

# Ototoxic effects of hydroxychloroquine

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## SUMMARY

**OBJECTIVE:** To present scientific evidence based on a systematic review of the literature (PRISMA), aiming to systematize evidence of the ototoxic effects of hydroxychloroquine (HCQ).

**METHODS:** The studies were selected using a combination based on the Medical Subject Headings (MeSH). The databases searched were MEDLINE (PubMed), LILACS, SciELO, and BIREME, encompassing articles from January 2010 to May 2020, with no restrictions of language and place of publication.

**RESULTS:** A total of 148 articles with the potential to be included were retrieved. Of these, two answered the research question, which consisted of seeking evidence of the ototoxic effects of hydroxychloroquine. These studies scored 11 in their quality assessment with the modified protocol by Pithon et al.<sup>13</sup>.

**CONCLUSIONS:** The studies reported possible ototoxicity of HCQ. Audiovestibular changes, such as hearing loss, peripheral vestibular syndrome, and tinnitus were evidenced in patients submitted to HCQ. The improvement in the audiological examinations and the regression in the vestibular syndrome after stopping the treatment with HCQ are strong arguments in favor of the ototoxicity caused by this medication. However, there are still divergences about the relationship between ototoxic effects and the use of HCQ.

**KEYWORDS:** Hydroxychloroquine. Hearing. Ototoxicity. Medication errors.

## INTRODUCTION

Hydroxychloroquine sulfate (HCQ) is analogous to chloroquine, which can inhibit plasma levels. It is an antimalarial agent used to treat diabetes mellitus, dyslipidemias, coagulopathies, infectious and certain autoimmune diseases, e.g., Sjogren's syndrome, rheumatoid arthritis (RA), and systemic lupus erythematosus (SLE)<sup>1</sup>.

HCQ is currently being investigated – without scientific evidence at this point—to be a possible treatment of choice for the new coronavirus (SARS-CoV-2) or COVID-19, which is responsible for the ongoing pandemic.

HCQ has side effects, the most common being nausea, diarrhea, pruritus, rash, and hyperpigmentation. However, the most serious side effect is ocular toxicity, which must be routinely

monitored<sup>2</sup>. Various publications point out the ototoxic effects of HCQ, which may be associated with varying degrees of destruction to the cochlear sensory hair cells. HCQ decreases the neuronal population, changes the supporting structures, and results in atrophy and vacuolization of the stria vascularis, a possible consequence of ischemia<sup>3</sup>. The main symptoms are tinnitus, sensorineural hearing loss, and vertigo<sup>4</sup>.

Medication-related ototoxicity is defined as either a temporary or permanent auditory and/or vestibular function disorder, induced by therapeutic substances<sup>10</sup>. This impairs functional activities and quality of life, and can appear after a relatively short period, in small dosages<sup>7,9,11</sup>. It is important to highlight the ototoxic effects of HCQ due to its indiscriminate use without clarity about pathological effectiveness.

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Therefore, this study presents scientific evidence for HCQ use and, based on a systematic review of the literature using preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines, aims to find answer to the following question: Does the use of hydroxychloroquine have ototoxic effects on patients?

## METHODS

### Research design and search strategies

For a systematic review, we followed the –PRISMA recommendations<sup>12</sup>. The search was conducted by two independent researchers, using MEDLINE (PubMed) (<https://www.ncbi.nlm.nih.gov/pubmed/>), LILACS (<http://lilacs.bvsalud.org/>), SciELO (<http://www.scielo.br/>), and BIREME (<https://bvsalud.org/>) databases, for scientific articles without restriction on language or geography from January 2010 to May 2020. In addition to this, manual searches were conducted using Google Scholar for the above criteria that include the gray literature. The result was structured using the population, intervention, control/comparison, outcomes and study type (PICOS) framework (Table 1).

Descriptors selected based on the dictionary of Health Sciences Descriptors and Medical Subject Headings (DeCS/MeSH) were hydroxychloroquine and chloroquine and malaria and COVID-19 or diabetes mellitus or systemic lupus erythematosus or rheumatoid arthritis or dyslipidemia or Sjogren's syndrome or ototoxicity and audiology.

