Front & Center

Adherence Packaging to Optimize Outcome of Treatment

Medication adherence is a worldwide problem of striking magnitude that compromises clinical and economical outcomes of drug treatments. The World Health Organization reports that on a global basis, about 50 percent of patients fail to take medications as prescribed for chronic conditions. The deeper problem is that no one knows which patients are adherent and which patients take medications sometimes, occasionally or not at all as prescribed. Currently labeled "smart packing," standard pharmaceutical packages with an embedded microchip to detect opening and closing, can give healthcare providers key information on precisely when each dose was taken—or when it was missed.

Prescribers traditionally rely on patients' self-reports of adherence. While nonadherence varies with the drug and the patient population, numerous studies with different agents and in unique populations over multiple decades agree that patient self-reporting is widely overstated. Because therapeutic adjustments are often made based on patients' own, possibly inflated reports of adherence, there is the very real possibility that therapeutic failure is not a failure of the drug but a failure of the patient to take the drug appropriately.

Smart packaging that automatically records and reports each dose taken can resolve many of the questions that surround medication adherence. Knowing that a patient has been adherent can help prescribers make better informed, more effective treatment decisions. Knowing that a patient has not been adherent can help providers work with patients to understand why adherence matters and build the appropriate medication taking habits. And knowing precisely how many doses have been taken during a clinical trial and when each was taken can help clinical investigators more accurately assess the safety and efficacy of agents being evaluated.

Bernard Vrijens, PhD, Chief Science Officer at WestRock Healthcare and Associate Professor of Biostatistics at the University of Liège, Belgium, has studied medication adherence issues in multiple drug and population settings for more than 20 years. Most of his research is founded on quantitative medication adherence data compiled using the Medication Event Monitoring Systems (MEMS) that incorporates a tiny electronic system to passively record the opening and closing of drug packaging. MEMS offers the best combination of reliable dosing history data, patient satisfaction and cost.

The Problem

Experienced prescribers recognize that most patients are less than fully adherent to drug regimens. The more complicated and bothersome the regimen, the more patients have difficulties implementing the regimen. But some patients are not adherent to even the simplest dosing regimens. And until the advent of electronic monitoring systems, there was no way to monitor adherence short of requiring patients to take each dose in the presence of a nurse or some other trusted third party. That kind of witnessed dosing is not only highly intrusive, it is hugely expensive and wildly impractical in most situations.

At the same time, the clinical and economic impact of nonadherence can be enormous. Nonadherence is the single largest source of treatment failure in current medical practice. Nonadherence has emerged as a major driver of side effects and, in the case of anti-infective agents, a major driver of treatment-emergent resistance. Inaccurate and incomplete adherence data have been identified as a largely unrecognized confounding factor in clinical trials. It is estimated that nonadherence is responsible for between eight and ten percent of the entire healthcare budget in most developed countries.

Unnecessary treatment escalation is one of the most common examples of excessive spending due to nonadherence. Medications for hypertension, hypercholesterolemia, diabetes, and other chronic conditions are large and growing components of most health care budgets. When a patient fails to respond to a first-line agent, the typical response is to increase the dose, perhaps add a second or third agent to the regimen or move to biologic agent if available. Not only does therapy escalation increase the direct cost of treatment, it often complicates treatment and may increase side effects, which ultimately reduces adherence.

Having accurate adherence information allows the prescriber to distinguish true treatment failure and failure due to poor adherence. For patients in whom drug therapy has truly failed, therapy escalation may be an appropriate response. But for patients who are not taking their medication appropriately, therapy escalation is a costly exercise in futility. The better response is to work with the patient to manage adherence and then reassess therapeutic response.

Unneeded therapy escalation may represent a relatively small additional cost for each patient suffering from common chronic conditions. But even a few additional dollars per patient adds up to significant waste across millions of patients. When unneeded therapy escalation

means a move to newer and significantly more expensive (bio)pharmaceuticals, the additional cost can distort even the largest healthcare budgets.

