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The Risk of Severe Depression, Psychosis or Panic Attacks with Prophylactic Antimalarials

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Abstract

Introduction/Objective: Experimental and observational studies have linked mefloquine use to an increased risk of developing neuropsychiatric adverse effects such as depression or psychoses. Most of these reports relied on interview-based information from travellers. We conducted a population-based observational study using a database of medical records to quantify and compare the risk of psychiatric disorders during or after use of mefloquine with the risk during use of proguanil and/or chloroquine, or doxycycline.

Study Design/Methods: The study population was drawn from the large UK-based General Practice Research Database (GPRD). Subjects were aged from 17–79 years and were exposed to mefloquine, proguanil, chloroquine or doxycycline (or a combination of these drugs) at some time between 1990 and 1999. We performed a person-time and a nested case-control analysis to assess the risk of developing a first-time diagnosis of depression, psychosis or panic attack during or after use of these antimalarial drugs.

Results: Within the study population of 35 370 subjects (45.2% males), we identified 580 subjects with a first-time diagnosis of depression (n = 505), psychosis (n = 16) or panic attack (n = 57) and two subjects committed suicide. The incidence rates of first-time diagnoses of depression during current use of mefloquine, proguanil and/or chloroquine, or doxycycline, adjusted for age, gender and calendar year, were 6.9 (95% CI 4.5–10.6), 7.6 (95% CI 5.5–10.5) and 9.5 (95% CI 3.7–24.1)/1000 person-years, respectively. The incidence rates of psychosis or panic attacks during current mefloquine exposure were 1.0/1000 person-years (95% CI 0.3–2.9) and 3.0/1000 person-years (95% CI 1.6–5.7), respectively, approximately 2-fold higher (statistically nonsignificant) than during current use of proguanil and/or chloroquine, or doxycycline. The nested case-control analysis encompassed 505 cases with depression and 3026 controls, 16 cases with psychosis and 96 controls, and 57 cases with a panic attack and 342 controls. Current use of mefloquine was not associated with an elevated risk of developing depression. In a comparison between patients currently using mefloquine with all past users of antimalarials combined, the risk estimate was elevated for current users of mefloquine for both psychosis (odds ratio [OR] 8.0, 95% CI 1.0–62.7; $p < 0.05$) and panic attacks (OR 2.7, 95% CI 1.1–6.5; $p < 0.05$).

Conclusion: The absolute risk of developing psychosis or panic attack appears low with all the antimalarials tested. No evidence was found in this large observational study that mefloquine use increased the risk of first-time diagnosis of depression when compared with the use of other antimalarials investigated in this study.

Introduction

There are reports in the scientific literature suggesting that mefloquine, a widely used antimalarial drug, is associated with an increased risk of neuropsychiatric reactions.[1-20] These reports include numerous traveller studies, a randomised trial,[21] and a large systematic Cochrane review.[22] There is, however, a considerable lack of specificity in many of the published reports, since they examine a combination of 'neuropsychiatric events' of various types ranging from fatigue and insomnia to psychosis, include mild as well as severe events, or rely on questionnaire responses or retrospective self report rather than a physician's diagnosis. The present study attempts to add to the current body of literature by evaluating the existence of potential increases in risk for three specific diagnoses: depression, psychoses and panic attacks. Moreover, medical records were used as a source of information, and a referral or prescription had to be present for a reaction to be counted. The underlying purpose of the study, then, was to address the question of whether or not, for these specific diagnoses, there is a prophylaxis-associated increase in reactions severe enough to be documented in the medical record and resulting in either treatment or referral.

In the absence of drug exposure, the prevalence rates of depression are relatively high in the general population; psychoses also occur in the general population in the absence of drugs, though less frequently than depression.[23-28]

In observational studies, a variety of potential confounders can distort the association between antimalarial drug use and the risk of developing depression or psychosis, such as sleep deprivation, stress, jet lag, circadian rhythm disruptions, dietary changes, alcohol consumption, or illicit drug use. Such potential confounders are difficult to control for and may limit the validity of observational studies, particularly if antimalarial drug users are compared with non-users. Therefore, the best method to study the potential relation of mefloquine to neuropsychiatric disorders in an observational study is to compare mefloquine users with users of other antimalarial drugs, since this comparison includes only travellers and controls, at least to some degree, for confounding.