### Selection criteria

#### Inclusion criteria

The selected literature includes descriptive cross-sectional studies, cohort studies, and case studies published from January 2010 to May 2020, without restrictions on language or geography.

**Table 1.** Description of the PICOS framework research model.

Acronyms	Definitions
P	Patients
I	Hydroxychloroquine
C	Ototoxicity
O	Medication
S	Descriptive study Cross-sectional study Observational study

Source: developed by the authors.

They were evaluated for quality, with a score higher than 6, as per the modified protocol given by Pithon et al.<sup>13</sup>

#### Exclusion criteria

Studies published as letters to the editor, guidelines, literature reviews, systematic reviews, meta-analyses, and abstracts were excluded.

#### Data analysis

For a systematic review, data were extracted from the selected studies in a spreadsheet developed by researchers using Excel®. The extracted data were selected by one researcher and validated by another. The data from eligible studies were transferred to the spreadsheet and organized as described in Figure 1.

Out of 148 articles selected, 145 unique studies were retained. After analysis, 138 papers were excluded as they failed to meet the inclusion criteria, and 7 articles remained. Out of these, 3 articles were excluded based on the information given in their abstracts. Among the rest, 2 more studies were excluded, leaving the last 2 articles for full review (Figure 1).

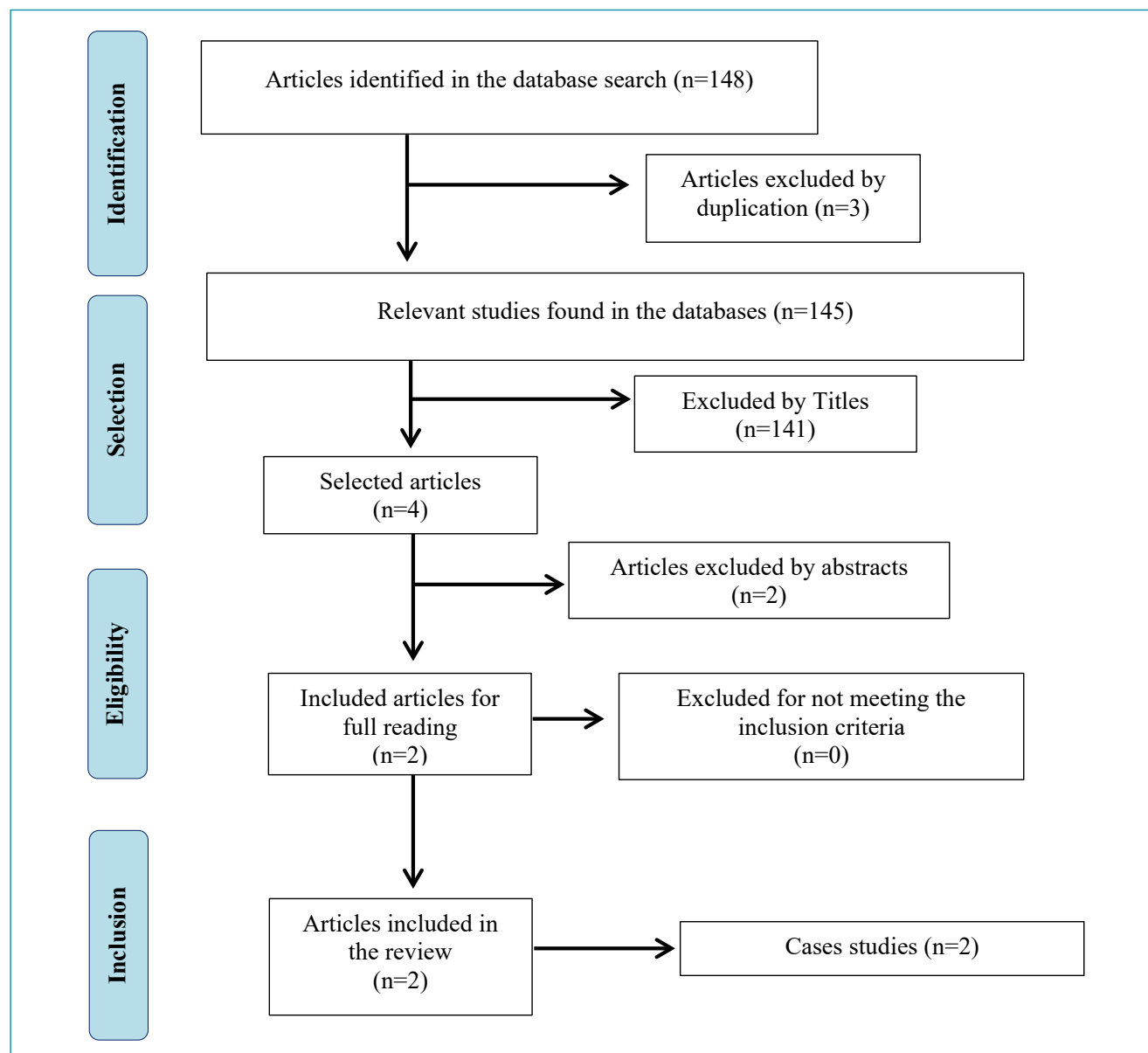
Data extracted from the studies were descriptively analyzed. Due to the small number of selected studies and the lack of homogeneity between extracted variables, the meta-analysis was not performed. The quality of the studies was carefully analyzed.

