5 Questions: Blaschke on patients who don't 'dose' properly

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Your doctor writes out a prescription that calls for you to take a pill twice a day for the next month. So, that's what you do, right? Wrong. A huge number of Americans fail to properly follow their doctors' orders. And while it may seem that their actions only hurt themselves, there's growing evidence that a culture of "non-adherence" to medication regimens has consequences for all of us.

Terrence Blaschke, MD, professor emeritus of medicine, is the co-author of a review published in February in the *Annual Review of Pharmacology and Toxicology* that documents the problems arising from the lack of proper adherence to medications. He spoke with science-writing intern Beth Mole on how taking medications improperly can skew the results of clinical trials, and how proper adherence could produce better health and lower health-care costs.

Q: What is meant by the term adherence?

Blaschke: It is multidimensional and describes a time-oriented series of events. The first of these is "initiation," which is when a medication is pre scribed and a patient must decide whether to take it. As many as 40 percent of patients in some clinical settings do not fill their prescription or decide not to take it after obtaining the medication.

Another big problem, especially in chronic conditions, is early "discontinuation" of a medication. "Persistence" is the length of time

between initiation and the last dose. In a study by one of my colleagues, Bernard Vrijens, about half of the patients taking hypertension medications had discontinued treatment by the end of the first year; other studies show that by the fifth year, only 10-15 percent of an original cohort of patients persisted with the prescribed treatment.

“Implementation” is the extent to which a patient’s actual dosing corresponds to the prescribed dosing regimen (for example, missing doses or taking doses at the wrong time), and this varies considerably among patients. On average, while patients are continuing with their medications, about 10 percent of doses are missed. These omissions might consist of occasionally missed doses or a series of consecutively missed doses, referred to as a “drug holiday.”

Q: Can taking medication sporadically be just as bad for your health as not taking your medication at all?

Blaschke: Yes! In many infectious diseases (tuberculosis, malaria, HIV and even more common infections), partial adherence can promote the emergence of resistant organisms, which can be very difficult to treat. An important example is the contribution of partial adherence to the development of multi-drug resistant tuberculosis that may then be transmitted to other individuals. A similar concern has been well-documented for patients infected with HIV. There is also some suggestion that partial adherence with oral cancer drugs may also contribute to drug-resistant cancers.

Q: In clinical trials, is it possible that the effectiveness of some drugs is underestimated if the prescribed dosing regimen is not followed?

Blaschke: This important consequence of partial adherence is often not

widely appreciated. It is often assumed that patients in clinical trials take the test medications correctly, but there is a substantial amount of information to show that this is not the case. As a result, the benefit of a drug for a condition for which it is being tested may be underestimated, and a company might stop further testing. By the same token, recommended doses are often overestimated during pre-market testing: about one drug in four undergoes at least a 50 percent reduction in dose within a year or two after market introduction. Conversely, the frequency of side effects may also be underestimated for those patients who, after the drug is approved, take the high doses that were tested, but not actually taken, during the clinical trials of the drug.

Q: Your paper points out that doctors may not realize their patients aren't taking the proper doses of prescribed medications and may react by increasing the dosage or adding more medications. How can this be prevented?

Blaschke: Physicians, while recognizing non-adherence as a problem in principle, generally overestimate the adherence of their own patients. For instance, among patients with so-called drug-resistant hypertension, we know that at least 40 percent are non-adherent. Identifying this as the problem is critical to proper disease management. The most important thing physicians can do is to consider the possibility of non-adherence as part of their differential diagnosis in non-responders, then ask about adherence in a non-judgmental way. Although less sensitive and less timely, prescription refill data can help identify patients who have discontinued therapy or who have poor implementation of the prescribed regimen. Physicians can also implement reminder systems for patient appointments and incorporate these for patients who are not following up on their appointments

Q: Are there any estimates of what better adherence might mean for health-care costs?

Blaschke: This question is important, but unfortunately the data are very limited, and better methods of assessment are needed. A recent publication looking at the impact of adherence in four major chronic diseases (congestive heart failure, hypertension, diabetes and dyslipidemia) found that better medication adherence increased the cost of medications, but also produced substantial, disease-specific medical savings as a result of reductions in hospitalization and emergency department use. There are a great many ideas for interventions to improve adherence, ranging from simple reminders (phone calls, apps, etc.) to the use of detailed adherence data to train patients and help providers guide patients to correct dosing. These approaches have not yet been evaluated in terms of their effect on health-care costs. It seems apparent, however, that better adherence is a win-win situation for all stakeholders.

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