We conducted an observational study using the UK-based General Practice Research Database (GPRD) to compare the risk of developing a first-time diagnosis of depression, psychosis or panic attack, or of committing suicide, among users of mefloquine. We compared the risk during current use of mefloquine with that of current users of proguanil and/or chloroquine, or doxycycline prescribed for malaria prophylaxis. Proguanil and chloroquine can be prescribed alone or, more commonly, in combination. We combined users of proguanil alone, users of chloroquine alone, and users of both in combination, in one group. The outcome had to be severe enough to cause hospitalisation, referral to a specialist or specific pharmacological treatment.

Methods

We conducted a follow-up study with a person-time analysis and a nested case-control analysis using data from the GPRD, a large database which encompasses over three million people who are enrolled with some 300 selected general practitioners (GPs).[29,30] The recorded information on drug exposure and the comprehensiveness of recorded diagnoses in the GPRD has been validated and proven to be of high quality.[31-33] Briefly, the GPRD encompasses people enrolled with GPs who use office computers and have agreed to provide data for research purposes. GPs have been trained to record medical information including demographic data, medical diagnoses, details of hospital stays, and deaths in a standard, anonymous form. The physicians generate prescriptions directly with the computer and this

information is automatically transcribed into the computer record. A modification of the Oxford Medical Information System (OXMIS) classification (similar to the International Classification of Diseases, Eighth Revision [ICD-8]) is used to enter medical diagnoses, and a coded drug dictionary based on the UK's Prescription Pricing Authority dictionary is used for recording prescriptions.

Study Population Definition and Follow-Up

The study population consisted of men and women aged 17–79 years who received between one and four prescriptions for mefloquine, proguanil and/or chloroquine, or subjects who received one prescription only for doxycycline between 1 January 1990 and 31 December 1999. Antimalarial drugs can be used for malaria prophylaxis, for treatment of an acute malaria infection, or as a reserve drug (i.e. the patient gets a prescription, but takes the drug only if high fever of unknown origin develops at the travel destination). In order to distinguish between these options, we included only those subjects whose medical record contained a code indicating that the person received the drug for malaria prophylaxis within 1 week of the prescription date (e.g. 'travel advice' or 'prophylactic drug use'). In order to further increase the likelihood of including only subjects who used the study drugs for malaria prophylaxis and not for the treatment of chronic diseases or for non-malaria-related indications (e.g. chloroquine for rheumatoid arthritis), we excluded subjects who received the study drugs on a longer-term basis.

Subjects had to be enrolled in the database for at least 12 months before the date of the first prescription for a study drug and had to have had some recorded activity (diagnoses or drug prescriptions) after the prescription(s) for an antimalarial drug in order to only include subjects whose outcome events would be captured in their medical records.

Case Definition and Validation

Within the study population we identified, by OXMIS- and/or ICD-8-codes, all subjects who developed a first-time diagnosis of depression, psychosis or panic attack. We also identified subjects who committed suicide during or after exposure to an antimalarial drug. Potential cases had to be aged 17–79 years at the date of the diagnosis (subsequently referred to as 'index date'). We excluded subjects with a history of alcoholism since alcoholism is a risk factor for neuropsychiatric disorders. We reviewed all computer records of potential cases and included or excluded cases based on the available clinical information, blinded to exposure status. We included all cases of suicide or panic attack (regardless of referral or treatment) and included cases of depression or psychoses if patients were referred to a specialist or to a hospital, or if they received a specific drug treatment for the disease at or after the index date (i.e. antidepressants for depression, or sedatives or antipsychotics for psychosis). Thus, mild and transient episodes of psychiatric disorders not requiring additional diagnostic steps or pharmacological treatment were not included.