## RESULTS

After careful evaluation, the two eligible articles<sup>2,14</sup> met all the pre-established criteria and answered the research question: Does the use of hydroxychloroquine have ototoxic effects?

The studies<sup>2,14</sup> in this review were case reports. In the final analysis, they were categorized according to the theme, focusing on the use of HCQ and its ototoxic effects when treating patients. With respect to the quality of evaluation, these studies achieved a score of 11, representing the rationale for their inclusion and in-depth analysis. Their main characteristics can be found in Table 2.

The first study was conducted by a French pharmacovigilance group<sup>14</sup>. It reports the case of a female, diagnosed with SLE, initially treated with HCQ. The exact dates of treatment were unknown, but when she was 33 years-old and many years after being on a dosage of 400 mg/day of HCQ, the patient had a sudden bilateral hearing loss associated with vestibular syndrome. Magnetic resonance imaging (MRI) did not find lesions in the brainstem. After administering three 1000 mg doses of methylprednisolone, the patient had a partial hearing recovery, assessed for improvement using control audiometry.



**Figure 1.** Flowchart of the research method and analysis. Source: Research model developed by the authors.

The researchers<sup>14</sup> hypothesized that the hearing loss was an effect of HCQ administration. Treatment was stopped and replaced with methotrexate (15 mg/week). In a clinical examination after 6 months of initial diagnosis, a regression was observed with sudden hearing loss, including hearing impairment, which was not perceived by the patient. For joint pain, methotrexate, in combination with glucocorticoids, was prescribed to the patient for approximately 15 years. In this context, HCQ treatment was resumed at 400 mg/day, 5 days/week. Three months later, the patient presented with peripheral vestibular syndrome, and diagnosed by an otorhinolaryngologist as neuritis. Brain MRI focused on the inner ear, and

pontocerebellar angles did not present any notable issues. HCQ administration was stopped in the following month (i.e., four months after the beginning of the treatment).

The otorhinolaryngologist confirmed a mild bilateral hearing loss (30 dB) at frequencies of 1000 Hz. In the next month, a dosage of 800 mg of methylprednisolone was given. For the next five months, no subjective improvement in auditory thresholds could be discerned. However, there was no recurrence of vestibular syndrome, and the patient's hearing loss did not become worse<sup>14</sup>.

The second selected study was published in the year 2020, conducted by the Department of Rheumatology and Clinical

Table 2. Summary of the selected research articles.

