



Open Letter by U.S. Doctors: JAMA Ivermectin Study Is Fatally Flawed

We the undersigned physicians present this letter to call attention to multiple, integral flaws in the Journal of the American Medical Association's recently published paper "[Effect of Ivermectin on Time to Resolution of Symptoms Among Adults With Mild COVID-19](#)"[1]. Above all, the data reported do not support the authors' conclusion that ivermectin is ineffective as a treatment for mild COVID-19.

The study's flaws span subject population, design, execution and controls. The small sample size (n = 400) had a median age of 37 and a BMI of 26, making them extremely low risk for COVID-19 hard endpoints. Faced with this low-relevance study group, the study authors improperly changed primary endpoint midway, moving the main endpoint to full symptom resolution by day 21. This self-reported subjective endpoint, obtained through telephone survey, is not credible for avoiding nondifferential nullward bias of the results.

We note other major errors in study conduct. The authors incorrectly administered ivermectin on an empty stomach, reducing drug bioavailability in lung tissue, the critical drug target, by a factor of roughly 2.5. Additionally, [ivermectin is readily available over-the-counter in Colombia](#), where sales have been ubiquitous (1.6 doses per COVID-19 case) in Cali during the study period.[2] Lack of serum testing in the study prevented identification of

subjects who may have used the drug at intervals longer than the study lookback.

Contrary to the authors' stated conclusion, the findings suggest lower rates of disease progression, hospitalization, ICU admission, and mortality with ivermectin, which might have been confirmed to be statistically significant with a larger sample and more rigorous study design.

Indeed, notwithstanding these limitations, [the available data indicate a 9% faster daily symptom resolution](#), which when generalized to large populations would have a meaningful impact.[3]

The severe weaknesses of this study make it uninformative about whether ivermectin is beneficial in early COVID-19 treatment. Yet, the authors misleadingly conclude that their findings “do not support the use of ivermectin for treatment of mild COVID-19”, as if they had enough quality data to make that case, which they do not.

Physicians have a solemn duty to care for patients, and randomized controlled trials can provide valuable information. But, as is the case here, they can also be flawed and must therefore always be weighed within the totality of evidence in order to provide the most appropriate patient care.

Over the past year, many government agencies, academic journals, the broader media, and medical associations have departed from historic norms and elevated the status of randomized controlled trials. Such trials are seemingly presented as the only valid basis for making clinical recommendations about COVID-19 treatment, no matter how flawed. This trend has severely hindered the ability of physicians to use clinical experience and observational trials to offer their patients guidance on early treatment for this still not well-understood infection.

We oppose this fixation on randomized controlled trials at the expense of other clinical and scientific evidence and urge medical policymakers to restore balance to the practice of medicine.

Physicians must be free to use all appropriate methodologies in determining the best approach to COVID-19, and to other conditions underlying health disparities throughout our country.

Respectfully,

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Note: An earlier version of this letter was submitted to the Journal of the American Medical Association but was not accepted for publication. If you are a doctor and would like to add your name to this letter, email sign@jamaletter.com with your full name, credentials, and location exactly as they appear above.

References

[1] López-Medina, Eduardo, et al. "Effect of Ivermectin on Time to Resolution of Symptoms Among Adults With Mild COVID-19." JAMA, March 4, 2021. [Doi:10.1001/jama.2021.3071](https://doi.org/10.1001/jama.2021.3071).

[2] Scheim, David, et al. "Protocol violations in López-Medina et al.: 38 switched ivermectin (IVM) and placebo doses, failure of blinding, widespread IVM sales OTC in Cali, and nearly identical AEs for the IVM and control groups." Preprint, March 8, 2021. [Doi:10.31219/osf.io/u7ewz](https://doi.org/10.31219/osf.io/u7ewz).

[3] McCullough PA, et al. "Multifaceted highly targeted sequential multidrug treatment of early ambulatory high-risk SARS-CoV-2 infection (COVID-19)." Rev Cardiovasc Med. 2020 Dec 30;21(4):517-530. [Doi:10.31083/j.rcm.2020.04.264](https://doi.org/10.31083/j.rcm.2020.04.264). PMID: 33387997.