Person-Time Analysis

Within the study population, we followed each subject from the start of follow-up (i.e. the first prescription for an antimalarial study drug) until the person became a case, died, or the computer record or the predefined follow-up period ended, whichever came first. We censored follow-up for 540 days (18 months) after the end of exposure to a study drug. We assessed the number of tablets recorded by the GP for each prescription for an antimalarial drug, to determine the time window of exposure. Incidence rates were estimated for 'current', 'recent' and 'past' use. 'Current use' started at the date of a prescription and ended 1 week after the end of the time-period for which the drug was prescribed. 'Recent use' started after the end of current exposure and ended 89 days later. 'Past use' started at day 90 and ended at a maximum of 540 days (i.e. 18 months) after the end of exposure to a study drug. For subjects who used several study drugs consecutively (other than the above-mentioned proguanil and/or chloroquine combination), exposure time for the first drug ended when another antimalarial drug was prescribed. From then on, the person contributed person-time to the latter drug. We assessed person-time in 10-year age strata and by gender.

We conducted person-time analyses using a multivariate Poisson regression model to separately assess incidence rates of first-time diagnoses of de-

pression, psychoses, or panic attacks, adjusting for age, gender and calendar year. For all age strata and for gender groups, we assessed incidence rates during current, recent or past use of mefloquine, chloroquine and/or proguanil, or doxycycline. We compared the incidence rates for current mefloquine use to the incidence rates for current use of proguanil and/or chloroquine, and current use of doxycycline and compared current use to all past-use person-time combined (regardless of what antimalarial drug was used last). This latter comparison was performed in order to gain statistical power, under the assumption that the outcome rates in the past use periods (regardless of the previously used antimalarial drug) are similar and that they reflect a baseline rate of psychiatric diseases in the population, independent of previous antimalarial drug use.

The base population for person-time analyses consisted of all subjects free of depression, psychosis or panic attacks at the start of follow-up.

Nested Case-Control Analysis

From the study population (i.e. users of antimalarial drugs), we randomly selected up to six controls per case, matched by age (± 2 years), gender, general practice attended, and calendar year (by using the same index date as for cases). Controls also had no history of depression, psychoses or panic attacks prior to use of an antimalarial study drug, had to be alive at the index date, and had to have some GPRD activity (diagnoses or prescriptions) recorded after the index date.

We classified subjects as current, recent or past users according to the same definitions as those used in the person-time analysis. We calculated relative risk (RR) estimates (as odds ratios [ORs]), using multivariate conditional logistic regression analyses, and controlled for age, gender, practice and calendar year (through matching) as well as smoking status (nonsmoker, current, past, unknown) and body mass index (BMI) <25, 25–29.9, 30+ kg/m^2. We included BMI as potential confounder since the pharmacokinetics of mefloquine, a highly lipid-soluble drug, may differ between lean and obese people, potentially affecting drug concentrations in the central nervous system and, consequently, the risk of neuropsychiatric disorders.

The statistical analyses were conducted using the software program SAS, Version 8.1 (SAS Institute Inc., Cary, NC, USA).

Results

The total study population consisted of 35 370 subjects (45.2% males); 16 491 subjects received mefloquine, 11 327 subjects received both proguanil and chloroquine, 1217 used proguanil alone 3585 used chloroquine alone, and 4574 used doxycycline. The numbers do not add up to the total due to some patients receiving more than one antimalarial during the study period. Within the study population, we identified 794 potential subjects with a first-time diagnosis of depression, psychosis, panic attack or suicide. Blinded to exposure status, we excluded 214 subjects because they had no referral and received no pharmacological treatment for the depression or psychosis at the index date. The remaining 580 subjects (68.8% females) were included in the analyses, consisting of 505 subjects with depression, 16 with psychosis, 57 with a panic attack and two subjects who committed suicide.

