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Deaths and parasuicides associated with mefloquine chemoprophylaxis: a systematic review.

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A systematic review of deaths and parasuicides associated with mefloquine when taken as prophylaxis

Abstract

Background

Mefloquine is recommended in international health guidelines for preventing malaria in travellers. Reports of psychosis and suicide are often alluded to but are not clearly established.

Methods

We carried out a systematic review to identify and critically appraise any death or parasuicide associated with mefloquine prophylaxis. We developed a comprehensive search that included publications up to 11 July 2017. We included case studies but excluded newspaper reports. Two

authors independently appraised each death or parasuicide against a standardised causality assessment tool. The protocol was registered on PROSPERO (CRD42016041988).

Results

We identified 527 articles that required full-text retrieval; of these 17 were unique publications that reported deaths or parasuicide. Eight unique publications had sufficient detail to be included in causality assessment. We identified 2 deaths with a probable association that appeared to be idiosyncratic drug reactions; we categorised the remaining 8 deaths as "unlikely" to be related to mefloquine, or "unclassifiable". There was one parasuicide with a possible causal association.

There were 9 additional publications that searched spontaneous drug reporting databases; none provided sufficient detail to perform a causality assessment.

Conclusions

Overall, the number of deaths that we could reliably attribute to the prophylactic use of mefloquine is very low.

Key words: mefloquine, malaria, chemoprophylaxis, side-effects

1 Introduction

Mefloquine has been widely available for use in Europe and the USA since the late 1980s. Many international health guidelines recommend mefloquine as standard prophylaxis in travellers to malaria endemic areas [1,2,3,4].

Mefloquine often causes mild headaches and dizziness [5], but also vivid dreams and mood changes. These effects have given rise to beliefs that the drug can result in suicide and psychosis. The occurrence, frequency and severity of these events and their attribution to mefloquine have been the subject of heated debate. In 2013, the US Food and Drug Administration (FDA) issued a "boxed warning" about mefloquine and risk of neurological or psychiatric events, with special warnings to be given to users. However, there remains a lack of clarity over the evidence base for this, and concerns these developments limit the use of an important drug in preventing malaria in travellers [6]. Nevertheless, recently the UK Defence Committee concluded that mefloquine should only be used as a "drug of last resort" [7].

The side-effects of mefloquine are well documented: abnormal dreams, insomnia, anxiety and depressed mood, as well as nausea and dizziness. The recent Cochrane Review documents this and estimates absolute effects [8]. Whilst this is not contested, what is uncertain is the evidence related to the drug causing death or suicide.

The previous edition of the Cochrane Review on mefloquine included a table in an annex that the authors' referred to in the review's discussion relating to mefloquine and death. The Cochrane Infectious Diseases Group editorial team audited this table, which listed case reports of deaths and deaths due to suicide that had been attributed to mefloquine [9]. Some of the sources listed were when the drug was used in treatment, and others counted deaths in reviews that were not verifiable, and there were other errors and double counting across reviews. The Co-ordinating Editor of the Group (who is the last author of this paper) made the decision to withdraw the review because this information appeared misleading. The Cochrane Review has now been replaced with a new 2017

edition, prepared by a new author team using up-to-date methods drawing on cohort studies as well as trials [8].

In parallel with the preparation of the new edition of the Cochrane Review, we have conducted a systematic review of all reports of deaths, which we report here. This review draws on all possible reports, and applies a standard causality framework as this appears to be the most useful approach to critically appraise and assess the quality of these reports. In light of suggestions that mood change and suicide with the drug were connected, we also sought and appraised reports of parasuicide. The author team wrote and agreed the review protocol in advance [10], and the objectives were as follows.

- To identify all possible reported deaths or episodes of parasuicide associated with mefloquine used at a prophylactic dose in publicly available literature.
- To critically appraise each case using a formal causality assessment.

2 Materials and methods

2.1 Inclusion criteria

2.1.1 Types of studies

We included all forms of prospective and retrospective studies of individual case reports or reviews of case reports that reported deaths or parasuicide. Newspaper articles were excluded.

2.1.2 Types of participants

Adults, including pregnant women, and children of all ages.

2.1.3. Types of interventions

Mefloquine at a prophylactic dose. This included the current recommendation (250 mg weekly), and previously used doses, such as 360 mg weekly, 180 mg weekly and 500 mg fortnightly.

2.1.4 Types of outcome measures

- Death.
- Parasuicide (the act of committing suicide without the resulting death. Objectively and subjectively, the actions taken were intended to result in death).

2.2 Search strategy

We attempted to identify all relevant studies regardless of language or publication status (published, unpublished, in press and ongoing).

