2.28 and 1.57; 95% confidence interval, 1.01-2.45), respectively.\textsuperscript{41}

A double-blind study of chemoprophylactic regimens showed a significant excess of moderate neuropsychological events with mefloquine compared with doxycycline and atovaquone-proguanil but not when compared with chloroquine-proguanil.\textsuperscript{37} Regression analysis between medications and sex showed that significantly more women taking mefloquine reported mild to moderate neuropsychological events (including headache and sleep disturbances) than those taking other drugs.\textsuperscript{37}

More recent studies\textsuperscript{33,36} have used electronic databases to define mefloquine exposure and outcome. The analysis of the UK–based General Practice Research Database compared the incidence of serious events was a US analysis of hospitalizations for neuropsychiatric events (1 seizure and 2 psychotic episodes). \textsuperscript{41}

The British army’s experience with mefloquine prophylaxis found the incidence of severe neuropsychiatric reactions to be 1 or less per 6000.\textsuperscript{49} A controlled monitoring of adverse events in Canadian travelers found 1 clinically significant neuropsychiatric AE, a moderate to severe anxiety attack, in 1 of the 251 mefloquine users.\textsuperscript{59} The most recent and comprehensive evaluation of serious events was a US analysis of hospitalizations that found no association between mefloquine prescriptions and any disorder including mental disorders and diseases of the nervous system, including serious adverse events (as measured by hospitalizations).\textsuperscript{33}

**Risk Factors Associated With the Incidence of Neuropsychiatric Adverse Events**

The mechanism underlying neuropsychiatric adverse events associated with quinoline-antimalarial (chloroquine, mefloquine, quinine) associated with neuropsychiatric adverse events is unknown. Other antimalarial drugs (di-hydrofolate reductase inhibitors, sulfonamides, tetracyclines, halofantrine, and atovaquone) do not have this profile of adverse events. Persons with a history of seizures or manic-depressive illness appear to be a major risk group for severe psychiatric reactions and convulsions,\textsuperscript{31} and all guidelines now recommend that mefloquine be contraindicated for persons with a personal or family history of such disorders and also for individuals with depression. Women are significantly more likely to experience mefloquine-associated adverse events.\textsuperscript{37,42,47,48,51} Studies differed on whether there is an association between low body weight and developing an adverse event while taking a mefloquine prophylaxis.\textsuperscript{47,60}

Anecdotal reports on the use of a split dose (a half tablet twice weekly) for women with low body weight suggest favorable results. Poorer tolerability in women may also be due to reporting bias, greater compliance with prescription or to sex-related pharmacokinetic factors. A role of mefloquine enantiomers and metabolites has not been confirmed.\textsuperscript{51} The concomitant use of mefloquine and recreational drugs\textsuperscript{47} has been suggested, and there may be an interaction between mefloquine and large, but not small, quantities of alcohol.\textsuperscript{62,63} Recently, it has been hypothesized that the neuropsychiatric adverse effects of mefloquine are associated with polymorphisms in the MDR1/ABCB1 gene that encodes for the efflux pump P-glycoprotein and this is an area that warrants further research.\textsuperscript{64}

**Latency of Mild Adverse Events**

Many studies have shown that mild, neuropsychiatric adverse events tend to occur early in prophylaxis. Schlegenhau et al\textsuperscript{31} found that most minor adverse events occurred early (after the first or second mefloquine dose), and this was also evident in the Australian study\textsuperscript{50} and other reports that detail latency (Table 3).

**Use of Mefloquine While Flying, Driving, or Diving**

Because many reports highlighted neuropsychological mefloquine events, concern has emerged that use of mefloquine may impair performance and precision while driving, operating machinery, or being in combat situations. A clinical toxicity study with alcohol challenge has shown that mefloquine, with or without small quantities of alcohol, does not impair driving.\textsuperscript{65} Although some diving schools...
prohibit the use of mefloquine, we found no scientific basis to support this ban. Table 4 summarizes findings from studies evaluating the impact of mefloquine intake on various activities.52,63,65-67 These controlled studies suggest that although mefloquine is associated with neuropsychiatric events in travelers, there is no performance deficit in persons who tolerate the drug.

