Why Your Patients' Believing Hydroxychloroquine and Chloroquine Are 90% Effective for COVID-19 Is 100% Dangerous

The Journal of Clinical Pharmacology
2020, 60(8) 949–953

DOI: 10.1002/jcph.1687

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Keywords
COVID-19, hydroxychloroquine, chloroquine

Some media sites broadly tout claims by the Association of American Physicians and Surgeons (AAPS) that hydroxychloroquine and chloroquine have 90% success for COVID-19.[1-3] This message was amplified by President Trump, who allegedly took hydroxychloroquine for 2 weeks after White House staff members contracted COVID-19.[4] AAPS has also shared these data on success with the governor of Arizona to influence state health policy.[3] The result was tens of thousands of patients flocking to their clinicians hoping to receive hydroxychloroquine prescriptions.[5]

An assessment of GoodRx prescription records for hydroxychloroquine and chloroquine from February 16 to April 25 found 483 425 additional prescriptions were filled over this period in 2020 versus 2019.[5] During the week of March 15 to March 21, hydroxychloroquine and chloroquine prescriptions for <28 tablets rose from 2208 to 45 858, 28- to 60-tablet prescriptions rose from 70 472 to 196 606, and >60-tablet prescriptions rose from 44 245 to 124 833 in 2019 versus 2020. At the end of the study, hydroxychloroquine and chloroquine prescriptions for <28 tablets were still 848% above normal and 28- to 60-tablet prescriptions were 53% above normal, but >60-tablet prescriptions were 64% below normal in 2020 versus 2019.[5]

In contrast, a National Institutes of Health panel with representatives of 14 national professiona societies and government agencies stated there is insufficient evidence to recommend for or against using hydroxychloroquine for the treatment of COVID-19.[6] Similarly, the American College of Physicians stated there was conflicting and insufficient evidence to support the use of hydroxychloroquine for the treatment or prevention of COVID-19, the Society of Critical Care Medicine said there was insufficient evidence for the treatment of critically ill COVID-19 patients, the Infectious Disease Society of America stated hydroxychloroquine should only be used in COVID-19 trials, and the American Thoracic Society suggested it only be used in a manner that would allow study of its efficacy and safety.[7-10]

Our Health Outcomes, Policy, and Evidence Synthesis group at the University of Connecticut performed the evidence review for the American College of Physicians Practice Points Panel.[7,11] In this editorial, we analyze the methods used by the AAPS in comparison with our own to identify why our conclusions differ so starkly. We then discuss why professional societies and clinicians alike need to call out this misleading information for the safety of the patients we serve and some tips to engage in discussions with patients asking for hydroxychloroquine.

How Does the AAPS Derive Its Conclusion?

The AAPS provides a link to its "frequently updated table of studies" to substantiate their claims.[12] It defined success as the "% of no mortality or probability of preventing death." For example, Dr Vladimir Zelenko told them he had treated 399 patients with hydroxychloroquine, and 2 of them died (397/399 lived = 99.5% success). Without a control group, we have no idea what would have happened if they had not received hydroxychloroquine. This would be a success if only

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Submitted for publication 28 May 2020; accepted 8 June 2020.

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2 people died when 4 people would have died without hydroxychloroquine, but a tragedy if no one would have died without it. Much of the data they use are from anecdotal experiences without any control group. Where controlled data are available, the effects seen in the control group are not used in their calculations, only those in the hydroxychloroquine and chloroquine arms.[12]

They also report another end point called "improved," and it is defined as: "improved or never contracted CoVID-19 despite being exposed."[12] They give no time frame over which they would determine that improvements happened. With COVID-19, patients either die or improve if you wait long enough so it is impossible to know if patients improved based on the body's response to the disease or hydroxychloroquine or chloroquine. In addition, if you erroneously assume that almost everyone in your community would be infected before giving them prophylactic hydroxychloroquine, can you really say you prevented COVID-19 in all those cases? This is the major issue with Dr Zelenko's data set; he was broadly providing hydroxychloroquine prophylaxis and claiming that those not contracting COVID-19 were all "improvements" and "successes."[12-14] Dr Zelenko's stated findings have been disputed by community leaders and a county health commissioner.[13,14] Given AAPS's methods, it erroneously claim 92% of patients improved.[12]

