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The Logic of Science and the Fallacies of Popular Medical Belief: Off-Label Uses of Existing Pharmaceuticals in COVID-19

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Description

The history and anthropology of medicine are rife with stories of novel treatments that have been widely accepted, even lauded, but that were eventually abandoned as useless. Whether laetrile, bloodletting, or sand painting, once a belief in the efficacy of a healing method becomes established in a population, disabusing adherents of this belief has always been a struggle.

Most patients receiving treatment for most diseases will recover. This is because diseases are so often self-limiting. Novel treatments are often administered when the disease seems particularly dire, and administration of what the patient views as a powerful new medicine can provide psychological benefits that, because of the mind body connection, may also trigger somatic improvements [1]. The power of the mind to heal is the essence of the placebo effect and the reason for the necessity of blinded drug trials.

When any treatment fails, and the patient dies, that death does not immediately disconfirm the treatment. Rather, adherents argue that in this particular case the treatment was delivered too late (or sometimes too soon), or administered improperly, or given in the wrong dosage, etc.) Thus, it was not the essential ineffectiveness of the treatment but errors in its application that led to the death. After all, just look at all those who received the same treatment and recovered.

Part of rigorous research training is the development of a nuanced understanding of causation. Causation can sometimes, but not always, be directly demonstrated through experimentation, but this is not always possible. For example, it is unethical to expose randomly allocated humans to suspected carcinogens [2]. Nor is it usually easy or ethical to have a placebo version of a surgical procedure. Thus, for some types of studies medicine is forced to rely on cross-sectional correlative studies that are replete with potential flaws. Biostatistical inference and epidemiologic practice are based on the understanding that "association does not imply causation." Graduate students in these fields learn this and often repeat these words as a mantra. Research designs meant to investigate association may not be able to determine causation. As a simple example, consider this scenario. During the summer, we buy popsicles. We also know that, in the warmer months, there are more drowning incidents. Thus, we can say that the number of the number of popsicles purchased is likely associated with drownings. However, there is absolutely no causal relationship. This example may sound silly, but it demonstrates the difference between association and causation. We tend to have drownings at the same time of year in which we eat popsicles because of a third factor-warm weather.

Fortunately, for establishing the efficacy of pharmaceuticals the blinded prospective randomized clinical trial (RCT) provides a powerful tool that overcomes many of the errors of observational retrospective and cross-sectional correlative designs [3]. Controlled clinical trials are considered the gold standard of investigations for determining treatment efficacy [4]. Without this type of investigation, demonstrating statistically significant benefit, there is no way to know that the benefits (or adverse events) we may observe anecdotally in patients using certain treatment options are, in fact, attributable to those drugs. This is the entire point of having a controlled clinical trial. Unfortunately, laymen, even those with considerable education, generally lack a clear understanding of the errors inherent in a series of case studies or a retrospective record review or of the much greater power of the RCT to detect causation.

Sadly, many clinicians also have little or no formal training in research methodology and therefore may be open to the same errors of logic.

This brings us to COVID 19 and the debate about several treatments that incorporate off-label uses of previously approved drugs. The onset of this pandemic has brought about much speculation and discussion regarding these innovative treatment options. These discussions are often very convoluted by personal experience, political preference, and the media. Frequently claims of powerful effects are shared on social media platforms, such as Facebook, YouTube, and Twitter. Recently some of these posts have been deleted by the host media sites because they were considered misinformation, resulting in claims of censorship [5] and assertions that these deletions are a violation of first amendment rights. Dialogue in these media becomes a giant mess, and the public is left uninformed, and confused. Although the concerns regarding censorship may be well taken, many of these platforms have policies on misinformation regarding the pandemic. Their actions reflect the fact that nothing has been scientifically proven to cure COVID-19 to date and stating otherwise is misinformation that may endanger people.

Practicing physicians have been very active in some of these claims, stating what they have observed about treatments in patients under their care. This is particularly concerning because most doctors are not experts in research methods. They may rely on research reports from others to inform them of available treatments, but most are not formally trained to conduct research. Therefore, they may engage in the same fallacious thinking as the broader public. One fallacy that frequently arises in claims of COVID "cures" is post hoc ergo propter hoc. "After this, therefore because of this". The interpretation of this is "Since event Y followed event X, event Y must have been caused by

event X. This is a common mistake in many applications and is one that is very familiar to clinical and translational research. One well known (and disproven) application of this which many people today are familiar with involves the potential association between vaccination for MMR and onset of autism in children. Many people believed that since the onset of symptoms often followed the MMR vaccine that it may have been caused by it. In fact, many people were so concerned about this that they refused to vaccinate their children around the turn of the century. Many investigations later disproved this assessment, determining that the association essentially had to do with the fact that the MMR was administered at 12 months, shortly before the onset of symptoms of autism in most children [6,7].

Pharmaceuticals are not indicated for a given disease unless they have been scientifically proven to be safe and effective. There are standards which determine proof and a whole cadre of scientists within the FDA whose job it is to assess this. Additionally, treatments that are safe and efficacious for a given condition, may not be safe or effective for a new indication. For example, Aspirin has been around for decades, but we now know not to give it to younger children with certain infections related to chickenpox or other infections presenting with flu like symptoms, because it can be harmful (causing Reye's syndrome). Aspirin still reduces fevers, so why not give it to children with fever like we used to? Because we have discovered that in some situations it is dangerous!

While scientific medicine requires proof before it accepts the idea that a treatment is safe and effective and allows it to be labeled for a given condition, there is a long history of "off-label" use by clinicians based on hunches, rumors or case reports. At times, these innovations have proven useful as was the case with beta blockers that moved from being introduced as an angina pectoris treatment, to expanded, then proven, use as anti hypertensives and then to a host of other uses.

Recently, claims have been made for great efficacy in COVID-19 for an established drug approved for use with lupus erythematosus and rheumatoid arthritis. Similarly, others have claimed that nebulized steroids are the "magic bullet" against this disease. Powerful political advocates and many practicing physicians have inserted themselves into these claims of "cure". There must be a strong burden of proof on any clinician investigators who advocate for a new use of an existing drug and on the drug company that developed it. This goes for all treatments for all kinds of medical conditions. This hurdle to approval is for the protection of patients. It prevents an unscrupulous company from marketing useless treatments marketed with slick advertising, Scientific proof is required. Science protects people in clinical care by forcing rigorous scientific proof on efficacy before a prescription medication can be recommended for a given purpose. The notions of scientific rigor in drug selection have, however, been undermined to some extent in the United States because of the widespread advertising on American television of FDA approved prescription medications, alongside dubious over the counter remedies and outright fraudulent remedies like unproven quick weight loss pills. This has blurred the distinction between prescription medications and OTC remedies in the minds of many consumers and led to a general distrust of medications and pharmaceutical companies, which adds to the heat of this debate.

It is incumbent on academic physicians, epidemiologists and biostatisticians to remind media and the general public as often as necessary (and that appears to mean with great frequency) that the test of a novel use of a medication must be a RCT and not a retrospective study, or worse, a series of case reports presented in a press conference. The public must be disabused of the faulty notion that any current drug has been demonstrated to be a "cure" for COVID 19. It will be an uphill fight, but it is absolutely necessary because the false belief in a "cure" not only may lead to wasteful therapeutic misadventures, but also may lure those convinced of the existence of a cure to drop the preventive measures of social distancing and face covering which appear to be working everywhere that there is adequate public support, and which are our current best bet to curb this pandemic.

Authors contribution

Both authors contributed equally.

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