Insights From Monitoring Adherence in Clinical Trials and in Clinical Care: Understanding the Key Question of Drug Forgiveness

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Disclosure: CEO of AARDEX Group
Advanced Analytical Research on Drug EXposure

Medication Event Monitoring System

MEMS Bibiometry
- 802 peer-reviewed publications
- 70k journal citations
- 138 h-index

March 2019, Google Scholar.
Case Study

Dosing History Data over 2 years (2011-2012)

Follow-up: 632 days – 14 days (2%) with double dose & 115 days (18%) no doses

⇒ 84% of prescribed doses taken

How much implementation is enough? DRUG’S FORGIVENESS
ABC Taxonomy & EMERGE guideline

Medication Adherence is the process by which patients take their medications as prescribed

A. Initiate
   - Patient does not initiate treatment
   - Binary (yes/no)

B. Implement
   - Patient delays, omits or takes extra doses
   - Dosing history

C. Persist
   - Patient discontinues treatment
   - Time to event

Different forms of nonadherence

EU-sponsored research

20 to 30% of patients do not initiate a new prescription

195,930 e-prescriptions for >75,000 patients

Figure 1. Primary non-adherence to newly prescribed medications. Patients aged 19 and over.

The Unfortunate 80% rule!

Each of these 6 patients took the same percentage (81%) of prescribed doses

Once daily dosing

Twice daily dosing
Overall, 40% of patients will have discontinued treatment by the 12th month of treatment.

N=16,907 participants from 95 clinical studies

The Adherence Gap

Potential consequences of this gap:

- Risk of failure related to lack of effectiveness
- Poor estimation of toxicity
- Inappropriate dosing regimen

Adherence is Becoming a Regulatory Priority

Draft guidance from the US FDA explicitly addresses adherence strategies


Seminal example: the contraceptive pill

Key learnings:

1. Today’s estrogen dose is one third lower than the first marketed oral contraceptive
2. 50-fold difference in efficacy between perfect use and typical use
3. When possible other delivery systems should be investigated
Adherence un-informed clinical development

« the quest for the magic dose »

- **Phase I**
- **Phase II**
- **Phase III**

**Drug development**

- **Market**

- **Formulation**
- **Adherence?**
- **PK/PD**

Compensate for diluted efficacy

Unexpected adverse drug reactions (ADRs)

Highest Safe Dose* (based on small, controlled, (adaptive) designs)
Adherence un-informed prescription leads to inappropriate treatment escalation & needless combination therapies

Sub-optimal adherence

Treatment failure

Disease progression
Acute event

More complex treatments
Adherence-informed development and prescription is urgently needed.

Medication adherence

Development

Prescription

Conservative approach & highly regulated

Inappropriate dose and dosing regimen, often too high doses and needless combinations

Disruptive innovations

Medication adherence

Safety & Effectiveness

Big Data analysis
Google, Apple, etc.
Digital Health
Powerful treatments require a major change in the care model

One dose fits all?

- Need knowledge at point of care
  - Precision medicine
  - Personalized therapy
  - Individualized treatment
  - Patient-centered care
  - m-health / e-health

➤ Medication Adherence is a vital sign to measure and manage

Peck R, Annual Review, 2018
The solution requires a systematic approach of each process

Variable adherence is a major source of variance in drug response

Variable adherence creates drug-specific issues of efficacy, safety, & drug resistance

Occasional toxicity

Periodic loss of effectiveness & emergence of drug resistance

The Concept of Drug Forgiveness
Or How Much Implementation is Enough?

Increased risk of toxicity

Periodic loss of effectiveness

Dosing time (Day)

« Avionics »
Beyond adherence, think drug forgiveness

The NOACs example:
Drug exposure simulations assuming $T_{1/2}=12h$; $T_{max}=3h$

- **Dose X: Once daily**
- **Dose X/2: Twice daily**

- 15% missed doses
- 15 once-daily missed doses vs. 30 twice-daily missed doses over 100 days

Management of adherence: A systems approach

**Definition**
“the process of monitoring and supporting patients’ adherence to medications by healthcare systems, providers, patients and their social networks”

**Objective**
“to achieve the best use, by patients, of appropriately prescribed medicines in order to maximize the potential for benefit and minimize the risk of harm”

The Challenge: Integration into care models

“The right dose for the right patient at the right time…”
But...

>1500 medicinal products for human use

Limited resources

- Time pressure
- Human limits (fatigue – memory – recall)
- Pts expectations
- Media
- Pharma
- Etc.
Digitally-Enabled Integrated Person-Centered Care
A Multi-Disciplinary Approach
The Age of Patient-Empowerment

Adherence-Informed Clinical Trials

- Greater efficacy and lower variability (increased power/decreased sample size)
- Better informed benefit/risk and developmental decisions
- Supports strategic trials (adaptive trials, baysian)
- Faster proof of efficacy
- Validation in broader populations
- Less trial failures

Adherence-Informed Digital Health

- More informative safety
- More effective dosing regimens
- Enable individualization / personalization of therapies
- Facilitate a multidisciplinary approach

Vrijens & Urquhart, CPT, 2014
“Drugs don’t work in patients who don’t take them.”

– C. Everett Koop, former US Surgeon General