Another example from the data set is a letter to the editor from China stating: "Thus far, results from more than 100 patients have demonstrated that chloroquine phosphate is superior to the control treatment in inhibiting the exacerbation of pneumonia, improving lung imaging findings, promoting a virus negative conversion, and shortening the disease course according to the news briefing."[15] The writers of the letter are not the holders of the data, and they did not personally treat the patients or generate their data, there is no reference provided, and no actual data to substantiate this assertion was ever published.[12] However, AAPS states, "100 [patients] will be used" in their calculations, "Up to 100% may have improved" and claims no one died, so there was 100% success.[12,15] The letter to the editor does not even say that all 100 patients received chloroquine. It could be interpreted that many patients may have been given control therapy.[15]

When you assess AAPS's data sheets, you will also note there are a number of cells with missing data or just question marks. This is highly irregular and weakens confidence in the robustness of vetting its data sources.[12] Finally, AAPS aggregated the results even though the extreme heterogeneity in their data set should have precluded it.[16,17] It did not use any meta-analytic techniques in its aggregation. In all aspects, the findings are based on weak methods and data sources that are hard to verify and prone to bias.[16,17]

How Did We Derive Our Conclusion for Mortality?

Our methodology was guided by the Agency for Healthcare Research and Quality and the Cochrane Collaborative guidance for how to search for evidence, assess it for risk of bias, and rate strength of evidence.[16-18] These are best practices that are required for investigators to publish the results of systematic reviews in many biomedical journals.

Our end point of overall mortality most closely links with what the AAPS defined as "success."[12] When we assessed the impact of hydroxychloroquine versus control, we found 2 studies with significant reductions in overall mortality of 27%, 2 studies with significant increases of 6% and 16%, 1 study with a nonsignificant increase of 10%, and 3 studies in which there was no difference between groups.[19-26]

These variable mortality findings between studies in our systematic review is likely related to the studies themselves.[11] One study could not be rated for bias (ie, not enough information), 2 had critical risk of bias, 2 had serious risk of bias, 2 had moderate risk of bias, and 1 had some concerns of risk of bias. None of the studies had a low risk of bias. Equally important, many studies were small, so interstudy differences could occur just by chance. We were precluded from meta-analyzing the studies because the heterogeneity in population, dose, duration, and use of adjuvant therapies was determined to be too great. Using standard guidance for determining strength of evidence, the only conclusion is that the current studies are insufficient to say whether hydroxychloroquine improved survival in COVID-19.[11,16,17]

If we had used the AAPS methodology, we would have said that 1030 of 1232 patients receiving hydroxychloroquine in these studies lived, so hydroxychloroquine had 83.6% success.[12]

Now that the preliminary results of the hydroxychloroquine arm of the Randomized Evaluation of COVid therapy (RECOVERY) trial are available, the totality of all the data makes it unlikely that there is any mortality benefit from hydroxychloroquine use.[27] A total of 1542 patients were randomized to hydroxychloroquine and 3132 patients to control therapy. There was no significant difference in the primary end point of 28-day mortality (25.7% hydroxychloroquine vs 23.5% usual care, $P = .10$). There was also no evidence of beneficial effects on hospital stay duration or other outcomes, and this study arm was stopped early.[27] We do need to await the full publication of these data to know all the specifics.

On June 3, 2020, the first controlled study of hydroxychloroquine to prevent COVID-19 was published in the *New England Journal of Medicine*.[28] This randomized, placebo-controlled trial of 821 patients exposed to SARS-CoV-2 showed a slight but nonsignificant reduction in developing COVID-19 when hydroxychloroquine was used (11.8% vs 14.3%, $P = .35$).[28] Further research is needed to determine the true effect of hydroxychloroquine with or without other adjuvant agents such as azithromycin or zinc to know if it is effective or not.

Where Should We Go From Here?