We searched the following databases using the search terms described in Figure 1: the Cochrane Infectious Diseases Group Specialized Trials Register; the Cochrane Central Register of Controlled Trials (CENTRAL), published in the Cochrane Library; PubMed (MEDLINE); Toxicology Literature Online (TOXLINE); Embase (OVID); the Science Citation Index Expanded™, accessed via Web of Science; and LILACS. We also searched the following ongoing trials registers: the *meta*Register of Controlled trials (www.controlled-trials.com); the U.S. National Institutes of Health Register

Figure 1. PubMed search strategy*

1. (("Mefloquine"[Mesh]) OR lariam OR mefloquin* Field: Title/Abstract
2. malaria* OR antimalaria* OR plasmodium OR prophyla* OR chemoprophyla* OR prevent* OR chemoprevent* Field: Title/Abstract
3. exp "Mental Disorders"[Mesh] OR (adverse OR neurotox* OR psychiatr* OR neuropsych* OR psycho* OR suicid* OR death* OR mortality OR fatal* OR neurol* OR ototox* OR depress* OR anxiety OR toxic* OR safety OR tolerab* OR reaction* OR "side effect*" OR severe OR disorder* OR dizziness OR headache* OR mental) Field: Title/Abstract
4. #1 and #2 and #3
5. ("Mefloquine/adverse effects"[Mesh] OR "Mefloquine/contraindications"[Mesh] OR "Mefloquine/poisoning"[Mesh] OR "Mefloquine/toxicity"[Mesh])
6. 4 or 5
7. ((military or soldier* OR army or force or defence or deploy* OR personnel)) Field: Title/Abstract OR "Military Personnel"[Mesh] OR "Military Facilities"[Mesh]
8. 1 AND 7
9. 6 OR 8

* Search strategies for the other listed databases are available on request.

(www.clinicaltrials.gov); and the World Health Organization (WHO) International Clinical Trials Registry platform (ICTRP) (www.who.int/trialsearch), to identify ongoing studies.

We searched the following websites: Medicines and Healthcare Products Regulatory Agency (UK; www.mhra.gov.uk); European Medicines Agency (www.emea.eu); Database of Adverse Effects Notification (Australia, www.tga.gov.au/database-adverse-event-notifications-daen); FDA Medwatch (USA, www.FDA.gov/safety/Medwatch)**;** UK Parliament website (www.parliament.uk/).

We checked the reference lists of each included paper for other potentially relevant studies. At full-text screening stage, we compiled a database of any articles that mentioned death or parasuicide associated with mefloquine prophylaxis. We then checked the reference list of each of these papers and retrieved the original full-text case reports (where available).

For each published review of deaths due to mefloquine, including the withdrawn Cochrane Review [9], we compared the primary citation for each death and compiled a list of the unique death reports. We contacted authors, where necessary, to obtain full descriptions of any deaths or episodes of parasuicide.

2.3 Methods

2.3.1 Selection of studies

Two authors independently screened the results of the literature search for potentially relevant trials, studies or case reports, and looked for multiple publications from the same data set. Full text copies were retrieved of all trials deemed potentially relevant.

Two authors then independently assessed all identified trials, studies or case reports for inclusion in the review using the pre-stated inclusion criteria. Any disagreement was resolved through discussion and where necessary a third author was consulted. We have reported all reasons for excluding any identified studies.

2.3.2 Data extraction and management

Two authors independently extracted data using a standardized and pre-piloted data collection form. When available, we extracted the following information.

- Study: design, year, country of origin and country of malaria exposure.
- Intervention: drug dose during prophylaxis, use of a loading dose, number of doses taken, frequency of drug administration and use of any co-interventions.
- Participant: age, sex, body mass index (BMI), occupation, past medical history, proceeding symptoms, use of other medications (prescribed and recreational).
- Outcome: circumstances of death or parasuicide, timing in relation to treatment, duration and frequency of monitoring, method of detection.

2.3.3 Assessment of causality

We extracted data on all reports of death. Two authors independently critically appraised each report using 'The WHO-UMC system for standardised case causality assessment' tool' (Figure 2) [11]. This classifies the event into "certain", "probable", "possible" or "unlikely" depending on the strength of the association with the study drug. Where the information presented was poor or conclusions could not be drawn, we categorised the event as "unclassifiable". We have included all reports in the final review, regardless of classification. Any disagreement was resolved through discussion, and where necessary a third author was consulted.

2.3.4 Dealing with missing data

If data from the papers was insufficient, unclear or missing, we contacted the authors for additional information.

Term	Description	Comment
Certain	"A clinical event, including laboratory test abnormality, occurring in a plausible time relationship to drug administration, and which cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (de-challenge) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory re-challenge procedure if necessary."	It is recognized that this stringent definition will lead to very few reports meeting the criteria, but this is useful because of the special value of such reports. It is considered that time relationships between drug administration and the onset and course of the adverse event are important in causality analysis. So also is the consideration of confounding features, but due weight must be placed on the known pharmacological and other characteristics of the drug product being considered. Sometimes the clinical phenomena described will also be sufficiently specific to allow a confident causality assessment.
Probable	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (de-challenge). Re-challenge information is not required to fulfil this definition.	This definition has less stringent wording than for "certain" and does not necessitate prior knowledge of drug characteristics or clinical adverse reaction phenomena. As stated, no re-challenge information is needed, but confounding drug administration and underlying disease must be absent.

