Neurotoxicity of antimalarial drugs: a systematic review

Reviewers

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Background

Malaria infection continues to be a major cause of human morbidity and mortality globally[(1)]. Four main species of malaria commonly infect humans, of which two (*Plasmodium falciparum* and *P. vivax*) have reported effects on the nervous system[(2, 3)]. A wide range of therapeutic agents are used to prevent and treat malaria, some of which have documented deleterious effects on the nervous system. It is often difficult to differentiate between the effects of malaria and the drugs on the nervous system.

One of the difficulties of identifying effects of antimalarial drugs on the nervous system is that malaria itself may result in neurological impairment, cerebral malaria (CM) being the most common severe neurological complication. In adults, cerebral malaria is a diffuse encephalopathy in which focal neurological signs are relatively unusual[(4)]. In African children growing up in malaria endemic areas, it manifests as seizures, impaired consciousness and metabolic acidosis presenting as respiratory distress or severe anemia[(4)]. Compared with adults,

children have a higher incidence of seizures. Recent studies have shown that neurological and cognitive deficits may persist in long-term survivors of CM. In African children, deficits in attention , memory and visual skills, speech and language have been reported[5]. Some of these effects have also been observed in other forms of malaria less severe than cerebral malaria such as malaria with multiple convulsions but no prolonged loss of consciousness[3]. It is also known that malaria may affect hearing, with hearing loss being reported as a complication of severe malaria[6, 7]. However, since antimalarial drugs are sometimes indicated for use in non-malarious conditions such as prophylaxis in healthy subjects, the comparison of drug effects in non-malarious conditions with those observed in the context of malaria can give useful information on toxicity attributable to antimalarial drugs.

Antimalarial drugs have selective actions on the different phases of the parasite life cycle, and may be indicated either for chemotherapy or chemoprophylaxis. They can be divided as follows into 6 major classes based on chemical structure:-

Aminoquinolines	*Amodiaquine, Chloroquine, Hydroxychloroquine, Pamaquine, Primaquine*
Biguanides	*Proguanil , Cycloguanil embolate*
Arylaminoalcohols	*Mefloquine, Quinine, Halofantrine, Lumefantrine*
Diaminopyridines	*Pyrimethamine*
Artemisinin derivatives	*Artemisinin,Artemether,Artesunate,Artenimol Arteether/Artemotil*
Others	*Sulphonamides, Doxycycline*

To reduce the pace of selection of drug resistance, the World Health Organisation (WHO) now recommends that all antimalarial therapies be deployed as combinations that include an artemisinin derivative as one of the partner drugs, a strategy referred to as artemisinin combination therapy (ACT)[8, 9].

Neurotoxicity has been reported for many of the antimalarial drugs. Choroquine prophylaxis has been associated with retinal dysfunction, and in high doses causes seizures and coma[10]. Quinine affects the auditory system causing reversible sensorineural hearing loss, tinnitus and vertigo [11].

The prophylactic use of mefloquine causes irreversible ototoxicity in healthy subjects[12]. Mefloquine has also been associated with severe dose dependent neuropsychiatric adverse reactions such as anxiety, delusions, hallucinations and psychosis[13]. Lumefantrine, like mefloquine, is a phenanthrene methanol derivative of quinine and has a moderately long terminal elimination half-life in malaria patients of 3-6 days[14, 15]. Although lumefantrine has not been reported to be neurotoxic in the clinical setting, it has been suggested that the prolonged exposure of auditory neurons to lumefantrine, as occurs under therapy with artemether-lumefantrine combination may sensitize neurons to harm by artemisinins, with cumulative harm occurring with successive dosing[16].

Whilst it has been reported that artemisinin antimalarials are well tolerated with few side effects[17-21], their association with neurotoxicity in animal models has raised concerns about their safety in humans[22]. The neuropathology observed in animals is unusual, appearing to selectively damage parts of the brainstem nuclei, particularly those involved in hearing and balance[23]. In humans, hearing loss, ataxia and tremor have been reported[24]. The prolonged presence of artemisinins upon slow release from oil-based intramuscular formulations appears to be the main cause of observed toxicity in preclinical animal studies[25, 26]. Although several studies have failed to demonstrate toxicity attributable to oral artemisinins in humans[27, 28], a recent study concerning Mozambican construction workers raised concerns and renewed interest in auditory impairment with artemether-lumefantrine (AL) when taken for uncomplicated malaria[24, 29]. In this study, no correlation was found between the degree of hearing loss and the time interval separating AL exposure and the follow-up audiogram, suggesting AL associated hearing loss to be irreversible[16, 24]. In support of this, *in vitro* studies suggest that artemisinin neurotoxicity does not manifest immediately upon exposure, but that once commenced it is inevitable and irreversible; extrapolation from *in vitro* data suggests that 14 days may possibly be required for full development[24, 30]. In practice artemisinins are often used in combination with other potentially neurotoxic antimalarials, making it difficult to attribute neurotoxicity to the artemisinin component alone.