Depression

Among the 505 subjects with a first-time diagnosis of depression, the incidence rate of depression did not differ during current use of mefloquine, proguanil and/or chloroquine, or doxycycline; incidence rates were also similar during current or past mefloquine use periods. The RR of depression for current mefloquine use, compared with current use of proguanil and/or chloroquine, was 0.9 (95% CI 0.5–1.6; table I). Table II presents similar comparisons, this time selecting all past users as the reference group.

The distribution of age, gender, BMI and smoking status of subjects and controls is shown in table III.

From the person-time analysis it was found that females (RR 1.9, 95% CI 1.6–2.3; $p < 0.05$, compared with males) and subjects aged between 40–49 years (RR 1.4, 95% CI 1.1–1.7; $p < 0.05$, compared with 17–29 years) were at a slightly higher risk of having a first-time diagnosis of depression in this study population.

Table I. Incidence rates and relative risks for depression (n = 505), psychosis (n = 16) or panic attack (n = 57). Comparison between current users of various antimalarials

Outcome	Cases	Person-years	IR/1000 person-years (95% CI)	RR (95% CI)
Depression				
Proguanil and/or chloroquine current	35	4614.4	7.6 (5.5–10.5)	1.0 (ref.)
Mefloquine current	21	3023.4	6.9 (4.5–10.6)	0.9 (0.5–1.6)
Doxycycline current	4	423.0	9.5 (3.7–24.1)	1.2 (0.4–3.0)
Psychosis				
Proguanil and/or chloroquine current	2	4614.4	0.4 (0.1–1.6)	1.0 (ref.)
Mefloquine current	3	3023.4	1.0 (0.3–2.9)	2.3 (0.4–13.7)
Doxycycline current	0	423.0	0 (0.0–9.0)	
Panic attacks				
Proguanil and/or chloroquine current	6	4614.4	1.3 (0.6–2.8)	1.0 (ref.)
Mefloquine current	9	3023.4	3.0 (1.6–5.7)	2.3 (0.8–6.4)
Doxycycline current	0	423.0	0 (0.0–9.0)	

IR = incidence rate; **ref.** = reference; **RR** = relative risk.

The nested case-control analysis in total encompassed 580 subjects and 3464 matched controls. In this analysis, the adjusted ORs of developing a first-time diagnosis of depression for current users of mefloquine was 0.9 (95% CI 0.5–1.6) compared with the reference group of current users of proguanil and/or chloroquine, and 0.5 (95% CI 0.3–0.9; $p < 0.05$) in comparison to the reference group of all past users combined (table IV).

Psychoses

There were 16 subjects with a first-time diagnosis of psychosis during follow-up. Of these, three subjects were currently exposed, one was recently exposed, and two had past exposure to mefloquine. Compared with current use of proguanil and/or chloroquine, current exposure to mefloquine was associated with a nonsignificantly increased risk of developing psychosis (RR 2.3, 95% CI 0.4–13.7; table I). Comparing current mefloquine use to all past users combined, the RR was 4.1 (95% CI 1.1–15.0; $p < 0.05$) regardless of antimalarial drug previously used (table II). The RR estimates for subjects with a first-time diagnosis of psychosis could not be adjusted for age or gender since the numbers were too small for the multivariate model.

In the nested case-control analysis, based on only three exposed subjects and four exposed controls, the OR for psychosis for current mefloquine use was 9.8 (95% CI 0.5–204), compared with current use of proguanil and/or chloroquine. When compared with all past users combined, the adjusted OR for current mefloquine exposure was 8.0 (95% CI 1.0–62.7, $p < 0.05$). The adjusted OR for current or recent exposure to the other antimalarial study drugs was either close to one or could not be calculated due to insufficient numbers in the strata (table IV).