A primary tenet of evidence-based practice is that therapy should only be used if the expected benefits are greater than the expected harm that could result from its use.[18] Because the benefits of hydroxychloroquine for treating COVID-19 are seemingly unlikely, the balance of benefits to harms is unfavorable. For prevention, the benefits are unknown, so the balance of benefits to harm cannot be determined.[11]

Hydroxychloroquine and chloroquine are generally safe and well tolerated but not free of adverse effects for patients or society.[16] In the limited experience with COVID-19, some patients have experienced QTc interval increases from baseline in excess of 60 milliseconds, others have QTc intervals exceeding 500 milliseconds.[11] In rare cases, torsade de pointes or the more general end point of ventricular arrhythmias have been noted.[11] In addition, prolonged hydroxychloroquine and chloroquine exposure can cause retinal damage, myopathy, neuropathy, aplastic anemia, leukopenia, and thrombocytopenia.[29] The chronic overexposure of the world's population to hydroxychloroquine or chloroquine poses potential risks that malarial resistance will increase in the future.[30] In addition, rapid changes in demand for hydroxychloroquine can cause localized shortages for patients suffering from inflammatory disorders such as systematic lupus erythematosus.[31]

These risks exist in the legitimate drug supply, but there are also patients who are obtaining counterfeit hydroxychloroquine and chloroquine for their personal use. Thousands of counterfeit drugs to prevent or treat COVID-19 have been seized at the port in Baltimore alone, including hydroxychloroquine.[32] Before COVID-19, hydroxychloroquine and chloroquine were common counterfeit medications around the world.[33] Many of the counterfeit drugs lack the correct dosage of the active ingredients and could contain adulterants and contaminants.[34] When using counterfeit medications, patients at high risk of adverse events cannot be steered away for using it by health professionals including patients with prolonged QTc intervals, electrolyte disturbances, or glucose-6-phosphate dehydrogenase deficiency.[29,34] Pharmacists cannot check for drug interactions or counsel about how to take counterfeit drugs properly.[29,34] One patient died and another was hospitalized because of a belief that the chloroquine used to treat tropical fish would provide protection from COVID-19.[35]

Many patients erroneously believe that hydroxychloroquine or chloroquine will prevent COVID-19 by 90% and cure 90% of people who have it.[1-5] Why stay at home, avoid hugging elderly loved ones, and wear a mask when in close contact with others when there is a 90% effective insurance policy that is easy to swallow? Why get a vaccine in the future if the risk of harm by COVID-19 is so low in those taking hydroxychloroquine or chloroquine? These patients are actively inquiring about hydroxychloroquine treatment with their prescribers.

The American Medical Association, American Society of Health-System Pharmacists, and the American Pharmacists Association came out with a joint statement for the treatment of COVID-19.[36] They stated, "Novel off-label use of FDA-approved medications is a matter for the physician's or other prescriber's professional judgment. We also strongly support a pharmacist's professional responsibility to make reasonable inquiries to a prescriber to resolve any questions about a prescription. If a prescription is not for a legitimate medical purpose, it should not be written, and it should not be dispensed. We encourage patient-centered care decisions, made on an individualized basis with patients' informed consent about the risks and benefits associated with any treatment regimen. However, evidence-based science and practice must guide these determinations. Physicians, pharmacists, and other members of the healthcare team are more than capable of working together and resolving questions."[36]

It is imperative that health professionals understand how the AAPS is deriving its data and defining its end points and are willing to educate their patients who are seeking hydroxychloroquine and chloroquine therapy. Patients need to understand that there is no equivalency between how myriad professional societies are determining the state of the evidence and how the AAPS performed its analyses.[6-10]

If patients are requesting hydroxychloroquine or chloroquine, ask them what they have heard about it. If they quote the 90% success that hydroxychloroquine allegedly has, ask them what they believe the AAPS meant by success. They are likely to express valid end points like not getting COVID-19, not receiving mechanical ventilation, or not dying. At that point, let them know how success was actually defined and express that you are very concerned about the data that

the AAPS used in their assessment. Let them know that many professional societies that you trust have each independently looked at the available studies and did not see evidence of benefits and the best clinical trial to date was stopped early because of a lack of benefit.

The AAPS is perpetrating a false narrative that can lead patients to harm themselves, their loved ones, and their community. Education from a trusted health professional is an important step in counteracting it.

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