Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Concerning Pathophysiology and Justifying Clinical Trials

To the Editor:

We thank Dr. McCullough et al for their paper "Pathophysiological Basis and Rationale for Early Outpatient Treatment of SARS-CoV-2 (COVID-19) Infection".[1] We agree that in the absence of RCT evidence, treatment decisions should be guided by arguments from biological plausibility or mechanistic reasoning, especially in times of crisis when new treatments are needed quickly. However, we disagree with both the specific assertion that hydroxychloroquine should be used for early outpatient treatment based on its biological plausibility, and the broader philosophical point that in the absence of trials for a specific population, we should defer to mechanistic reasoning rather than extrapolating from the results of existing trials.

Strong evidence already exists that HCQ is ineffective for both treating and preventing COVID-19, the disease related to infection with SARS-CoV-2.[2] Moreover, this evidence was already available in August 2020, when the paper by McCullough et al. was first published online.[3,4,5,6] It was probably also already available when their manuscript was first submitted. Specific to outpatients and those with mild-to-moderate symptoms not requiring hospitalization, evidence exists that hydroxychloroquine is ineffective in that population, as well, with results of two RCTs available as of July 2020.[7,8] Even if these specific studies had not yet been conducted, extant data from related trials of HCQ for Covid-19 should have been convincing enough to conclude that it is ineffective.[9]

To both broaden and make our argument more explicit: it is the nature of modern clinical research that data derived from randomized trials must always be applied to patients who were not included in those trials, and who might not have met their (often stringent) inclusion criteria. It is unreasonable to expect that a particular treatment will be tested in RCTs for every possible patient population. Once a promising treatment has already been tested in a reasonably representative population, and has failed to demonstrate efficacy, researchers should be expected to offer a convincing justification as to why it should be tested again: redundant research is certainly wasteful and can even be harmful. To argue that a treatment should be adopted as standard care on the basis of "biological plausibility," months after evidence to the contrary is widely available, has no rationale.

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