Smart Packaging: The Missing Link in the Two-Step Adherence Puzzle

Non-adherence to medication has been costing lives and money for decades – but cutting-edge solutions are now on hand to solve the age-old problem

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It is no secret that the medical community has a problem with non-adherence to medication. The issue drives health outcomes down, forces cost up, and has been well documented over the last few decades (1). How to deal with the issue, however, is less clear cut. Many current measures are imperfect, biased, and inaccurate, and the huge variety of barriers to compliance rule out a one size fits all solution.

A new generation of connected smart packaging is offering healthcare providers and researchers with the ability to take an informed, patient-centred approach, and overcome the adherence puzzle once and for all.

Avoidable Mortality and Morbidity

Prescription drugs can offer life-changing results, but they only work if people take them as prescribed. That is not always easy, especially for people with long-term conditions who require regular, ongoing treatment to prevent disease progression or complications. The consequences

can be dire. A study of more than 65,000 people with Type 2 diabetes, for example, found poor medication adherence in the two years after diagnosis was associated with an increased risk of all-cause mortality and cardiovascular disease (CVD). In fact, it raised the mortality rate by 45%, and the incidence of CVD by 41% (2).

"Interventions to improve medication adherence to a maximum level may reduce the five-year cumulative mortality rate from 7.46% to 5.06% among patients with poor medication adherence," said the authors, adding that such a move could prevent 240 deaths and 152 cases of CVD per 10,000 people.

Another paper looked at the association between poor adherence and poor outcomes in hypertension, diabetes, and hyperlipidaemia. Using data from the Korean National Health Insurance Claims Database, the authors defined poor adherence as being less than 80% of medication possession ratio (MPR), a pill count method based on prescription refill

volumes, over 12 months (3). It found that hypertensive patients with poor adherence were 10.9% more likely to experience disease-specific hospitalisations than their adherent counterparts within two years. What's more, the likelihood of all-cause hospitalisation was higher among patients who had poor medication adherence across all groups. People with hypertension and an MPR of less than 80% were 32% more likely to need hospital treatment within two years than those with an MPR of more than 80%. That figure was 16% in hyperlipidaemia and 32% in diabetes.

As these studies illustrate, people can pay the ultimate price for not taking their medication as prescribed – across Europe, medication non-adherence contributes to an estimated 200,000 premature deaths every year (4).

Avoidable Costs

Aside from the devastating human costs, poor adherence costs the sector millions in terms of healthcare

costs and lost revenues. According to the New England Healthcare Institute, medication non-adherence is responsible for around $100 billion in excess hospitalisations every year (5). The report said this increased risk of hospitalisations due to poor health outcomes translates to significant excess costs.

Several studies have found that overall healthcare costs are much higher for patients with poor adherence. For example, among diabetes patients, those with high levels of adherence had total annual healthcare costs of $8,886 while patients with low levels of adherence had almost twice the total annual healthcare costs, totalling $16,498.

The costs to drug developers and manufacturers are equally eye-watering. A 2018 report estimated that non-adherence costs the global pharmaceutical industry $564 billion every year (6).

Not only does the problem have direct impact on revenue in terms of unfilled prescriptions, but it also reduces the perceived value of efficacious products that have been meticulously developed and diligently brought to market.

Interventions to improve medication adherence should be top priority for the pharma industry and will prove beneficial to all stakeholders.

Increasing adherence rates by only 10% would translate into a $41 billion pharma revenue opportunity in the US, and $124 billion globally, accompanied by improved health outcomes and decreased healthcare spending (6).

Medication Adherence in Drug Development Trials

In product development, non-adherence to study medications can result in drug efficacy being underestimated to the point of trial

failure, compromise patient safety, and complicate regulators' benefit-risk assessments (7).

Studies show that each Phase III trial participant is responsible for an average of $42,000 in costs, yet almost a third, 30%, are non-adherent by day 100 (7-8). Across all clinical trial phases, 50% of participants admit to not adhering to the dosing regimen set out in the protocol (9).

It drains study power and has a direct effect on the cost and duration of clinical trials. Crucially, it can delay the approval of investigational products – at a cost of between $600,000 and $8 million a day in lost revenues (10).

Measures and Approaches

Over the years, the industry has developed several measures and approaches to monitoring and mitigate the risk of non-adherence.

