Supplements for the Treatment of Mild COVID-19—Challenging Health Beliefs With Science From A to Z

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"The good thing about science is that it's true whether or not you believe in it."
Neil deGrasse Tyson[1]

Coronavirus disease 2019 (COVID-19) is a major cause of death and disability worldwide, totaling 89.4 million cases and 1.9 million deaths globally as of January 9, 2021.[2] As a result of high-quality science, several vaccines efficacious against the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) have been developed in record time and deployment started, offering hope for an end to the pandemic. However, given the limited availability and uptake of vaccines, the emergence of new, more infectious variant strains of the virus, and the potential for future seasonal outbreaks, the identification of therapies that can effectively improve prognosis in patients infected with SARS-CoV-2 remains a critical area of research.

Commonly available oral supplements, such as zinc and ascorbic acid (ie, vitamin C), have been proposed to reduce the duration and severity of viral infections by boosting immune response.[3] Even former US President Donald Trump was reportedly treated with zinc and vitamin D throughout his COVID-19 treatment in October 2020.[4] Although the evidence supporting supplements as a treatment for viral infections is rather limited,[3] in a context of rapidly increasing COVID-19 deaths and urgent need for effective therapeutic options, whether these molecules could benefit patients with COVID-19 is a research question worth evaluating.

Thomas et al[5] report the results of the COVID A to Z Study, an open-label, 4-group, randomized clinical trial (RCT) that tested the efficacy of high-dose zinc gluconate, ascorbic acid, and their combination for their ability to shorten the duration of COVID-19–related symptoms compared with usual care alone. The authors planned to include 520 adult outpatients with confirmed SARS-CoV-2 infection, and the primary end point was the number of days required to reach a 50% reduction in symptom severity. However, after an interim analysis, the safety monitoring board recommended the study be stopped early for futility after enrollment of only 214 participants because of the low probability of detecting significant differences between the study groups in terms of the primary end point.

Some limitations of the study by Thomas et al[5] are worth discussing. First, enrollment was restricted to outpatients, thus limiting generalizability to hospitalized patients with COVID-19. Second, interventions were not blinded, a placebo was not used in the control group, and outcomes were reported by study participants. This could have exaggerated the potential benefit of the interventions; yet, the study yielded null findings, providing further reassurance that the early trial termination did not conceal detection of a true benefit. Finally, the small size prevented conducting subgroup analyses by relevant clinical characteristics, although those would have to be interpreted cautiously in the context of overall null findings.

The supplement industry is estimated to be worth approximately $300 billion globally.[6] More than one-half of US adults report taking at least 1 vitamin or supplement for various health reasons, with little evidence of efficacy to support their widespread use.[7] The best evidence to guide clinical recommendations comes from well-designed RCTs. Given the widespread public use of supplements, such as zinc and ascorbic acid, for the prevention and treatment of viral infections, we

applaud the COVID A to Z Study[5] investigators for adding rigorous science by testing their efficacy and challenging popular beliefs. Unfortunately, these 2 supplements failed to live up to their hype.

There is frequently disconnect between mechanistic and/or observational research and the eventual findings from well-conducted RCTs. Specifically, research on the health effects of both supplements and therapies for COVID-19 has been rich in examples of this disconnect. Low vitamin D levels have been associated with multiple adverse health outcomes, including cardiovascular disease, in several observational studies, and the mechanistic rationale for increasing vitamin D levels seemed compelling. However, subsequent RCTs of vitamin D supplementation consistently yielded null results for cardiovascular disease, even among individuals with low baseline levels.[7] The previously reported associations of vitamin D and cardiovascular outcomes were likely driven by confounding from other risk and health factors. The same had been true for multiple other vitamins and mineral supplements,[7] with discordance between observational and trial evidence. It is likely that other health-seeking behaviors characteristic of supplement users confounded the observational studies. Enthusiasm for other COVID-19 treatments has been similarly dampened after completion of RCTs. Hydroxychloroquine, an antimalarial drug widely repurposed as drug candidate for COVID-19 prevention and treatment, also failed to demonstrate efficacy in RCTs.[8]

What are the implications, moving forward, of yet another null COVID-19 trial?[5] Given current projections that in coming weeks the pandemic will continue to peak worldwide, together with the potential for future outbreaks, this new disappointment should not discourage further research efforts. Those will be critical to eventually identifying truly efficacious therapeutic options to help reduce the burden of death and other severe complications. The groundbreaking developments in antiviral therapeutics against a foe as challenging as HIV provide strong, evidence-based reasons for hope in science and human discovery.

Despite the urgency, we suggest that some pause may be needed moving forward. Although supplements are generally thought of as benign because of their over-the-counter availability, they are not necessarily free from adverse effects. Indeed, in the COVID A to Z Study,[5] more adverse effects (nausea, diarrhea, and stomach cramps) were reported in the supplement groups than in the usual care group. Safety has also been a concern with other COVID-19 candidate therapies. For instance, in the recently published phase 3 hydroxychloroquine trial (BCN-PEP-CoV2),[8] which tested prophylactic use among contacts of patients with confirmed COVID-19, a striking 56% of participants in the hydroxychloroquine group developed adverse effects compared with only 6% in the control group, with 5-fold increases in moderate and severe adverse effects with hydroxychloroquine. Solid phase 1 and 2 data should be generated before drugs with potential to cause harm are administered to large study populations in phase 3 trials. In a context of limited resources for costly experimental research, funding agencies could prioritize candidate interventions on the basis of their safety and favor those with the strongest body of preliminary evidence.

Finally, although studies on the efficacy of pharmacotherapies for COVID-19 are certainly needed and this has been an active area of research since the start of the pandemic, in stark contrast, there has been a lack of experimental research on policy and social interventions. Multiple observational studies have identified adverse socioeconomic circumstances and limited access to care as powerful factors associated with adverse COVID-19 outcomes in the US, with a disproportionate impact on historically marginalized groups. This was echoed by a report from the Centers for Disease Control and Prevention,[9] and yet, large studies evaluating related interventions have remained scarce. For instance, we need to better understand how to increase access to risk-mitigation measures and testing among those most often exposed to SARS-CoV-2 infection, typically essential workers of socioeconomically vulnerable groups. Beyond molecules and drugs, the time may have come for funding agencies to boost research on more upstream interventions, and, if they are proven effective, for the US Congress to invest in their implementation.

In recent years, misinformation has permeated health discussions, including those involving COVID-19 therapies. The Biden-Harris administration has expressed a will to embrace science, and we hope that 2021 will start an era in which high-quality research will inform political and public health

decision-making, an era in which scientists, public health officials, and government can be invested together in addressing key research gaps, generating and disseminating highest-quality information, and tackling key unmet social needs of the country—during and beyond the pandemic.

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