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# Novel Framework to Improve Adherence

**M**edication adherence is a broadly recognized problem that affects patients worldwide. While the magnitude of nonadherence depends on the drugs and the specific patient population, the World Health Organization reports that 50 percent of patients do not take medications as prescribed on a global basis. A novel framework that distinguishes different phases of nonadherence and promotes specific strategies that are appropriate to each phase promises to improve adherence, improve clinical outcomes and reduce overall healthcare spending.

Traditional models identify adherence as a yes or no issue, or perhaps a continuum extending from perfect adherence to total nonadherence. A growing body of evidence identifies three distinct phases of adherence: initiation of therapy, implementing dosing on a regular basis and persisting with treatment for the indicated duration. Each of these phases presents distinct barriers to adherence and provides distinct opportunities for interventions to improve adherence.

The World Health Organization addressed this novel framework during a Global Forum on Innovation for Aging Populations held in Kobe, Japan held during October, 2015. Bernard Vrijens, PhD, Chief Science Officer at WestRock Healthcare and Associate Professor of Biostatistics at the University of Liège, Belgium, highlighted the three phases of adherence and strategies the pharmaceutical industry must implement to improve adherence.

These strategies include improving the use of adherence measures in clinical trials, improving access to medications, improving the packaging of medications and improving

communications between healthcare providers and patients in order to boost adherence.

## Defining and Achieving Adherence

Adherence is simply the process by which patients take medications as prescribed. But achieving adherence lies between difficult and impossible. Taking a medication is a new behavior, a novel habit that must be accepted, adapted and followed on a routine basis.

More than two decades of research using electronic monitoring devices across multiple drugs, patient populations and countries has found that adherence is composed of three distinct phases or behavior patterns. Patients must first choose to initiate treatment. Once they have begun treatment, they must implement the dosing regimen on a regular basis. Finally, they must translate their regimen into a habit and persist with the new habit for the duration of treatment.

Each of these three phases, initiation, implementation and persistence, offers unique barriers and unique opportunities for intervention.

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## Initiate Treatment

The traditional view of adherence assumes that after a health-care provider prescribes a medication, the patient fills the prescription and begin taking it as prescribed. In reality, 30% of patients in developed economies never even fill that initial prescription and never initiate treatment.

Even in the in the most affluent economies some patients cannot afford medications. Cost can be a major barrier to initiating treatment in conditions such as hepatitis C, HIV and oncology. Health insurance may help, but many health plans employ tools such as prior authorizations, mandatory step therapy and acuity measures to limit access to higher-cost medications.

Cost is a common barrier in less developed economies where many people may not be able to afford adequate nutrition, much less medications. Patients who cannot afford medications cannot initiate treatment and will never develop the behaviors that contribute to adherence.

Lack of physical access is another common barrier. Patients who must travel for injections, infusions or directly observed medication administration may find the trip too long, too expensive or too bothersome, especially if the journey must be repeated at regular intervals. Uncertain supply chains, lack of refrigeration or other adequate storage, shortages of trained healthcare providers and similar infrastructure deficits also impede access. Patients who cannot access medications cannot initiate treatment and can never become adherent.

Lack of engagement with treatment is another key barrier. The morbidity associated with some chronic conditions may not be apparent to patients until their disease has progressed to the point at which it can no longer be treated effectively. Patients who are told that they should begin medication for hypertension, type 2 diabetes, hyperlipidemia or other conditions do not always accept the need for the prescribed medication.

## Implement Treatment

Once patients have initiated treatment, they must implement dosing on a regular basis. Some medications require patients to do little more than remember to take a single tablet at about the same time every day or every week.

For other medications, implementation can be complex. Some medications must be taken with food, others without. Some must be taken at precise intervals, every four, six, eight

or 12 hours without regard to sleep, family, work or other considerations. Polypharmacy multiplies the complexity of treatment, especially if different medications have different, potentially conflicting, requirements. The more complex the regimen, the less likely the patient is to implement dosing.

Medication formulation can also hinder implementation. Inhaled asthma medications are notoriously difficult to take correctly. Inhaled medications may cause bothersome irritation to the mouth and throat, which can discourage regular use.

Medication timing is another barrier. Many traditional medications such as metformin for type 2 diabetes or statins for hyperlipidemia have very wide therapeutic windows. Taking a dose early or late, or even missing a single dose, seldom has significant clinical effects.