Panic Attacks

There were 57 subjects with a first-time diagnosis of panic attack during follow-up. Of these, nine subjects were currently exposed, six recently exposed, and eight had past exposure to mefloquine. Compared with current use of proguanil and/or chloroquine, current exposure to mefloquine was associated with a statistically nonsignificantly increased risk of developing panic attacks (RR 2.3, 95% CI 0.8–6.4; table I). Compared with all past users combined, the RR was 4.1 (95% CI 1.9–8.6; $p < 0.001$) for current mefloquine use (table II). Again, these RR estimates could not be adjusted for age or gender since some numbers were too small for the multivariate model. The risk was higher for females than males (RR 2.0, 95% CI 1.1–3.6; $p < 0.05$), and subjects aged 40–49 were at a nonsignificantly higher risk compared with subjects aged <30 years (RR 1.7, 95% CI 0.8–3.6).

In the nested case-control analysis, the OR of developing a first-time diagnosis of a panic attack for current users of mefloquine, compared with cur-

Table II. Incidence rates and relative risk estimates for depression (n = 505), psychosis (n = 16) or panic attack (n = 57). Comparison of current or recent users of various antimalarials with the reference group of all past users

Outcome	Cases	Person-years	IR/1000 person-years (95% CI)	RR (95% CI)
Depression				
All past use	353	36 863	9.6 (8.6–10.6)	1.0 (ref.)
Mefloquine current	21	3023.4	6.9 (4.5–10.6)	0.7 (0.5–1.1)
Mefloquine recent	32	3474.4	9.2 (6.5–13.0)	1.0 (0.7–1.4)
Proguanil and/or chloroquine current	35	4614.4	7.6 (5.5–10.5)	0.8 (0.6–1.1)
Proguanil and/or chloroquine recent	50	4807.7	10.4 (7.9–13.7)	1.1 (0.8–1.5)
Doxycycline current	4	423.0	9.5 (3.7–24.1)	1.0 (0.3–2.2)
Doxycycline recent	10	1225.6	8.2 (4.4–14.9)	0.8 (0.4–1.4)
Pychosis				
All past use	9	36 863	0.2 (0.1–0.5)	1.0 (ref.)
Mefloquine current	3	3023.4	1.0 (0.3–2.9)	4.1 (1.1–15.0)[a]
Mefloquine recent	1	3474.4	0.3 (0.1–1.6)	1.2 (0.2–9.3)
Proguanil and/or chloroquine current	2	4614.4	0.4 (0.1–1.6)	1.8 (0.4–8.2)
Proguanil and/or chloroquine recent	1	4807.7	0.2 (0.1–1.2)	0.9 (0.1–6.7)
Doxycycline current	0	423.0	0 (0.0–9.0)	
Doxycycline recent	0	1225.6	0 (0.0–3.1)	
Panic attacks				
All past use	27	36 863	0.7 (0.5–1.1)	1.0 (ref.)
Mefloquine current	9	3023.4	3.0 (1.6–5.7)	4.1 (1.9–8.6)[b]
Mefloquine recent	6	3474.4	1.7 (0.8–3.8)	2.4 (1.0–5.7)[a]
Proguanil and/or chloroquine current	6	4614.4	1.3 (0.6–2.8)	1.8 (0.7–4.3)
Proguanil and/or chloroquine recent	8	4807.7	1.7 (0.8–3.3)	2.3 (1.0–5.0)[a]
Doxycycline current	0	423.0	0 (0.0–9.0)	
Doxycycline recent	1	1225.6	0.8 (0.1–4.6)	1.1 (0.2–8.2)

a $p < 0.05$.

b $p < 0.001$.

IR = incidence rate; **ref.** = reference; **RR** = relative risk.

rent users of proguanil and/or chloroquine, was 1.7 (95% CI 0.5–5.7). In comparison with all past users combined, the adjusted OR for current mefloquine exposure was 2.7 (95% CI 1.1–6.5; $p < 0.05$). Other ORs for mefloquine or other antimalarials are displayed in table IV.

Suicide

There were two subjects who committed suicide during the follow-up period. Both were males (age 28 and 29 years, respectively) and had stopped treatment (mefloquine in both cases) ≥90 days before the index date (i.e. past users).