Possible	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.	This is the definition to be used when drug causality is one of other possible causes for the described clinical event.
Unlikely	A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations.	This definition is intended to be used when the exclusion of drug causality of a clinical event seems most plausible.
Un-assessable/ unclassifiable	A report suggesting an adverse reaction which cannot be judged because information is insufficient or contradictory, and which cannot be supplemented or verified.	This definition is used when insufficient information is available to perform a causality assessment.

Figure 2. Framework for causality assessment [11]. These descriptions are based on the WHO-UMC causality assessments, with appropriate modifications for this review.

3 Results

3.1 Description of studies

Our electronic search was performed on 11 July 2017 and identified 2523 citations. Screening the reference list of all papers referring to deaths associated with mefloquine prophylaxis identified an additional 2 case reports. After removal of duplicates, 2521 articles were retrieved.

Of these, we excluded 1993 at the title and abstract screening stages and retrieved 528 full-text reports. We did not identify any ongoing studies or studies awaiting classification.

Of these 528, 457 did not meet our inclusion criteria and were excluded for the reasons detailed in Figure 3.

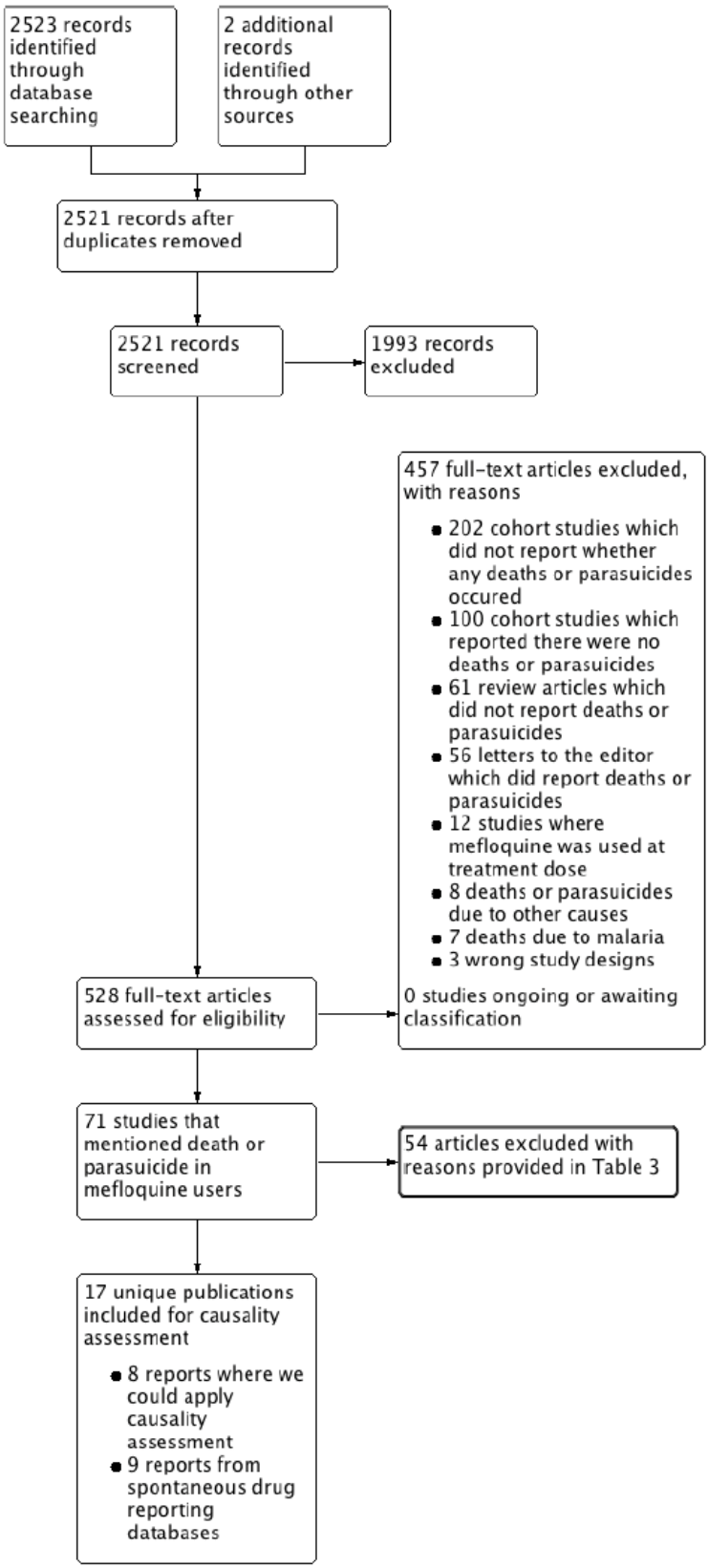
A total of 71 studies mentioned mefloquine being potentially linked to death or parasuicide. Of these, 17 were unique publications which referred to death or parasuicide in users of mefloquine prophylaxis. Fifty-four articles were excluded after full-text assessment.