**Summary of Mefloquine Tolerability**

The use of the literature to clarify the adverse event profile of mefloquine has limitations and is subject to potential bias. Few trials are designed to investigate the neuropsychiatric adverse event profile of mefloquine. Information on latency, duration and outcome of adverse events is limited. Studies of mefloquine tolerability involving more than 5000 participants have found a low incidence of serious adverse events.55,41,53,56 Studies of minor adverse events have shown that mefloquine's adverse event profile is of the neuropsychiatric-neuropsychological type with an excess of events in women.

Careful prescribing with attention to contraindications is essential, as is clear warning about the potential adverse effects. Before prescribing mefloquine, it is prudent to discuss the pros and cons of alternative chemoprophylactic regimens that are not associated with a potential for severe neuropsychiatric reactions. Because many mefloquine-associated adverse events occur early in dosing, starting mefloquine prophylaxis 2 to 3 weeks before departure may allow for evaluation of tolerability to the regimen. Stopping the drug with early signs of such events should minimize the severity and duration of an adverse event.

**Destinations with Predominant or Significant P Vivax**

**Chemoprophylaxis for Short-term Travelers to P vivax-Predominant Areas**

The primary goal of malaria chemoprophylaxis is to prevent deaths from malaria, which are largely caused by *Plasmodium falciparum*.

Another important goal is to prevent clinical malaria, which can lead to hospitalization with health and economic consequences. The currently recommended first-line drugs for chemoprophylaxis are 80% to 90% effective in preventing clinical episodes of primary malaria infection.68,69

The antimalarial agents commonly used (eg, chloroquine, mefloquine, doxycycline, atovaquone-proguanil) that are active against the blood stage parasites, however, do not prevent relapsing infection caused by *Plasmodium vivax* and *Plasmodium ovale*. These *Plasmodium* species are biologically different and can cause latent infection with hypnozoites in the liver that are not killed by the antimalarials active against the blood stages. Not only can hypnozoites survive despite the presence of a blood stage antimalarial during and after travel, they may emerge to cause symptoms months later. The late appearance of vivax or ovale malaria in a returned traveler who has taken antimalarials as prescribed reflects the different biological characteristics of vivax and ovale malaria. Resistance of vivax malaria to chloroquine has been well documented,70,71 although some reports of resistance may reflect relapses of the surviving liver forms. Use of agents active against the blood stage does not prevent infection but delays the first clinically apparent

<table>
<thead>
<tr>
<th>Table 4. Performance During Use of Mefloquine*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type of Study</strong></td>
</tr>
<tr>
<td>-------------------</td>
</tr>
<tr>
<td>Driving</td>
</tr>
<tr>
<td>Vuurman et al,63</td>
</tr>
<tr>
<td>Fying</td>
</tr>
<tr>
<td>Schlagenhauf et al,63</td>
</tr>
<tr>
<td>Diving</td>
</tr>
<tr>
<td>Other clinical toxicity studies</td>
</tr>
<tr>
<td>Hesen-Soderman et al,65</td>
</tr>
<tr>
<td>Davis et al,61</td>
</tr>
</tbody>
</table>

*We could find no studies or evidence of an adverse impact of mefloquine on diving.*
attack of malaria. Although atovaquone-proguanil may have some activity against the liver stage of *P. vivax*, it does not reliably prevent vivax malaria relapse.72-74

How big is this problem? Vivax malaria is the most geographically widespread of the malarial species and is estimated to cause 70 to 80 million acute episodes per year in endemic areas.75,76 *P. vivax* causes more than 50% of malaria infections outside of Africa and about 10% of those in Africa.77 In parts of Africa, (eg, Ethiopia and other parts of eastern and southern Africa and Madagascar), *P. vivax* may cause up to 20% of malaria cases.75 Among the vivax cases outside of Africa the majority (80%-90%) occur in Asia, the Middle East, and the Western Pacific, and only 10% to 15% in Latin America.75