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Measures tend to include direct methods, such as observing therapy intake, or measuring blood or urine titre level. Indirect methods, such as patient questionnaires and self-reporting, pill counts and rates of prescription refills, or the assessment of clinical responses or physiologic markers, are also common. For more than four decades, numerous research on how to properly measure and quantify medication adherence has been conducted but none can be counted as the gold standard.

A review of the measures published in 2015 quoted that different tools have been designed and validated for different conditions, in different circumstances (1). What's more, traditional measures have inherent limitations – they can be subjective or inaccurate. In many cases, they provide just a yes/no answer, rather than actionable insight into the reasons behind the problem.

In addition to the absence of a reliable, one-size-fits-all measure, the industry also lacks a universal, effective intervention. Barriers to medication adherence, which might be intentional or non-intentional, are multiple. The problem might be socioeconomic, or it might be related to the therapy, the condition, or to the patient themselves. It could stem from the relationship between the person and their healthcare team, or a lack of health literacy. Each reason requires a bespoke, person-centred, tailored intervention. Some people might need additional education, or behavioural counselling. Others may benefit from an improvement in communication between them

and their healthcare team, while some might simply need to be reminded. This complexity of joining accurate measurements to effective interventions means that, to date, overcoming the adherence conundrum has proved elusive.

The Intelligent Solution

Solving the adherence puzzle takes a two-step approach: accurate measurement followed by appropriate management. Electronic monitoring, widely recognised as the most objective and precise form of medication adherence monitoring, is the key to step one.

Smart packaging, which can accurately record dosing events, is now available for a wide range of administration routes. Topical

treatment caps and tubes, (reusable) electronic blister packs and pill boxes, smart injectable therapy containers and inhalers are all part of a new generation of intelligent monitoring.

They feature an electronic microcircuit which automatically generates a timestamp every time the patient takes or applies their medication. This information is stored on the packaging's memory before being wirelessly transferred to a central, cloud-based software system for analysis and interpretation.

Smart packaging enables healthcare teams and researchers to map real-life, rather than estimated, adherence, over time, and provides accurate, objective results. But such devices cannot solve the puzzle alone. By connecting this cutting-edge hardware to cutting-edge software, we can drill down into medication behaviours to understand habits, detect issues, and recommend appropriate interventions.

Data visualisation and algorithms can spot typical behaviour changes, such as drug holidays, weekend drop offs, and different intake times. They offer insight on whether such changes are 'one offs' or might be cause for concern.

Armed with this information, healthcare teams and researchers can quickly detect potential problems, and work with patients to provide individual advice and develop appropriate interventions.

Next Generation Adherence Solutions

Advanced digital monitoring provides complete oversight of the adherence metrics and risk indicators that matter the most. Studies have shown that smart electronic packaging and device monitoring is 97% accurate. That compares to 70% accuracy for drug levels and markers, 60% for pill counts, 50% for healthcare professional ratings, and just 27% for patient self-reporting, including electronic patient diaries (11).

Smart packaging is passive and friction-less, placing no burden on the patient. That makes it more effective than app-based methods, which introduce additional tasks to the medication routine, and tend to struggle to obtain accurate data from those most at risk from non-adherence.

Connected smart packaging creates an ecosystem that joins measurement and intervention – a closed feedback loop that can optimise medication efficacy, maximise outcomes, and reduce unnecessary costs for healthcare systems and industry players alike. Ultimately, it can help people to live longer, healthier lives, while ensuring maximum return on investment for drug developers and manufacturers.

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Dr Bernard Vrijens, Scientific Lead at **AARDEX Group,** holds a PhD from the Department of Applied Mathematics and Informatics at Ghent University, Belgium.

He currently leads a research program investigating: the most common errors in dosing using a simple but robust taxonomy; particular dosing errors that can jeopardise the efficacy of a drug; and the optimal measurement-guided medication management program that can enhance adherence to medications and maintain long-term persistence.

Bernard is also the co-author of seven book chapters, over 100 peer-reviewed scientific papers, and named as inventor on six patents. He is a founding member of the International Society for Medication Adherence (ESPACOMP), and an active member of several EU- and US-funded collaborative projects around the theme of adherence to medications.