Descriptive Characterisation of Exposure Timing in Cases with Current Mefloquine Use

We further characterised subjects with a first-time diagnosis of depression, psychosis or panic attack during current exposure to mefloquine according to previous exposure duration at the index date.

There were 21 subjects with depression during current exposure to mefloquine. For 16 subjects the first-time diagnosis of depression was recorded after the first mefloquine prescription and for five it occurred during a second course of mefloquine. The median exposure time (i.e. the time between the date of the prescription and the date of the recorded first-time depression diagnosis) in the 16 subjects with one prescription was 46 days.

Table III. Characteristics of cases and controls with a first-time diagnosis of depression, psychosis or panic attack

	Depression			Psychosis			Panic attack		
	cases (n = 505)	controls (n = 3026)	OR (95% CI)	cases (n = 16)	controls (n = 96)	OR (95% CI)	cases (n = 57)	controls (n = 342)	OR (95% CI)
Age (y)									
17–29	120	735	NA	6	36	NA	12	83	NA
30–39	104	640	NA	3	16	NA	13	73	NA
40–49	130	706	NA	4	20	NA	17	87	NA
50–59	84	554	NA	2	18	NA	11	69	NA
60–69	53	294	NA	1	6	NA	4	27	NA
70+	14	97	NA	0	0	NA	0	3	NA
Gender									
Male	155	930	NA	7	42	NA	17	102	NA
Female	350	2096	NA	9	54	NA	40	240	NA
Smoking									
Non-smoker	257	1870	1.0 (ref.)	8	45	1.0 (ref.)	31	215	1.0 (ref.)
Current smoker	123	414	2.2 (1.7–2.9)[a]	2	22	0.5 (0.1–2.6)	13	51	1.8 (0.9–3.8)
Ex-smoker	45	208	1.6 (1.1–2.3)[b]	1	5	1.0 (0.1–10.0)	3	24	0.9 (0.3–3.1)
Unknown	80	534	1.1 (0.8–1.4)	5	24	1.3 (0.3–5.2)	10	52	1.4 (0.6–3.0)
BMI (kg/m^2)									
<25	223	1385	1.0 (ref.)	6	38	1.0 (ref.)	29	168	1.0 (ref.)
25–29.9	115	589	1.2 (1.0–1.6)	1	14	0.5 (0.1–4.7)	11	69	0.9 (0.4–2.0)
30+	30	226	0.8 (0.6–1.3)	2	3	3.4 (0.5–23.4)	4	28	0.8 (0.3–2.6)
Unknown	137	826	1.0 (0.8–1.3)	7	41	1.0 (0.3–3.7)	13	77	1.0 (0.5–2.1)

a $p < 0.001$.

b $p < 0.05$.

BMI = body mass index; **NA** = not applicable; **OR** = odds ratio; **ref.** = reference.

Table IV. Association between antimalarial drug exposure and depression, psychosis or panic attack in nested case-control analyses

Exposure status	Study population		OR (95% CI)[a]	OR (95% CI)[b]
Depression	Cases (n = 505)[c]	Controls (n = 3026)[c]		
All past users combined	362	1960	1.0 (ref.)	
Mefloquine current	21	200	0.5 (0.3–0.9)[d]	0.9 (0.5–1.6)
Mefloquine recent	29	223	0.7 (0.5–1.1)	
Proguanil and/or chloroquine, current	33	259	0.7 (0.5–1.0)	1.0 (ref.)
Proguanil and/or chloroquine recent	46	312	0.8 (0.6–1.2)	
Doxycycline current	3	12	1.2 (0.3–4.3)	1.7 (0.4–6.6)
Doxycycline recent	8	52	0.7 (0.3–1.6)	
Psychosis	Cases (n = 16)	Controls (n = 96)		
All past users combined	9	61	1.0 (ref.)	
Mefloquine current	3	4	8.0 (1.0–62.7)[d]	9.8 (0.5–204)
Mefloquine recent	1	5	2.4 (0.1–39.1)	
Proguanil and/or chloroquine current	2	13	1.1 (0.1–8.5)	1.0 (ref.)
Proguanil and/or chloroquine recent	1	8	0.7 (0.1–7.8)	
Doxycycline current	0	2		
Doxycycline recent	0	3		
Panic attack	Cases (n = 57)	Controls (n = 342)		
All past users combined	28	227	1.0 (ref.)	
Mefloquine current	9	27	2.7 (1.1–6.5)[d]	1.7 (0.5–5.7)
Mefloquine recent	6	21	2.3 (0.8–6.1)	
Proguanil and/or chloroquine current	6	32	1.5 (0.6–3.9)	1.0 (ref.)
Proguanil and/or chloroquine recent	7	30	1.9 (0.7–4.9)	
Doxycycline current	0	1		
Doxycycline recent	1	4	2.0 (0.2–19.0)	