Author(s)/ Year/Place of publication	Objective(s)	Examinations	History of medications	Results	Conclusion(s)
Chatelet et al. <sup>14</sup> , 2017  France	To report the case of a patient treated with HCQ. She presented hearing loss, which improved when the medication was discontinued.	Auditory assessment with pure-tone threshold audiometry (PTA); diagnosed with sudden bilateral hearing loss. Brain MRI revealed the absence of lesions in the brainstem. A new visit to the otorhinolaryngologist, 4 months after discontinuation of HCQ for the second time, when the stabilization of the hearing loss was evidenced.	Use of 400 mg/day of HCQ. Ototoxicity was treated with three 1000-mg doses of methylprednisolone. Use of methotrexate (15 mg/week) in combination with glucocorticoids, for 15 years. Reintroduction of HCQ, 400 mg/day, 5 days a week, posteriorly removed	After using methylprednisolone, the hearing loss was partially solved, with an improvement in the audiometry. The hypothesis of hearing loss related to HCQ was considered, and the treatment was stopped. After 15 years of treating with methotrexate in combination with glucocorticoids, it was necessary to reintroduce HCQ. The patient presented peripheral vestibular syndrome 3 months after resuming the drug and was shortly after diagnosed with a mild bilateral hearing loss. After final discontinuation, there was neither recurrence of the vestibular syndrome nor worsening of the hearing loss.	Possible ototoxicity related to the use of HCQ.
Patil et al. <sup>2</sup> , 2020 India	To report the case of a middle-aged woman who developed auditory toxicity in relation to the use of HCQ	Audiological follow-up with PTA, in which the patient was diagnosed with a mild idiopathic sensorineural hearing loss. The thresholds worsened 6 months after beginning the treatment with HCQ. However, these symptoms improved after intervention.	Treated with HCQ (400 mg/day) and steroids (40 mg/day of prednisolone gradually reduced to 5 mg/day and maintained) for 1 year. After intervention, the patient was treated with mycophenolate mofetil and with increased the dosage of prednisolone to 10 mg/day	During therapy, the patient complained of tinnitus and gradual worsening of hearing. There was no history of vertigo, vomit, or other characteristics of involvement of the vestibular system. Diagnosed with mild idiopathic sensorineural hearing loss. The patient did not use any medication with the potential for auditory toxicity other than HCQ. A new audiogram obtained after stopping the use of HCQ showed auditory stabilization, with an improvement in the auditory thresholds, bilaterally.	Ototoxicity related to the use of HCQ was demonstrated.

HCQ, hydroxychloroquine; PTA, pure-tone threshold audiometry. Source: data from Chatelet et al., 2017<sup>14</sup> and Patil et al., 2020<sup>2</sup>.

Immunology of India<sup>2</sup>. This work examined the case of a 51-year-old female patient, diagnosed with mixed connective tissue disease (MCTD), and treated with HCQ (400 mg/day) and steroids (40 mg/day of prednisolone, gradually reduced to 5 mg/day, maintained for one year). After six months of therapy, the patient complained of tinnitus and a gradual loss of hearing. She had no history of vertigo, vomiting, or involvement of the vestibular system. The otorhinolaryngologist diagnosed a mild idiopathic sensorineural hearing loss.

Pure-tone threshold audiometry (PTA), performed 6 months after starting HCQ administration, showed progression of the loss, with a decrease of approximately 20 dB in both the ears. The otorhinolaryngological assessment did not reveal any anatomic cause. Blood sugar levels and thyroid function were found normal. Her medication history was analyzed, which indicated that she had not taken any other medication with potential auditory toxicity, except HCQ. Treatment with HCQ was stopped and continued with mycophenolate mofetil and with an increased dosage of prednisolone (10 mg/day). PTA was repeated 3 months after the suspension of HCQ administration, which confirmed stabilized hearing and improved thresholds.

## DISCUSSION

This study presents the evidence of ototoxic effects of HCQ. Antimalarial medications have been prescribed for years, given their low cost and good results<sup>15</sup>, especially HCQ<sup>16</sup>. Nevertheless, some cases of audiovestibular toxicity along with the use of HCQ were reported in the literature<sup>6,7,9,11,17</sup>.

Studies selected for this research<sup>2,14</sup> confirmed ototoxic effects of HCQ. In one of the studies<sup>2</sup>, this was understood as the patient had no history of ototoxic medications, other than HCQ. Moreover, the patient had no anatomic, blood sugar level, or thyroid function changes. Her hearing stabilized, as some auditory thresholds improved. In the other study<sup>14</sup>, ototoxicity was attributed to HCQ, with auditory and vestibular effects (sudden hearing loss associated with vestibular syndrome); this regressed soon after the medication was stopped. The patient developed peripheral vestibular syndrome with hearing loss 3 months after reintroducing the medication.