Eight publications were individual reports of death or parasuicide and are included with a full causality assessment (Table 1). Three of these were case reports in peer-reviewed journals and one additional case report was from a drug safety newsletter. Two were retrospective cohort studies and one was a randomised controlled trial in pregnant women. The eighth publication was a review article about suicide in US soldiers.

Nine publications included multiple reports of death reported in reviews that had been derived from spontaneous drug reporting databases. All of these reports had insufficient information to apply causality assessment (Table 2). These publications searched a total of five databases across a variety of dates including the National French Pharmacovigilance database, the Roche Drug Safety Department, the Spanish Pharmacovigilance System, the UK Medicines and Healthcare Products Regulatory Agency Yellow Card Scheme and the US FDA.

The 54 publications excluded after full-text assessment are detailed in Table 3. Thirty articles referred to publications included in our main analysis; 7 made reference to mefloquine being linked to suicide, but did not provide a reference; 6 referred to case reports of mefloquine being linked to suicide, however, the reference(s) provided did not include any reports of death or parasuicide; 3 were case reports in which mefloquine was used at treatment dose; 3 did not provide sufficient detail to meet our inclusion criteria (for example, dose not specified); 3 referred to a death in a user of mefloquine prophylaxis but the reference provided was a newspaper article; and 2 were excluded for other reasons.

Figure 3. Study flow diagram



3.2 Causality assessment

For the 8 publications that we applied the formal causality assessment, the results are shown in Table 1. We identified 2 deaths with a probable causal association with mefloquine prophylaxis, and 1 parasuicide with a possible causal association. The probable deaths were caused by what appeared to be idiosyncratic drug reactions (pulmonary fibrosis; exfoliative illness with neutropenia). We classified 8 other individual reports of death as “unclassifiable” or “unlikely” using the causality framework.

4. Discussion

We identified two deaths with a probable causal association with mefloquine prophylaxis, and one parasuicide with a possible causal association. The application of rigorous procedures, ensuring deaths were not double counted, and applying a causality assessment results in a much smaller number of deaths than previously cited in the discussion section of an older edition of the Cochrane Review on the topic which reported that 22 deaths, including 5 suicides, were caused by mefloquine [8,30].

Whether the reported deaths were correctly attributed to the use of mefloquine prophylaxis is an important clinical question, as the risk of death in a previously healthy population is unacceptable to both prescribers and users of malaria prophylaxis. As this old data set was contained as an annex with no methods, we have repeated the analysis with a new search strategy and formal causality assessment. Our assessment indicates the previous estimate was incorrect.

We were rigorous in our application of the criteria and in resolving discrepancies so that the approach was standardised across all cases identified. However, there are some, it has been pointed

out to us, such as Table 1 FDA 2008 [15] might be better classified as “unlikely” or “unclassifiable”. Whilst we would agree these are difficult decisions, our approach has been to maintain the judgements made by the team, rather than adjusting in the light of subsequent comments on selected cases. Determination of causality is very complicated where people are in highly stressful situations which in themselves can cause sleeplessness and stress; and psychological and psychiatric disturbances after active military duty can be common: Marvasti 2013 in Table 1 illustrates this [16].

Designing a systematic review to assess the risk of a rare outcome of an intervention, such as death, poses specific methodological challenges. Randomised controlled trials and cohort studies are usually not powered to detect uncommon outcomes. Therefore, systematic evaluation of these outcomes requires the inclusion of other study designs such as case reports, case series and spontaneous reporting systems [31]. These study designs have their own limitations [32].

One problem with these methods of pharmacovigilance is that death is too rare an outcome to allow a robust statistical analysis to evaluate the likelihood that a particular treatment is the cause of a particular adverse event [33]. Therefore, each individual case report requires a formal causality assessment. Many different methods have been proposed; however, so far no approach has shown consistent and reproducible results and therefore there is currently no gold standard methodology [33]. The WHO-UMC system used in this paper was designed as a combined assessment, considering the clinical-pharmacological aspects of the case history and the quality of the recorded observations [11]. Despite its limitations, this remains the most widely used method in causality assessment, largely due to its ease of use and easy-to-follow classification system [33].