a Current or recent mefloquine, doxycycline or chloroquine and/or proguanil use, compared with all past users combined, adjusted for smoking status (non, current, ex, unknown) and BMI (<25, 25–29.9, 30+ kg/m^2).

b Current mefloquine or doxycycline use compared with the reference group of current chloroquine and/or proguanil use, adjusted for smoking status (non, current, ex, unknown) and BMI (<25, 25–29.9, 30+ kg/m^2).

c Cases and controls do not add up to 505 and 3026, respectively. Three cases and eight controls are not listed in the table as they had meaningless risk estimates due to mixed exposure (e.g. mefloquine recent and doxycycline past).

d $p < 0.05$.

BMI = body mass index; **OR** = odds ratio; **ref.** = reference.

There were three subjects with psychosis and nine with a panic attack during current exposure to mefloquine. Among these 12 subjects, there were two whose index date was recorded after the second or third prescription. For the remaining ten, the first-time diagnosis of psychosis/panic attack was recorded after the first mefloquine prescription, with a median exposure time of 40 days.

Discussion

This large UK-based observational study did not find any evidence that depression is more common during or after mefloquine exposure than during or after exposure to other antimalarials. This conclusion is based on a direct comparison of the incidence rates of depression between various antimalarials as well as between various exposure periods. The study does suggest, however, that first-time diagnoses of acute psychoses or panic attacks may be more common during current exposure to mefloquine compared with current exposure to other antimalarials, as well as compared with past use periods. These findings are based on a small number of cases despite the relatively large base population of 16 491 mefloquine users, and some risk estimates were only marginally statistically significant or did not reach statistical significance. The fact that the number of cases with psychosis or panic attack was small

means that the absolute risk of developing psychosis or panic attack during mefloquine use is low. The incidence rate estimate for psychosis was 1.0/1000 person-years (95% CI 0.3–2.9), and for panic attacks it was 3.0/1000 person-years (95% CI 1.6–5.7) during current use of mefloquine. The average use of mefloquine lasts 8 weeks, or 0.15 years. Therefore, an incidence rate of one to three cases/1000 person-years would correspond to one to three cases during approximately 6700 treatment courses. These crude estimates give a feel for the absolute risk, but have to be interpreted with caution given that the statistical precision is limited and that there are some methodological limitations which are discussed below.

Through matching, we controlled the nested case-control analyses for the potential confounders age, gender, practice attended and calendar year. In addition, we adjusted the multivariate analyses for smoking status and BMI (table III). We found that current smokers receiving antimalarial medication had an increased risk of depression (OR 2.2, 95% CI 1.7–2.9; $p < 0.001$ vs non-smokers receiving antimalarial medication). A similar but non-significant association was found for panic attacks (OR 1.8, 95% CI 0.9–3.8). These findings may reflect real associations, but these associations may also be confounded since smoking is a marker for additional life-style or personal characteristics that may themselves be related to the risk of developing depression or panic attacks. However, in light of recent published data, a causal association between smoking and the risk of developing depression or panic attacks in patients receiving antimalarials cannot be ruled out.[34,35]

We made two separate comparisons in the analyses: (i) we directly compared the risk of developing an outcome of interest between current users of various antimalarials; and (ii) we compared the risk of developing an outcome during current use of antimalarials with the reference group of all past users combined, regardless of antimalarial drug used. This technique is based on the assumption that outcome events occurring during the past use period (i.e. ≥90 days after the end of drug use) are not related to previous drug use and reflect the baseline risk of developing an outcome of interest in the study population. This latter approach yielded point estimates that were similar to those of the direct comparison between current use of different antimalarial drugs, but with tighter CIs due to a gain in statistical power.