Neurological impairment is associated with morbid consequences, and continues to place a big socio-economic burden, especially in developing countries which have few resources to deal with such problems. Children are particularly more vulnerable, as effects of neurotoxicity,

particularly hearing or visual impairment may affect the child's linguistic, cognitive and educational developments later on in life[31]. The benefits of artemisinin combination therapy have been demonstrated in a large meta-analysis of nearly 6000 patients which shows that combining existing antimalarial drugs with an artemisinin derivative reduces patients risk of treatment failure (by 75%) and lessens the pool of infectious parasites (gametocytes) that transmit the disease to others, an effect that is of both clinical and public health benefit[32]. However, whilst these studies have clearly demonstrated that ACT is efficacious and have promoted the wide deployment of these combination therapies in Africa and Asia, uncertainty remains over the potential neurotoxicity of artemisinins, and whether combining artemisinins with other potentially neurotoxic antimalarials may increase the risk of harm. This systematic review of the available literature on neurotoxicity of antimalarial drugs aims to inform policy and guide best practice regarding the use of antimalarial drug combinations in chemoprophylaxis and treatment. We propose to identify antimalarials with the least neurotoxic effects, when used alone or in combination, information which together with efficacy data, would be useful when choosing the most suitable antimalarials for ACT.

Review Question/Objective

The objective of this systematic review is to examine the neurotoxic effects of antimalarial drugs.

More specifically, we propose to identify which antimalarials have the least neurotoxic effects, information which together with efficacy data would be useful in choosing the most suitable antimalarials for combination therapy.

Inclusion criteria

Types of studies

The review will consider randomized controlled trials. In the absence of any RCTs, other quantitative study designs such as quasi randomized controlled trails, non-randomized controlled trials, case control studies, clinical studies, before and after studies and cohort studies will be considered for inclusion in a narrative summary. This will enable the identification of current best evidence regarding the use of antimalarial drugs in combination therapy.

Types of Participants

The types of participants in the studies being reviewed will include adults and children with no specific age limitation.

Types of Interventions

We will review studies that evaluate combinations of antimalarial drugs.

Types of outcome

We will evaluate studies that consider the following outcome measures: neurotoxicity, which is defined as effects on the central and /or peripheral nervous system.

Search Strategy

The search strategy aims to find both published and unpublished studies published in English language between 1966-2007. A three-step search strategy will be used in each component of this review. An initial search of MEDLINE, CINAHL, Cochrane Library and EMBASE will be undertaken followed by analysis of the text words contained in the title and abstract, and of the index terms used to describe article. A second search using all identified keywords and index terms will then be undertaken across all included databases. Thirdly, the reference list of all identified reports and articles will be searched for additional studies.

The databases to be searched include: MEDLINE, CINAHL, Cochrane Library, EMBASE Current Control Trials Register, TRoPHI, Australian Clinical Trials Registry, www.scirus.com, SCOPUS, Clinical Pharmacology, Current Contents, Web of Science, WHO (and regional offices)

The search for unpublished studies will include:

a) Dissertation Abstracts International

b) WHO Library

c) Proquest Digital Theses

d) Theses Canada Portal

e) AHRQ (Agency for Healthcare Research and Quality)

f) Australasian Digital Thesis (ADT) Program

g) BVS Virtual Health Library

h) Popline (Population Information Online)

i) Grey Literature Report (via New York Academy of Medicine website)

j) Primary Care Clinical Practice Guidelines

k) National Library of Medicine (NLM)

l) LILACS database (Latin American and Carribean Health Sciences Literature)

m) Index to Theses

n) Grey Source: A Selection of Web-based Resources in Grey Literature

o) Geneva Foundation for Medication Education and Research (GFMER)

p) British Library

Initial keywords to be used will be:

Malaria drugs, neurotoxicity, neurotoxin, ototoxicity, hearing impairment, visual impairment, retinopathy, malaria, drug, neurologic impairment, neurological impairment, malaria chemotherapy, malaria vaccine/vaccines, neurotoxic, central nervous system affects, amodiaquine, chloroquine, hydroxychloroquine, pamaquine, primaquine, Proguanil , cycloguanil embolate, mefloquine, quinine, halofantrine, lumefantrine, pyrimethamine, artemisinin, artemether,artesunate ,artenimol , arteether, artemotil, sulphonamides, dapsone, doxycycline

Assessment of methodological quality

Quantitative papers selected for retrieval will be assessed by two independent reviewers for methodological validity prior to inclusion in the review using standardized critical appraisal instruments from the Joanna Briggs Institute Meta Analysis of Statistics Assessment and Review Instrument (JBI-MAStARI) **[Appendix 1: Appraisal tool]**. Any disagreements that arise between the reviewers will be resolved through discussion, or with a third reviewer.