In travelers, the percentage of infections caused by *P. vivax* varies widely depending on the common destinations for travelers from that geographic area. In the United States, among reported, imported cases of malaria from 2001-2004 for which the species was identified, *P. vivax* caused from 22.9% to 27.8% and *P. ovale* caused from 2.0% to 3.6%.77,78 In European centers, *P. vivax* caused from 9.3% (the Netherlands)79 and 10.4% (Paris)80 to 29.4% (Munich, Germany).81 *P. vivax* accounted for 12.9% of 4801 cases of imported malaria reported to TropNetEurop (European Network on Imported Infectious Disease Surveillance) between January 1999 and September 2003.82 *P. vivax* accounted for 44% to 51% of malaria in Canada (Toronto, Montreal),83,84 and 63% to 74% in Australia (Brisbane, Melbourne),85-87 reflecting the travel of Australians to vivax-dominant areas in Asia. These studies demonstrate that *P. vivax* contributes significantly to the burden of malaria in travelers and that its relative importance varies by travel destination.

The most common countries or regions of origin for vivax malaria cases in the United States in recent years are: Asia (especially, India, and Pakistan), Africa (especially, Ethiopia, Ghana, Kenya, and Nigeria), Central America (especially, Honduras, and Guatemala), Oceania (especially, Papua New Guinea), South America, and Mexico.77,78 Despite the large volume of travel from the United States to Latin America, the absolute risk of vivax malaria in those areas is extremely low. Among cases reported to TropNetEurop, 33% of vivax malaria (1999-2003) was acquired in sub-Saharan Africa.82

Although an episode of vivax malaria is less likely to be fatal than infection with *P. falciparum*, vivax malaria can be severe, and rarely, fatal. Despite its name, benign tertian malaria, vivax malaria in its initial clinical presentation can be indistinguishable from falciparum malaria.86,88 Levels of inflammatory cytokines and tumor necrosis factor are often higher in vivax than in falciparum malaria.89-91 A recent study from India reported 2 deaths among 11 patients with severe vivax malaria (in whom coinfection with *P. falciparum* was excluded by polymerase chain reaction testing), and a woman in her third trimester delivered an infant who died.92 The complications of vivax malaria include acute respiratory distress syndrome, renal failure, jaundice, cerebral complications, bleeding, and splenic rupture.92-99 TropNetEurop found that 60% of 526 patients with confirmed or probable isolated *P. vivax* infection were hosp-
talized (median 4 days), including 7 with severe disease, although all survived.\textsuperscript{82}

Diagnosis may be problematic. Infections caused by \textit{P vivax} manifest later than those caused by \textit{P falciparum}, especially, in persons who have taken prophylactic agents. The time of relapse also depends on the geographic origin of the parasite; those with parasites of tropical origin have a higher probability of relapse and a shorter interval to relapse than those with parasites of temperate origin, eg, Korea.\textsuperscript{100-102} Relapses may be multiple (especially with tropical strains)\textsuperscript{74} and can occur more than a year after travel to a malarious area. The late appearance of vivax may delay diagnosis. In the United States, 12\% to 15\% of imported vivax malaria in 2003-2004 had onset more than 6 months after return.\textsuperscript{77,78} In Europe, half of patients with vivax became ill more than 60 days after return from an endemic area.\textsuperscript{82}

Returned travelers and their health providers may not perceive the risk for vivax malaria when prophylaxis has been taken as prescribed. Among Israeli travelers with vivax malaria, 80\% had taken suppressive prophylaxis.\textsuperscript{103} In addition, parasitemia in vivax is typically lower than in falciparum, so laboratory personnel reading the malaria slides may not find the parasites. In Belgium, 9 (25\%) of 36 of untreated patients with vivax malaria had parasitemia levels of less than 500/µL, a level that may be difficult to detect in laboratories in which technicians have limited experience reading malaria smears.\textsuperscript{88} The rapid diagnostic tests, currently unavailable in the United States, also are less likely to be positive in vivax malaria.\textsuperscript{88}