However, regardless of the methodology used to determine causality, our main limiting factor was the poor reporting of this topic within the academic literature. Despite extensive searching, we only found a few reports that provided us with sufficient detail to perform a formal causality assessment. Even where case reports did provide sufficient information, quality concerns remained; a good

example comes from a widely-reported case [34,35] that contained significant discrepancies regarding the dose of mefloquine across different publications of the same report. We received confirmation through personal communication with the author that mefloquine was in fact taken at a treatment dose for presumed malaria illness and thus excluded from our analysis (Jousset, personal communication).

Case reports or case series are absolutely confounded by publication bias. In other words, if the event occurs then such cases are likely to be written up and reported in a journal, whereas if there is no event they will not be reported. However, what was striking here was how few reports we found, despite exhaustive searching.

Publications that included analyses of spontaneous drug reporting databases provided additional interesting information. These databases were developed after the thalidomide incident and are used in the identification of signals of new, rare and serious adverse drug reactions [36]. They provide a large volume of reports, but often contain little or no additional information, and usually have insufficient detail to critically appraise causality. These reports have appeared in previous reviews of severe adverse effects of mefloquine, but when we examined the information reported none had sufficient detail to apply the causality framework. We have intentionally not provided a summary estimate of the number of deaths associated with mefloquine use in these analyses (Table 2). Collections of adverse reactions to spontaneous reporting systems occur from all available sources including the lay and scientific press, national and international regulatory authority databases, consumers and medical and paramedical practitioners. Therefore, it is likely that events are reported more than once, by different doctors or by both doctor and patient, as well as to more than one spontaneous reporting system. There are also discrepancies between different searches of the same database. Only one of these analyses performed a causality assessment of the reported cases [21], and there was insufficient detail for us to provide a robust estimate ourselves.

Our findings differ from previous analyses of the same topic [9, 30], which have included several references to grey literature, including newspaper articles; in our opinion this should be avoided in the scientific analysis of controversial topics such as this one.

Overall, the number of deaths that we could reliably attribute to the prophylactic use of mefloquine was much lower than has previously been reported. However, due to poor reporting of this topic within the literature, we cannot provide a single summary estimate.

Declarations of interest

PG was an author on the 2000 edition of a Cochrane Review of mefloquine that reported on 4 deaths due to mefloquine [46]. PG is the Co-ordinating Editor of the Cochrane Infectious Diseases Group and was responsible, with three other colleagues, for withdrawing the Cochrane Review that discussed an unpublished review with higher estimates of death [9]. The other authors have no competing interests to declare.

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Table 1. Case reports of deaths in users of mefloquine prophylaxis: causality assessment				
Primary reference	**Type of study**	**Clinical summary**	**Classification**	**Justification**
Anon 2001 [12,13]	Case report in a peer-reviewed journal	A previously healthy 22 year old began mefloquine prophylaxis 1 week prior to travel. 8 days later he developed fever, chills, headache and cough. He was diagnosed with malaria and bronchopneumonia and was treated orally with halofantrine, dirithromycin and acetylcysteine. Two days later, he stepped from a car, complained of a 'head rush', then collapsed and died. Autopsy revealed a previously undiagnosed atypical asymmetric hypertrophic cardiomyopathy.	Unlikely	Halofantrine has been commonly associated with cardiac arrhythmias as it causes prolongation of the QT interval (it was discontinued for this reason) and is the more likely cause of a potential dysrhythmia in this patient with previously undiagnosed cardiomyopathy.
Eick-Cost 2017 [14]	Retrospective cohort study	Two soldiers who received a prescription for mefloquine (from a cohort of 36,538) committed suicide. In the same cohort study, 15 soldiers who received a prescription for doxycycline (cohort size 318,421), and one who received a prescription for atovaquone-proguanil also committed suicide (cohort size 12,881).	Unclassifiable	This was a retrospective analysis of prescription data and the individuals were never contacted. Therefore, it is not possible to confirm whether the mefloquine prescriptions was ever taken and, if so, the occurrence of this event in relation to treatment use. There is also no past medical history and no information about any co-medications for either participant.
FDA 2008 [15]	Case report in a drug safety newsletter	A 4 year old female patient died from pulmonary fibrosis and interstitial pneumonitis. She was started on mefloquine 75 mg per week prior to travelling. The patient had previously taken mefloquine (unknown date). During	Probable	The event occurred following a reasonable time sequence to when the drug was taken. There was no past medical history and

		the trip, she experienced rash and fever at night, but was afebrile during the day. She was given an antibiotic for a suspected infection, although subsequent tests revealed no evidence of this. On her return, she was hospitalized with suspected inflammatory disease, but no specific diagnosis was given. She was continued on the mefloquine and received corticosteroids which led to some improvement. After 45 days, her general state of health worsened. She started to cough and developed interstitial pneumonitis. Mefloquine was discontinued. A chest radiograph showed bilateral infiltration confluent in the lung. She was intubated and ventilated due to her rapidly progressive lung failure. A pulmonary biopsy showed autoimmune interstitial alveolitis. She was treated with high dose corticosteroids, plasmapheresis and immunoglobulins. After five weeks of extracorporeal membrane oxygenation (ECMO) treatment, the patient died suddenly.		no alternative drug regime used to provide an alternative explanation. Symptoms continued to progress despite the withdrawal of mefloquine, making de-challenge difficult to analyse. This is presented as a series of 12 cases where mefloquine was associated with pneumonitis.