Potential solutions to measure and manage medication adherence

Three major categories of smart solutions designed to manage patient adherence to medications have been developed in recent decades: smart packages, smart pills and patient diaries.

Patient diaries were initially a written record of each dose taken. Today, electronic diaries typically are combined with a reminder. If a patient fails to enter an expected dose, the system sends some sort of prompt. But these prompts can be intrusive and easy to ignore or to answer and forget. All patient diaries: paper, electronic, and some combination, share a common weakness: the time of intake is disconnected from the time of diary entry, and thus affected by desirability bias.

More recently, photographic or video documentation of drug intake has been proposed to potentially solve the time disconnection problem. The concept seems simple given that most patients have easy access to a mobile phone or some other imaging device; the practice is much more complex and burdensome. Taking photos or video that shows the medication container and the act of taking the dose takes three hands, one to hold the camera, one to hold the medication container and one to take the dose. The more intrusive the method and the more burdensome it becomes, the less likely patients are to accept and use it.

Ingestible sensors, often called "smart pills," are the latest development. An electronic sensor incorporated into each pill is tracked as each dose is taken and passes into the body.

The concept is appealing because tracking each dose as it is taken eliminates the possibility that patients may be opening a drug vial but not taking the dose. The practice is more complicated.

Because each dose contains a tracking sensor, the entire system is subject to regulatory approval, which adds significantly to product development time and cost. Sensors incorporated into doses must be sufficiently robust to withstand administration but cannot interfere with bioavailability of the drug product. Devices must also be biologically inactive and either dissolve without effect or be eliminated intact.

And because each dose must be tracked as it enters and passes through the body, the patient must wear some sort of tracking device or remain in physical proximity to an external monitor that can detect the dose. Both alternatives are intrusive and interfere with the activities of daily life.

Furthermore, smart pill systems are not 100% accurate even when used perfectly. The latest reports show a two percent rate of false negative errors, meaning the dose has been taken but not recorded by the sensor. If combined with an automated reminder system, the patient will be prompted to take a second dose, leading to overmedication and potentially serious adverse events.

Most smart pill systems rely on sensors attached to the skin using an adhesive patch. About 40 percent of users report patch-related skin irritation, another significant barrier to use.

Smart packages

Electronic medication monitoring systems (MEMS) is the first smart package to capture opening and closing of a dosing container. This approach has now been successfully extended to blister packaging, inhalers, injections, or to capture the disposal of used needles. MEMS have a significant advantage: they are entirely passive from the patient's perspective. The chip can be integrated into pharmaceutical packages of various design, which detect, time-stamp, and store the maneuvers needed to remove a dose of the drug.

The entire operation is automatic and requires no input by the patient and no change in daily activity beyond taking each dose as prescribed.

The Case for MEMS

Repeated trials have shown that electronically compiled dosing history data as reported by MEMS predict serum levels of the drug being taken with less than 3% discrepancies. Where trials of diary-based adherence tracking shows a 20 to 30 percent discrepancy between patient reports of drug-taking and serum concentrations of drug. While it is possible for patients to game MEMS by opening the container and not taking the drug, such gaming does not appear to be a significant problem in patient populations.

The most important impediment to implementing MEMS lies in using evidence of nonadherence to feedback to the patient and improve appropriate dose-taking. Medication adherence is a habit that can be learned and reinforced. Sharing adherence data with the patient can help solidify the new habit and provide a strong base for changing adherence behavior as needed.

Knowing that a patient has or has not been adherent can help prescribers make better informed, more effective treatment decisions. And of all the systems and technologies that have been developed to monitor adherence, MEMS continues to offer the best combination of reliable and unobtrusive data reporting, patient satisfaction and cost. Their use has been reported in more than 700 peer-reviewed publications and cited in the scientific literature more than 55,000 times.