**Box 1. Most Reliable and Easily Accessible Resources for Clinicians for Malaria Epidemiology**

**World Health Organization International Travel and Health**
http://whqlibdoc.who.int/publications/2005/9241580364_country_list.pdf

**World Health Organization Global Atlas**
http://www.who.int/globalatlas/DataQuery/default.asp

**Centers for Disease Control and Prevention**
http://www2.ncid.cdc.gov/travel/yb/utils/ybGet.asp?section=YBAll&cssNav=browseyob

**Centers for Disease Control and Prevention Regional Malaria Information**

**Health Protection Agency Guidelines for Malaria Prevention in Travelers from the United Kingdom**
http://www.hpa.org.uk/infections/topics_az/malaria/ACMP.htm

**International Association of Medical Assistance to Travelers**
http://www.iamat.org/pdf/WorldMalariaRisk.pdf

**Box 2. Card for Travelers Who Expect to Be in Areas Endemic for Malaria**

**Malaria Information for Traveler**
You will be visiting countries with malaria and may be exposed to malaria, which can progress rapidly and kill.

**Ways to Reduce Risk**
Stay in accommodations with screens in windows and doors.
Go indoors from dusk to dawn.
Use an effective insect repellent, such as one that contains diethyltolvamide (DEET).
Treat your clothing with insecticide, such as permethrin.
Sleep under an insecticide-treated bed net.
Take medication that suppresses malaria as recommended by a travel medicine specialist.
If you tolerate malaria medication well, continue taking it even if others tell you there is no need.

**Symptoms of Malaria**
Symptoms may start as early as 7 to 8 days after exposure but may be delayed for weeks or months (rarely > 1 year) after exposure.
Symptoms include fever, which may be intermittent; body ache; weakness; headache; vomiting; abdominal pain; cough.

**Seek Medical Attention**
If you have any of the symptoms, seek medical evaluation as soon as possible, even if fever is not constant.
Inform the clinicians that evaluate your fever that you may have been exposed to malaria.
Check blood tests, including malaria smears, every 12 to 24 hours until at least 3 sets of smear results are negative for malaria.
known as postexposure prophylaxis or terminal prophylaxis), and radical cure-to-treat-established infection with *P. vivax* or *P. ovale*. Only the first 2 will be discussed herein. Primaquine is active against all malarial species. Primaquine has protective efficacy of more than 85% for *falciparum* malaria and primary infections with *P. vivax*. In healthy nonimmune Colombian soldiers going to a malarious area, primaquine 30 mg daily provided protective efficacy of 94% against *P. falciparum* and 85% against *P. vivax* compared with placebo, although follow-up was only for 3 weeks in base camp. Primaquine can eliminate liver hypnozoites and is the only drug currently available with such activity. Although studies show that primaquine is effective as primary prophylaxis of malaria, it is not currently approved by the US Food and Drug Administration (FDA) for this indication mainly due to financial obstacles. The FDA granted license for primaquine in the 1950s for radical cure and the drug has long lost patent protection; the cost to obtain FDA approval for the indication of primary prophylaxis would rest on the investigational new drug holder, an expensive process that no one wishes to bear. When given as presumptive antirelapse therapy, it is administered to overlap with the blood-stage active agent; though data demonstrating the efficacy of presumptive antirelapse therapy are lacking. Studies done more than 50 years ago suggested that primaquine is more active against hypnozoites when given with chloroquine (or quinine).