Marvasti 2013 [16]	Review article about suicides in US soldiers	1. Thirty-six-year old male who committed suicide during an 'uncontrollable rage' three weeks after returning home, having served 10 months in Iraq. It is reported that he drank excessively and 'self-medicated' in the time leading up to his suicide. 2. A military policeman in Baghdad (unknown age), who took mefloquine during his operations. He suffered from long term nightmares and sleeplessness following his return home. It is reported that he had returned home 'months' before his suicide.	Unclassifiable	For both cases, no information is provided regarding the dose used, how long it had been taken for and the timing of the event in relation to treatment. There is also no past medical history given for the individual concerned and minimal information regarding any co-medications.

McBride 1997 [17]	Case report in a peer-reviewed journal	A 6-year-old healthy girl resident in the UK of Nigerian descent visited Nigeria on a 4-week holiday. She commenced mefloquine 125 mg weekly 1 week before travel and was still taking this medication on her return. 35 days after starting mefloquine she developed blistering of her lips and oral mucosa with periorbital and facial swelling. She subsequently developed erythema and blistering of her face, trunk, limbs, and perineum which progressed to exfoliation of 95% of her body surface over 48 h. Complications over 10 days included pyrexia, hypotension, diarrhoea, neutropenia, anaemia, paralytic ileus, and klebsiella septicaemia. On day 19 of admission she developed cardiac asystole and resuscitation was unsuccessful.	Probable	The symptoms occurred in a reasonable time sequence to when mefloquine prophylaxis was taken. Extensive investigations revealed no alternative cause and the patient was not taking any other medications and had no past medical history. The occurrence of SJS/erythema multiforme has been documented elsewhere in association with mefloquine. No information is available regarding de-challenge.
Meier 2004 [18]	Retrospective cohort study	Two individuals who received a prescription for mefloquine (from a cohort of 16,491) committed suicide during the 'follow up period' of this retrospective cohort study. Both were males and had stopped treatment over 90 days before the date of the event.	Unclassifiable	This was a retrospective analysis of prescription data and the individuals were never contacted. Therefore, it is not possible to confirm whether the prescriptions were ever taken and if so, the duration of treatment. There is also no past medical history and no information about any co-medications for either participant.

Nosten 1994 [19]	Randomised controlled trial	"One woman in the mefloquine group died of septic shock after an emergency caesarean section for obstructed labour"	Unlikely	This patient died of complications related to labour rather than mefloquine use.
Rodor 1990 [20]	Case report in a peer-reviewed journal	Case of 22-year-old woman who took a 250 mg of mefloquine for malaria prophylaxis. On day 2 after intake, she experienced episodes of crying, emotional detachment, and low mood. Her symptoms ameliorated on day 5 and 6. One week later (following the next dose) there was a relapse of symptoms with ideas of reference, of guilt, of death, and feelings of body transformation. Five days later she was hospitalized after a suicide attempt by drowning. Physical examination and routine blood tests, ECG and EEG were normal. She was discharged from hospital three weeks later.	Possible	The symptoms occurred in a reasonable time sequence to starting mefloquine prophylaxis. The patient was released from hospital after 3 weeks, which is the half-life of mefloquine. No information is provided regarding this patient's past medical history or any other medications she had taken or was currently taking.

Table 2. Reports of death from spontaneous drug reporting databases with insufficient information to apply causality assessment					
Database searched	Reference	Type of study	Dates of search	Search criteria	Description of included cases
National French Pharmacovigilance database	Angles 2003 [21]	Peer-reviewed journal article	1 January 1996 to 31 December 2000	Included all drugs used for the treatment or prophylaxis of malaria in France apart from Doxycycline. Excluded foetal effects in pregnancy, voluntary overdose, insufficient available information regarding the event, and instances in drugs were not used for malaria	- Ventricular fibrillation in a 53-year-old man with no history of previous cardiac problems
Roche Drug Safety Department	Bem 1992 [22]	Peer-reviewed journal article	1985 to May 1991	All spontaneously reported adverse drug reactions	- No deaths were reported. - 1 suicide attempt in a 45 year old female in 1988 who took mefloquine for malaria prophylaxis for 3 weeks, who was hospitalized. She had a history of paranoia after taking chloroquine and had an (unspecified) family history of mental health problems. She was also taking gringko, gemfibrozil and nomogestrol. - 1 suicide attempt in a 33 year old male in 1989, who took mefloquine for malaria prophylaxis for 3 weeks. States he had no risk factors.