Data collection/extraction

Data extraction will be managed using the appropriate JBI data extraction tool **[Appendix 2]**. In some cases revision of the data extraction tool will occur after the full search has been conducted.

Data synthesis

Quantitative papers will, where possible be pooled in statistical meta-analysis using the Joanna Briggs Institute Meta Analysis of Statistics Assessment and Review Instrument (JBI-MAStARI) **[Appendix 3: Synthesis tool]**. All results will be subject to double data entry. Odds ratio (for categorical data) and weighted mean differences (for continuous data) and their 95% confidence intervals will be calculated for analysis. Heterogeneity will be assessed using the standard Chi-square. Where statistical pooling is not possible the findings will be presented in a narrative form.

Conflicts of interest

There are no known conflicts of interest regarding this systematic review.

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Appendix 1: Assessment Tool

JBI Critical Appraisal Checklist for Experimental Studies

Reviewer _____ Date _____

Author _____ Year _____ Record Number _____

	Yes	No	Unclear
1. Was the assignment to treatment groups truly random?	☐	☐	☐
2. Were participants blinded to treatment allocation?	☐	☐	☐
3. Was allocation to treatment groups concealed from the allocator?	☐	☐	☐
4. Were the outcomes of people who withdrew described and included in the analysis?	☐	☐	☐
5. Were those assessing outcomes blind to the treatment allocation?	☐	☐	☐
6. Were the control and treatment groups comparable at entry?	☐	☐	☐
7. Were groups treated identically other than for the named interventions?	☐	☐	☐
8. Were outcomes measured in the same way for all groups?	☐	☐	☐
9. Were outcomes measured in a reliable way?	☐	☐	☐
10. Was appropriate statistical analysis used?	☐	☐	☐

Overall appraisal: Include ☐ ☐ Exclude ☐ ☐ Seek further info. ☐

Comments (Including reasons for exclusion)

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JBI Critical Appraisal Checklist for Descriptive/ Case Series

Reviewer _____ Date _____

Author _____ Year _____ Record Number _____

	Yes	No	Unclear
1. Was study based on a random or pseudo-random sample?	☐	☐	☐
2. Were the criteria for inclusion in the sample clearly defined?	☐	☐	☐
3. Were confounding factors identified and strategies to deal with them stated?	☐	☐	☐
4. Were outcomes assessed using objective criteria?	☐	☐	☐
5. If comparisons are being made, was there sufficient descriptions of the groups?	☐	☐	☐
6. Was follow up carried out over a sufficient time period?	☐	☐	☐
7. Were the outcomes of people who withdrew described and included in the analysis?	☐	☐	☐
8. Were outcomes measured in a reliable way?	☐	☐	☐
9. Was appropriate statistical analysis used?	☐	☐	☐

Overall appraisal: Include ☐ Exclude ☐ Seek further info ☐

Comments (Including reason for exclusion)

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JBI Critical Appraisal Checklist for Comparable Cohort/ Case Control

Reviewer _____ Date _____

Author _____ Year _____ Record Number _____

	Yes	No	Unclear
1. Is sample representative of patients in the population as a whole?	☐	☐	☐
2. Are the patients at a similar point in the course of their condition/illness?	☐	☐	☐
3. Has bias been minimised in relation to selection of cases and of controls?	☐	☐	☐
4. Are confounding factors identified and strategies to deal with them stated?	☐	☐	☐
5. Are outcomes assessed using objective criteria?	☐	☐	☐
6. Was follow up carried out over a sufficient time period?	☐	☐	☐
7. Were the outcomes of people who withdrew described and included in the analysis?	☐	☐	☐
8. Were outcomes measured in a reliable way?	☐	☐	☐
9. Was appropriate statistical analysis used?	☐	☐	☐

Overall appraisal: Include ☐ Exclude ☐ Seek further info ☐

Comments (Including reason for exclusion)

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Appendix 2: Data Extraction

JBI Data Extraction Form for Experimental/ Observational Studies

Reviewer _____ Date _____

Author _____ Year _____

Journal _____ Record Number _____

Study Method RCT ☐ Quasi-RCT ☐ Longitudinal ☐

Retrospective ☐ Observational ☐ Other ☐

Participants

Setting _____

Population_____

Sample size

Intervention 1 _____ Intervention 2 _____ Intervention 3 _____

Interventions

Intervention 1 _____

Intervention 2 _____

Intervention 3 _____

Clinical outcome measures

Outcome Description	Scale/measure

Study results

Dichotomous data

Outcome	Intervention ( ) number / total number	Intervention ( ) number / total number

Continuous data

Outcome	Intervention ( ) number / total number	Intervention ( ) number / total number

Authors conclusions

Comments