Individuals considered as possible candidates for primaquine must be screened first for glucose-6-phosphate dehydrogenase deficiency. Administration of primaquine to individuals with deficient glucose-6-phosphate dehydrogenase levels can have serious, even lethal, hemolysis. Primaquine should never be given as primary prophylaxis or as presumptive antirelapse therapy to individuals with glucose-6-phosphate dehydrogenase deficiency. Although screening needs to be done only once, it involves the expense of testing and delays in decision making.

Some strains of *P. vivax* are relatively resistant to primaquine and high failure rates have been reported with the regimen used in the past (15-mg base daily or 26.3-mg primaquine phosphate for 14 days). High rates of failure have occurred in persons with the Cherson strain of *P. vivax* from Papua New Guinea and in persons infected in Southeast Asia. A higher dose of 30-mg base (or 2 tablets of 26.3 mg primaquine phosphate) daily is now recommended. The total dose may be more important than the schedule of its delivery. Weight-adjusted dosing of primaquine (0.5 mg/kg per day × 14 days) has been recommended to prevent additional relapses in patients with *P. vivax* infection.

Primaquine primary prophylaxis could be considered after screening to establish normal levels of glucose-6-phosphate dehydrogenase for individuals with contraindications to or intolerance of recommended first-line antimalarial agents; multiple, short exposures to malaria endemic areas; or travel to *vivax*-dominant areas (Figure). Presumptive antirelapse therapy should be considered for individuals who have had prolonged stays in malarious areas where *P. vivax*, *P. ovale*, or both are present (even if *P. falciparum* is the predominant parasite); specific high-risk itineraries (including participation in a trip in which others in the group have developed *P. vivax* infection). Because primaquine is not currently approved for use as a primary prophylaxis, the clinician should document in the medical record the reasons for its use and note that it is being given off-label.

For travel to areas with low risk of exposure to *P. vivax*, the primary emphasis should be on prompt diagnosis and treatment of relapse of vivax malaria (but also use of blood schizonticide, if significant risk of *P. falciparum* exists). In areas with high risk of exposure to vivax malaria, use of primaquine, either as primary prophylaxis or as postexposure antirelapse therapy, is an option.

**CONCLUSIONS**

Sources of controversy in malaria prevention include the absence of data, conflicting data from different studies, and conflicting recommendations. Misconceptions about the seriousness of malaria, the tolerability of chemoprophylaxis drugs, and the efficacy and safety of repellents fuel the controversy. These controversies and misconceptions limit compliance with measures to prevent malaria. Improved access to information may reduce confusion (Box 1). Consensus guidelines could reduce the conflicts, and improve compliance with chemoprophylaxis.

Pretravel advice and the choice of antimalarial drug should be an evidence-based decision that considers the profile of the individual traveler and the risk of malaria. It is crucial to screen medical histories and inform mefloquine users of potential adverse events with advice on how to avoid such events and ways to respond should they occur. Open discussion may decrease the anxiety toward the chemoprophylaxis and improve adherence. Careful prescribing and observance of contraindications is essential.

Finally, an important reason for development of late *P. vivax* is failure of the usual chemoprophylactic agents to clear liver-stage infection. Guidelines should consider the use of primaquine primary chemoprophylaxis for certain travelers. If travelers are given only blood stage active agents for travel to areas where vivax is common, they must be instructed that their pills do not prevent all forms of malaria and they must seek immediate treatment in the event of febrile illness (Box 2).

**Author Contributions:** All authors had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Chen, Wilson, Schlagenhauf. Acquisition of data: Chen, Schlagenhauf. Analysis and interpretation of data: Chen, Wilson, Schlagenhauf. Drafting of the manuscript: Chen, Wilson, Schlagenhauf. Critical revision of the manuscript for important intellectual content: Chen, Wilson, Schlagenhauf. Administrative, technical, or material support: Chen, Schlagenhauf. Study supervision: Schlagenhauf.

**Financial Disclosures:** Dr Chen reports that she has received honoraria for serving on the editorial board of *Travel Medicine Advisor*, AHC Media LLC. Dr Schlage-