					- 1 suicide attempt in a 29 year old female in 1989, who took mefloqine for malaria prophylaxis for 2 weeks. States she had no risk factors. - 1 suicide attempt in a 23 year old female in 1990, who took mefloquine for malaria prophylaxis for 2 weeks. States she had no risk factors.
	Nosten 1999 [23]	Peer-reviewed journal article	Unclear	Not specified	- Reports 4 deaths in users of mefloquine due to: fatal toxic epidermal necrolysis, myocardial infarction (following halofantrine treatment), pulmonary carcinoma and myocarditis
	Schlagenhauf 2001 [24]	Conference proceedings	1985 to June 2000	Serious adverse event reports of suicide and/ or depression. Exclusion criteria included treatment dose, overdose, indication and dose unknown and prescribing errors.	Reports 8 cases of suicide in participants who had used mefloquine, all male aged 23-55 years old. Three cases had pre-existing psychiatric disorders, 4 did not and one case was unknown. In four cases the latency period was 3-47 days. In 2 cases the suicide occurred months or years after prophylaxis use.
	WHO 1991 [25]	WHO report	September 1985 to July 1991	Adverse events which occurred during clinical trials or during routine use of the	- No deaths were reported - 1 suicide attempt in a 33 year old male who took mefloquine

				drug	for malaria prophylaxis for 3 weeks. Reports he had no family history of mental health problems - 1 suicide attempt in a 22 year old female who took mefloquine for malaria prophylaxis for 2 weeks. Reports she had no family history of mental health problems
Spanish Pharmacovigilance system	Aldea 2012 [26]	Peer-reviewed journal article	2004 to 2009	Adverse drug reactions in individuals aged 0 to 17 years	- 1 sudden death in a 1 year old male in 2006 - 1 sudden death in a 2 year old male in 2006
UK Medicines and Healthcare Products Regulatory Agency Yellow Card Scheme	Smith 1999 [27]	Peer-reviewed journal article	Up to July 1998	Not specified	"A total of 8 fatal reactions"
	Thomas 2014 [28]	Peer-reviewed journal article	1964 to 25th January 2012	All reports associated with the Higher Level Terms (HLTs) from the Medical Dictionary for Regulatory Affairs (MedDRA): (a) Depressive disorders; and (b) Suicidal and self injurious behavior.	Reports 8 suicides associated with mefloquine

US Food and Drug Administration (FDA)	Anon 2002 [29]	Commentary in non-profit organization review article	October 2000 to 2001	Unclear	Among 600 reports related to mefloquine, “13 who had suicidal thoughts, 4 who attempted suicide, and 1 who committed suicide.”

Table 3. Characteristics of excluded studies

Reference	Reason for exclusion
Anonymous 1990 [37]	Refers to a 'Cardiopulmonary arrest one patient who was taking propranolol (Inderal; and others) after a single dose of mefloquine'. No reference is provided and the dose used was not mentioned.
Anonymous 1996 [38]	Refers to 3 users of mefloquine prophylaxis with 'suicidal tendencies', but does not provide sufficient detail to meet our definition of para-suicide.
Anonymous 2000 [39]	Refers to a case report of a suicide in a Dutchman who took mefloquine at a treatment dose.
Anonymous 2009 [40]	Refers to a case report of death already included within our analysis [12,13].
Abecasis 2009 [41]	Refers to a death and does not provide a reference. However, the description of the case matches an included case report [12,13].
Alisky 2006 [42]	Refers to a cohort study already included within our analysis [18].
Alikadi 2007 [43]	Refers to case reports of mefloquine being linked to suicide, however, the reference(s) provided do not include any reports of death or parasuicide [44].
Chattopadhyay 2007 [45]	Refers to a case report already included within our analysis [17].
Croft 2000 [46]	Refers to a case report(s) of death already included within our analysis [17,27,37], as well as review articles we have screened separately.
Croft 2007 [47]	Refers to a review article, which we have analysed separately within the review [46].
Croft 2007a [48]	Refers to case report(s) of death already included within our analysis [12,13,34,35,37].
Croft 2007b [49]	Refers to a case report(s) of death already included within our analysis [12,13,17,34,35], as well as review articles we have screened separately.
Croft 2007c [50]	Refers to a review article, which we have analysed separately within the review [49].
Croft 2008 [51]	Refers to a case report(s) of death already included within our analysis [17], as well as review articles we have screened separately.