A strength of the current population-based study is that we used a database containing drug exposure and medical information that was recorded in the absence of any study hypothesis as a routine procedure to maintain a patient's longitudinal medical record. In contrast, several previous studies exploring the safety of antimalarial drugs used interview-based questionnaires.

This study has some potential limitations. First, although the GPRD contains GP-recorded drug exposure information, specialised travel clinics also prescribe antimalarials in the UK, and proguanil and chloroquine can be purchased in pharmacies without prescription. Thus, not all antimalarial drug use is necessarily captured by this database. For the current study, we only included subjects who received at least one prescription for an antimalarial study drug from the GP. Thus, we may have missed subjects who may have received an antimalarial drug elsewhere, but this is more likely to have diminished the study size rather than introduced any substantial misclassification. Secondly, patients taking different antimalarials are likely to have different travel destinations. We were not able to adjust for 'travel destination' since this information is not routinely recorded in the GPRD. While the travel destination is related to the choice of an antimalarial drug, it seems unlikely that there is also a consistent and strong association between travel destination and the risk of developing psychiatric outcomes. Thirdly, it would have been desirable to better distinguish between subjects who indeed took antimalarial drugs for malaria prophylaxis and those who received a prescription but did not take the drug due to poor compliance, poor tolerability, or having the drug as reserve medication. The latter can occur if travellers go to a destination with low malaria risk, where the drug is carried for use in an emergency situation (e.g. high fever), but not ingested on a regular basis for prophylaxis. Such subjects may have been classified as users and contributed exposed person-time to this analysis, despite the fact that they did not take the drug. It is not possible to reliably quantify this misclassification, which we acknowledge is present

to some degree in the current study. Fourthly, GPs may have missed episodes of depression or psychoses if the disease occurred on the trip and never came to the attention of the GP in the UK. Since we aimed at studying severe and pharmacologically treated episodes of depression or acute psychoses rather than mild mood disorders, there is an assumption that a high proportion of these events may have been reported to the GP after return to the UK for further diagnostic procedure and/or follow-up treatment. In order to make sure that we only included subjects who returned to the UK after a trip (as opposed to users of antimalarials who emigrated and left the national health system), we only included subjects who had some activity recorded in the GPRD by the GP (i.e. diagnoses, drug prescriptions) at some point in time after the prescription for an antimalarial drug. In addition, even if some cases were missed, it is unlikely that these cases were more likely to be exposed to any one of the antimalarial drugs.

There is evidence from a case-report that the combination of substantial alcohol consumption together with mefloquine may increase the risk of severe neuropsychiatric effects.[36] We did not study this potential interaction since alcohol consumption on a trip abroad cannot be reliably recorded in a database such as the GPRD. On the contrary, in order to reduce the risk of possible confounding by alcohol consumption, and since alcoholism itself is associated with neuropsychiatric disorders, we *a priori* excluded subjects with a recorded history of alcoholism.

In summary, we explored the association between use of mefloquine or other antimalarials and the risk of developing a first-time diagnosis of depression, psychosis or panic attack. We did not find evidence that the risk of developing a first-time diagnosis of depression is increased during or after use of mefloquine. On the other hand, psychoses and panic attacks were observed slightly more frequently in current users of mefloquine than in current or past use of other antimalarials. These findings need to be interpreted in the context of the above discussed methodological limitations of this observational study and of the relatively wide CIs of some risk estimates.

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