A growing number of highly effective medications have very narrow therapeutic windows. Timing can be critical for oral oncolytic agents, oral anticoagulants and oral hepatitis C agents. Narrow or precise dosing windows complicate the regimen, making it more difficult to implement treatment.

## Persist with Treatment

Once patients implement treatment, they must transform the regimen into a habit. The longer the duration of treatment, the more difficult it can be to persist. Persistence of treatment is a particular problem in chronic conditions with lifetime regimens.

Persistence is more difficult in conditions such as hyperlipidemia or hypertension where adherence brings clinical benefits but the patient feels no better. Lack of adherence can lead to significant long term health consequences, morbidity or even premature death while persisting with treatment brings no obvious benefit.

## Strategies to Overcome Adherence Barriers

Biopharma manufactures can implement strategies to reduce barriers in all three phases of adherence. A key first step is to implement adherence measures in clinical trials. Repeated studies using electronic monitoring devices have shown that actual adherence in clinical trials is far lower than reported adherence.

This unacknowledged and largely undocumented adherence gap can significantly alter trial results. Adherence directly affects participants' actual exposure to the agent being trialed.

Exposure affects both the clinical and statistical outcomes of the trial. Analyzing and stratifying outcomes by adherence in addition to other variables could improve the success rate of clinical trials that are otherwise obscured by varying levels of adherence. It is only when adherence is measured and documented that the optimal dosing regimen can be identified and the relevant deviations can be recognized and managed.

A second step is implementing automated adherence monitoring for select products and populations. Electronic monitoring could be particularly helpful for medications in which precise adherence is critical to clinical effect. A recent study at the University of Alabama Birmingham found that 40 percent of children with acute leukemia failed to achieve levels of adherence sufficient to cure their disease. Children who were less adherent had higher relapse rates. Systematic monitoring in populations in which precise adherence is critical could improve treatment outcomes and potentially improve payer coverage. The current cost of electronic monitoring is minimal and will fall rapidly as the technology is scaled up.

Industry can improve implementation by improving access to medications. In some locations, improved access could mean bolstering the healthcare infrastructure and supply chain. In other locations, it could mean making medications affordable to all.

Improving access also means improving delivery devices and making medication easier to open. The calendar-type packages that have been so successful in improving adherence for oral contraceptives could be expanded to other medications. Smartphone apps and other electronic devices to remind patients of doses are available, but not widely studied or implemented. Industry routinely spends hundreds of millions of dollars to improve candidate molecules and virtually nothing to improve delivery strategies and devices that could enhance adherence, thereby improving outcomes and boosting sales.

### **Non-Physician Providers are Key**

Improved communications can help bypass many of the barriers to adherence. Communication can help patients who

are not engaged with treatment initiate the first prescription. Communication can encourage patients who have trouble implementing regular dosing or doubt the need for persistence.

Physicians rarely have the time to engage patients on a regular basis. Pharmacists and nurses have both the training and the time to address adherence. Industry can not only take the lead in advancing adherence-informed clinical trials and adherence-improving packaging, but also in promoting adherence-improving professional services.

Improving adherence clearly brings direct and measurable benefits for patients, healthcare providers, product manufacturers, regulators, patient advocacy groups, payers and other stakeholders that far outweigh the costs. When a hyperlipidemia patient on statins fails to show improvement, for example, current treatment algorithms call for increased dosing or a new, usually more expensive agent. For most patients in this situation, poor adherence is the root problem. Adherence monitoring, possibly using pharmacy dispensing records or electronic monitoring, could be a more clinically effective and cost-effective strategy.

Randomized trials and longitudinal studies in clinics for hyperlipidemia, hypertension, asthma, type 2 diabetes and other chronic conditions have repeatedly showed that improved communication and coaching from a pharmacist or nurse, based on reliable and precise adherence data, is more effective and less costly than increased dosing. Industry must take the lead in transforming the lessons from these largely academic studies into practical healthcare policy that improves clinical outcomes and reduces overall spending by improving the three stages of adherence.

Applying this novel framework for adherence and implementing strategies such as improving the use of adherence measures in clinical trials, improving access to medications, improving the packaging of medications and improving communications between healthcare providers and patients, will improve all three stages of adherence. The ultimate goal of improved adherence is to improve clinical outcomes and reduce overall spending on health care.

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