Croft 2010 [52]	Refers to a review article, which we have analysed separately within the review [8].
Croft 2015 [53]	Refers to a death in a user of mefloquine prophylaxis, but the reference provided is a newspaper article.
Croft 2016 [54]	Mentions that "on or around 20 December 1995, a UK soldier who was taking mefloquine during an Army run clinical trial in Kenya killed himself". However no reference is provided and there is no information about the mefloquine dose used.
Eaton 2009 [55]	Refers to a review article, which we have analysed separately within the review [8].
Eber 2003 [56]	Reports that "rare cases of suicide have been reported" [with mefloquine use] but does not provide a reference.
Embrey 2009 [57]	Reports that "rare cases of suicide and suicidal ideation have been reported" [with mefloquine use] but does not provide a reference.
Fauman 2012 [58]	Refers to an internal policy memorandum within the US military which we have analysed separately [57].
Forrester 2016 [59]	Refers to a review article, which we have analysed separately within the review [60].
Gogtay 2015 [61]	Refers to "suspected reactions of …depression, sometimes leading to suicide" but does not provide a reference.
Jousset 2006 [34, 35]	Two different publications were available describing this case. Through personal communication with the author we were able to establish that both publications refer to the same case, and that mefloquine was taken at treatment dose.
Hennequin 1994 [62]	Refers to case reports of mefloquine being linked to suicide. However, the reference(s) provided do not include any reports of death or para-suicide [63].
Jacquieroz 2009 [30]	Refers to a case report(s) of death already included within our analysis [12, 13, 17, 18, 27, 34, 35, 39], as well as review articles we have screened separately and newspaper articles.
Jacquieroz 2015 [9]	Refers to a case report(s) of death already included within our analysis [12, 13, 17, 18, 27, 34, 35, 39], as well as review articles we have screened separately and newspaper articles.
Jha 2006 [64]	Refers to a drug database analysis we have already included in our analysis [27]

Jong 2001 [65]	Refers to review articles, which we have analysed separately within the review [66].
Kingma 2002 [67]	Reports that “rare cases of suicide and suicidal ideation have been reported” [with mefloquine use] but does not provide a reference.
Kukoyi 2003 [68]	Refers to case reports of mefloquine being linked to suicide. However, the reference(s) provided do not include any reports of death or para-suicide [69]. Also includes references to newspaper articles.
Livesey 2016 [70]	Reports that “neuropsychiatric side effects attributed to mefloquine use [include] suicide” but no reference is provided.
Lopez-Velez 2003 [71]	Refers to review articles, which we have analysed separately within the review [24, 46].
Luzzi 1993 [72]	Refers to review articles, which do not include any reports of death [63].
Mawson 2013 [73]	Refers to a death in a user of mefloquine prophylaxis, but the reference provided is a newspaper article.
McCarthy 2005 [74]	Refers to “mefloquine [being] responsible for fatal assaults committed by Canadian soldiers in Somalia and British soldiers in Sierra Leone” but does not provide a reference.
McCarthy 2015 [75]	Refers to a case report of death already included within our analysis [34,35], as well as review articles analysed separately.
McEvoy 2015 [76]	Refers to a case report of death already included within our analysis [34,35].
Nevin 2010 [77]	Refers to a death in a user of mefloquine prophylaxis, but the reference provided is a newspaper article.
Nevin 2012 [78]	Refers to a case report of death already included within our analysis [34,35].
Nevin 2012a [79]	A case report which includes a description of an “impulsive act” “designed to feel fear”, which does not meet our definition of para-suicidal.
Nevin 2012b [80]	Refers to a case report of death already included within our analysis [34,35], as well as a review article we have analysed separately [49]
Nevin 2015 [81]	Refers to review articles, which we have analysed separately within the review [60,82] as well as newspaper articles

Nevin 2015a [82]	Refers to case report(s) of death already included within our analysis [34,35] as well as review articles we have analysed separately [49].
Nevin 2016 [83]	Refers to case report(s) of death already included within our analysis [34,35,39].
Nevin 2017 [84]	This paper performed a drug safety database analysis of the US Food and Drug Administration Adverse Event Reporting System. However, they did not report individual cases, and instead reported on “suicidal and self injurious behaviour" which does not meet our inclusion criteria.
Ritchie 2013 [60]	Refers to a case report(s) of death already included within our analysis [17,34,35], as well as review articles we have screened separately and newspaper articles.
Schlagenhauf 1999 [66]	Refers to case report(s) of death already included within our analysis [17].
Tango 2003 [85]	Refers to case reports of mefloquine being linked to suicide. However, the reference(s) provided do not include any reports of death or para-suicide [86], as well as a review articles we have analysed separately.
WHO 2001 [87]	Refers to a review article, which we have analysed separately within the review [23].
Willmore 2006 [88]	Refers to a drug safety database analysis which we have analysed separately within the review [25].
Wittes 1995 [69]	Refers to a review article, which we have analysed separately within the review [22].
Wooltorton 2002 [89]	Refers to case reports of mefloquine being linked to suicide, however, the reference(s) provided do not include any reports of death or para-suicide [44,69]