What Have We Got to Lose by Prescribing Unproven Drugs for Covid-19?

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Few things are harder for a health care provider than to watch a patient under their care get sicker, and sometimes die, without being able to offer any curative therapy. Distressingly, this is happening every day with covid-19. Naturally, patients and those close to them are eager to have access to drugs that are claimed to be of benefit, no matter how meager the evidence. Even if there's no clear proof that a drug works, patients and their advocates might reasonably ask, what have we got to lose?

I've reviewed in detail reports claiming that various drugs are effective for the treatment of covid-19. These include the very small French study involving hydroxychloroquine and (in some patients) azithromycin. It's frequently cited as evidence that these drugs are effective for covid-19. Usually, I suspect, people making these claims haven't read the report. And those who did read it and still urge the use of these drugs are unlikely to have the background to properly evaluate the data. The fact is, this is a very flawed study. Anyone who, like me, has spent much of his professional career designing and evaluating clinical trials would almost certainly agree. It clearly should not be the justification for prescribing these medications to any of the many thousands of patients with coronavirus infection.

To name just a few of the flaws: patients were not randomized to treatment; the "control" group was inappropriate, misleading, and poorly matched; and a substantial number of patients who received hydroxychloroquine— including three who were transferred to the ICU and one who died--were dropped from the study without being analyzed as part of the hydroxychloroquine group. Nonetheless, this report has led to huge interest in hydroxychloroquine and its close relative, chloroquine for the treatment of covid-19.

The same French group released another unpublished report on their website on 27 March. It involved 80 patients with covid-19 who were treated with hydroxychloroquine and azithromycin. This was an uncontrolled study—all patients received the drugs--and it included patients who had already been reported in their earlier study. Without a control group it's impossible to know whether this conglomeration of new and recycled patients might have done just as well, or perhaps even better, if they had not been given these drugs. The clinical course of covid-19 is so variable that it's virtually impossible to tell whether a drug is beneficial when given to individual patients, or groups of patients without a control group.

Of note, a Chinese study, which has gotten far less publicity, represents substantially better science than either of the French reports. Though also small, it had the virtue of patients with covid-19 being properly randomized to hydroxychloroquine or "conventional treatment." It showed no benefit for hydroxychloroquine. Compared with the French reports, its conclusions are much more likely to be accurate.

Another Chinese clinical trial, not yet published or peer-reviewed, was put online on 1 April. It was limited to patients hospitalized with "mild illness," who were randomized to hydroxychloroquine or "controls." It claimed some success with the study drug: fever and cough were said to resolve about a day sooner in the hydroxychloroquine group, lung CT scans tended to be more improved, and more patients randomized to the control group "progressed to severe illness". However, most of these differences were not "statistically significant;" that is, they could well have occurred by chance. There are numerous other problems with this small study, which I may describe in detail subsequently. To name a few: although patients were randomized, controls received no placebo; therefore, patients and caregivers may have been "unblinded" to treatment. Moreover, physicians were able to freely administer a whole range of other medicines thought to possibly be beneficial for the treatment of covid-19, muddying the water. The two patient groups were not well-matched at baseline on several key measures; data are reported only for Day 5; and very curiously, over 40% of the patients who entered the study had neither fever nor cough, though these features were two of the outcome measures. There are substantial problems with the statistical analysis, including that there was no primary endpoint and no "correction for multiple comparisons". Because of these and other serious issues in design, conduct, and analysis, in my view this report offers no reliable evidence that hydroxychloroquine is effective in the treatment of covid-19.

But as I asked earlier, even without good data that hydroxychloroquine (or other unproven drugs) are effective for treating covid-19, what have we got to lose by giving them to patients? The clear answer is that we've got a lot to lose. The losses can be grouped in several categories:

Inducing drug side-effects. No medicines are completely safe. Each time a physician prescribes a drug, they are implicitly making a judgement that the potential benefits outweigh the known risks. Occasionally these risks can be quite serious. For example, among the many hydroxychloroquine (and chloroquine) side effects is a heart conduction abnormality called QTc prolongation, which may lead to serious and sometimes fatal rhythm disturbances. Ironically, the companion drug in the French studies, azithromycin, has a similar side-effect, which could be additive to that of hydroxychloroquine. Moreover, many drugs—including hydroxychloroquine--interact unfavorably with other medicines. One authoritative source lists 329 known hydroxychloroquine drug interactions, 58 of which are considered "major." We know that patients most at risk with covid-19 infection are those with additional medical

problems—precisely the group that is likely to be taking multiple medicines, and thus at highest risk for drug interactions. Finally, some drugs, notably including hydroxychloroquine, can cause devastating complications in people with certain chronic diseases. So from the perspective of the individual patient ill with covid-19, prescribing hydroxychloroquine may introduce considerable risk. In my view it's simply unethical to give a patient a treatment with no established value that has the potential of causing numerous side-effects, some of which may be severe and even life-threatening. As physicians pledge when they take the Hippocratic Oath, "first, do no harm."

