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When Off-Label Prescribing Becomes Politicized: Do No Harm

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We are living in times of extreme polarization and the politization of medical and scientific facts, and no one seems to be immune from this "propaganda." The late senator Daniel Patrick Moynihan said, "Everyone is entitled to his own opinion, but not his own facts." The COVID-19 pandemic in the United States has resulted in a myriad of expert and non-expert assertions of demonstrably false statements regarding public health, scientific facts, biomedical research, and medical treatments. At the same time, our appreciation of the value of certain public health measures, such as mask wearing or social distancing, changed as new information became available. However, as a result of a lack of understanding about the dynamic nature of science and the iterative quality of scientific inquiry, the public was left confused, and previously trusted sources of guidance, such as the Centers for Disease Control and Prevention (CDC) and the National Institute of Allergy and Infectious Diseases (NIAID), have lost credibility among many. Although public mistrust was exacerbated by the CDC's *unforced error* discouraging "people who are well [from] wearing a face mask to protect themselves from respiratory diseases, including COVID-19,"[1] the problem is far larger than this and has left a vacuum, which the public has filled with dubious statements from credentialed and lay sources. Further compounded by a general distrust of official news sources, many in the public have sought scientific and medical information from unvalidated sources like social media. And it is abundantly clear that many of the social media sources have prioritized clicks over truth.

A lack of understanding about the dynamic nature of science and the "hyperpoliticization" of public health facts has also affected the prescribing practices of physicians, especially off-label prescribing for COVID-19-related conditions. Off-label use enables physicians to prescribe drugs for uses beyond US Food and Drug Administration (FDA)–approved indications, including the unstudied treatment of different diseases or age groups and the use of alternative dosing or routes of administration. Although pharmaceutical companies are not allowed to advertise a drug for any purpose other than its approved indication, off-label use is generally legal unless it violates ethical guidelines and safety regulations. The regulatory approval for each specific drug indication requires a critical mass of evidence that is costly to generate. There are not enough resources or enough time to test every drug for every potential indication, especially during a pandemic when time is of the essence, resources are scarce, and medical evidence and scientific understanding is evolving with the disease. Therefore, the regulatory approach to

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therapy holds that anything not explicitly forbidden will require more information and additional studies. In the meantime, any extrapolation should be done by a licensed prescriber based on clinical judgment and the clinical scenario. It is important to note that standard-of-care prescribing for many conditions involves off-label uses: it can be a safe and efficacious way of treating a variety of common diseases and conditions that lack safe, effective treatments, such as migraines, especially when randomized clinical trials support the use.[2] However, off-label use may also entail health risks and legal liability.

Off-label prescribing is often done using older, generic medications with well-documented safety profiles, that have found new uses but have not had the formal studies done as required by the FDA for new approved indications. In many cases, there is extensive medical literature to support the off-label use. But as reported by Serra-Garcia, the reproducibility of published research has dramatically worsened: only 62% of studies published in *Nature* and *Science* are replicable,[3] with nonreplicable publications being cited more than replicable ones. There are multitudes of reasons for irreproducibility, such as the size of the original effects, limitations of sample size and power, and overinterpretation of weak relationships, as well as our bias towards publishing unexpected positive and novel results. Further, authors citing the works of others often do not carefully evaluate the published findings, uncritically choosing those that support their conclusions. We value novelty; even the review standards are relaxed for interesting papers on exciting subjects. Retraction Watch lists 205 COVID-19-related retractions as of December 2021.[4] We find ourselves in a perfect storm: in the midst of a pandemic, we are unduly influenced by social media and the dissemination of unproven therapies and misleading faux medical and scientific assertions. And it is not just the lay press that gets things wrong. Medical journals have added to the confusion by overemphasizing novel findings and therapies, spurred in part by the need for authors from academic faculties to publish their research findings. When confronted with the need to retract an article, journals often absolve themselves from responsibility for accuracy, stating that "All the authors reviewed the manuscript and vouched for the accuracy and completeness of the data." Combining this with complex governmental and regulatory bureaucracies, hyped interpretations of scientific discoveries, politicized prescribers, and an undereducated public results in the creation of a picture rivaling the *Garden of Earthly Delights* by Bosch.[5] We must get back to "basics." Academic honesty and the fair unbiased review of scientific data are the cornerstones of research and are critical to scientific and medical advances. As is academic discourse, the iterative process of scientific discovery, and rigor, as well as the censure of fraudulent scientists and physicians. However, humility and an open mind to alternative explanations that may not be aligned with the current scientific or medical dogmas should also be at hand in our physician's bag. At the beginning of a pandemic, when almost nothing was known about the SARS-CoV-2 virus, almost any reasonably plausible idea deserved some consideration. As we quickly gained more scientific information about the pathobiology and epidemiology of the virus, the line between plausible and implausible became easier to discern. However, much of the misinformation had already taken root among the public and the prescribers, leaving us to sift information, check facts, and re-educate ourselves and the public, as we raced to hasten the end of the COVID-19 pandemic.

We academic scientists and clinicians must confront health and prescribing misinformation. The US Surgeon General's Advisory on Building a Healthy Information Environment identified COVID-19 misinformation as an "urgent threat."[6] The prestige of our institutions and science itself depends on credibility. We are the stewards of scientific facts, their dissemination, and ultimately of medical progress. As prescribers, we need to stick to the basics and "first do no harm." No amount of refresher course material or continuing medical education credits will fix our current COVID-19-driven off-label prescribing dilemma. We need to identify the sources of misinformation and discuss possible options to counteract them through persuasive and effective education on best prescribing practices, in order to protect public health and advance medicine and science. Similarly, it is of paramount importance to educate the public about the real dangers of politically influenced off-label prescribing, and false statements in health, medicine, and science. When a licensed physician with a high profile on conventional or social media publicly endorses the off-label use of a drug for which there is strong evidence of nonefficacy or harm, we, the academic clinicians and scientists, must be willing to publicly censure the individual and immediately engage with the public in a discussion of the pharmacotherapeutic issues. Science and the art of medicine are ultimately self-correcting, but self-correction often takes time and consumes resources, and any delay threatens harm to our patients. Primum non nocere.

Unfortunately, the COVID-19 pandemic and its devastating and unpredictable physiological and societal effects seems to give prescribers, and even courts that consider appeals of refusal to use nonindicated therapies, license to support untested and potentially dangerous off-label therapies that were too often promoted by politicians and celebrities. Cicero's lament, "O tempora, o mores!," seems especially apt now.[7] We cannot sit on

the sidelines, this is "our lane." Therefore, in conclusion, we would like to propose a few actionable items:

1. Health professionals should communicate with patients about off-label prescriptions as part of shared decision making with patients and families whenever possible, but particularly when the use of the medication has had little or no evidence of efficacy for the condition for which it is being prescribed and there are recognized alternatives.
2. Education should be developed for practicing prescribers about the ethical and legal issues surrounding off-label prescribing. A brief training module should be considered as a rountine part of the licensing process.
3. Information about the effectiveness of the off-label use of medications should be collected and shared. There should be tracking of off-label prescriptions and the required reporting of any adverse events.

Conflicts of Interest

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