Ototoxicity of HCQ may be related to differing degrees of deterioration of cochlear sensory hair cells, atrophy, and vacuolization of the stria vascularis<sup>18</sup>. Tinnitus, sensorineural hearing loss, and vertigo are the leading symptoms<sup>4</sup>.

In the French pharmacovigilance databank (since December 2015), there were 23 registered cases of hearing loss with HCQ treatment—none in which a positive reintroduction was observed<sup>14</sup>. In 17 of the registered cases, HCQ was the

only questionable medication. Hearing loss was frequently sudden, either unilateral (eight cases) or bilateral (seven cases). In almost half of the cases, this was associated with cochleoves-tibular symptoms, such as dizziness and/or tinnitus; the disorders occurred within days to years of treatment. Most often, the damage was irreversible. However, in seven cases a total or partial improvement of hearing was observed; in two cases, however, this was not reported<sup>14</sup>.

A study at the Medical University of Lodz (Poland) found that 28.6% ( $n=10$ ) of the subjects developed sensorineural hearing loss with 80% treated with chloroquine diphosphate. This research revealed that dizziness and tinnitus were the most frequently reported vestibulocochlear symptoms, with at least 1% population on this drug<sup>17</sup>. These complaints were described in other studies<sup>18,19</sup>, with tinnitus reported in one study, which was selected for our systematic review.

On the other hand, a recently published study reported that auditory changes occurred in patients on HCQ, as a consequence of the pathology being treated. Most changes were found in patients not using antimalarials<sup>20</sup>.

The studies in this review diverged from the use of HCQ administration and the identification of the onset of auditory and vestibular effects. In one study, the patient used the drug for many years before the symptoms appeared<sup>14</sup>; in the other, symptoms occurred a few months after the treatment began<sup>2</sup>. Auditory changes after prolonged therapy with HCQ<sup>5-7</sup>, or its ototoxic effects in the short time use<sup>8,9,11</sup>, were already reported in the literature.

In the research with a total of 28 people, audiovestibular symptoms occurred in four patients within 24 hours of HCQ administration. However, 53% of the complications were reported a month after starting the medication. Two subjects had serious adverse effects, with significant irreversible functional sequelae (hearing loss in one patient, and hearing loss and vertigo in another)<sup>21</sup>.

Some authors suggest that most HCQ-related ototoxicity takes place after its prolonged use<sup>11</sup>. Previous reports suggested that HCQ ototoxicity was related to higher HCQ dosages along with its prolonged use<sup>5</sup>.

Another aspect is the reversibility of auditory and vestibular effects, which vary within and between studies. In the first episode, change was observed in the first study<sup>14</sup>, with reversibility of effects after the discontinuation of HCQ and switching to methylprednisolone. Effects that appeared after reintroducing HCQ were not completely resolved, without any subjective improvement in auditory thresholds. In the second study<sup>2</sup>, PTA was repeated 3 months after interrupting HCQ administration, showing the hearing stabilized and the thresholds improved. There is no consensus in the literature on the reversibility of

auditory and vestibular changes, with some studies found to be reversible<sup>8,9</sup> and with some others, irreversible<sup>5,7</sup>.

Some studies suggest that HCQ-related ototoxicity is reversible when it is detected early. However, the first manifestations of a cochlear lesion can only be detected with auditory-evoked potentials<sup>10</sup>.

## CONCLUSIONS

The studies<sup>2,14</sup> reported possible ototoxicity of HCQ. Audiovestibular changes such as hearing loss, peripheral vestibular syndrome, and tinnitus were found in patients administered with HCQ. The improvement in the audiological examinations and the regression in the vestibular syndrome after

discontinuing HCQ are strong indications of ototoxic effects of HCQ. However, there are still more studies required to establish the relationship between ototoxic effects and the use of HCQ.

## AUTHORS' CONTRIBUTIONS

**LFG:** Conceptualization, Investigation, Methodology, Writing – Original Draft. **PH:** Conceptualization, Data Curation, Formal Analysis, Methodology, Supervision, Validation, Visualization, Writing – Original Draft. **FSAP:** Data Curation, Formal Analysis, Supervision, Validation, Visualization, Writing – Review & Editing. **KMP:** Data Curation, Formal Analysis, Supervision, Validation, Visualization, Writing – Review & Editing.

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