Making medical care even more difficult. The medical care system has been extraordinarily stressed by the coronavirus pandemic. Administering hydroxychloroquine to a patient with covid-19 may complicate medical care even further. For example, ideally all patients, and particularly older and sicker ones who will be given hydroxychloroquine will need to be screened before dosing starts and then monitored periodically during treatment for QTc prolongation. This makes care more difficult (an EKG technician or nurse may need to do a special electrocardiogram, and thus be exposed to an infected patient), and adds an unnecessary distraction. Moreover, when a patient takes a turn for the worse, the physician must consider whether it could be the result of hydroxychloroquine side-effects or drug interactions. Such investigations can be complex and time consuming, and take away from examining other potential causes of a declining clinical course.

Diverting scarce medical and logistical resources. At the instigation of the Federal government, major resources are being deployed to make millions of doses of hydroxychloroquine and chloroquine available. FEMA has been directed to track down drug supplies, potentially distracting them from other vital work. And various Federal agencies are working out mechanisms to make it easier for physicians to prescribe these drugs for covid-19. Meanwhile, pharmaceutical companies are being encouraged to manufacture large quantities of these drugs, and hospital and freestanding pharmacies are stocking them. Such activity may divert from other vital work involved in caring for patients with covid-19, including producing, distributing and stocking other drugs that are critical in the care of these patients. For example, the supplies of drugs associated with intubating patients and properly maintaining them on ventilators are already running dangerously short.

Creating shortages of drugs needed for legitimate purposes. According to recent news accounts, "off-label" prescriptions for hydroxychloroquine and chloroquine have skyrocketed. There are numerous reports of doctors and even dentists writing prescriptions for these drugs for themselves, family, and friends. And pharmaceutical companies have donated over 30 million doses to the US government. The result is that patients who depend on hydroxychloroquine and chloroquine—in the US and Europe mostly for treatment of serious rheumatic diseases like lupus and rheumatoid arthritis—are having great trouble refilling their prescriptions. Such patients are only part of the

collateral damage from the push to use these unproven drugs for the treatment of covid-19.

Sabotaging the identification of medicines that truly work. There are a number of ongoing attempts to perform randomized clinical trials to determine whether various drugs, including hydroxychloroquine, are safe and effective for the treatment of covid-19. On 30 March the FDA made the unfortunate decision to authorize the use of hydroxychloroquine for the treatment of covid-19. (The European regulatory agencies wisely declined to take a similar step.) To make matters worse, there are reports that various government agencies are exploring ways to encourage physicians to prescribe the drug, and planning for covering the cost to patients. With these developments, why would anyone who believes even some of the claims for hydroxychloroquine's efficacy in covid-19 elect to enter a clinical trial? Even a trial involving this drug would be unattractive, since there's a possibility that they might be randomized to receive placebo. The more patients who are prescribed hydroxychloroquine, or demand it from their physician, the fewer will be available to enroll in properly designed clinical trials to test the effectiveness of this and other drugs. This will considerably slow the process of identification of truly helpful treatments, which is an urgent need.

Instilling false hope. When a high government official declares that hydroxychloroquine has "a real chance to be one of the biggest game changers in the history of medicine." people listen. And, especially when the FDA sanctions its use, the government stockpiles millions of doses, encourages physicians to prescribe it, and intends to offer it without cost to people with covid-19, expectations for a cure are high. But with no good evidence that hydroxychloroquine (or chloroquine) is actually effective, and with some evidence to the contrary, the likelihood is that these drugs in fact won't prove to be beneficial. After all the hype, patients and their families will become angry and bitter if the treatment outcome is not favorable. Such anger may well be directed against the medical care team and the institution where care was given, making their already difficult jobs even more difficult and sowing even more confusion and distrust.

As a physician who has taken care of many patients with serious conditions, I know how heartbreaking it is to be responsible for a patient with a serious and progressive illness without being able to provide specific effective treatment. In this situation it's very tempting to grasp at straws and prescribe any drug that someone has said may be beneficial no matter how poor the evidence. But as I've tried to make clear, a physician's first responsibility is to do no harm. Irresponsibly prescribing drugs of unproven benefit, particularly in the setting of a pandemic, can make things worse for the many patients suffering from covid-19, for those who may develop it in the future, and for patients with other conditions who depend on such drugs.