High-fidelity measurement of patients’ medication adherence: A missing link in precision medicine

Bernard Vrijens, PhD
Chief Science Officer, WestRock Healthcare
Associate Professor of Biostatistics
University of Liège, Belgium
One size does not fit all patients

"Individual Variations"

**WHAT IS IT?**

**Precision medicine** is an emerging approach for disease prevention and treatment that takes into account people’s individual variations in genes, environment, and lifestyle.

The Precision Medicine Initiative® will generate the scientific evidence needed to move the concept of precision medicine into clinical practice.
Variable adherence is a major source of variance in drug response.

Why is high-fidelity measurement of medication adherence a missing link?

NEAR-TERM GOALS

Intensify efforts to apply precision medicine to cancer.

Innovative **clinical trials** of targeted drugs for adult, pediatric cancers

Use of **combination therapies**

Knowledge to overcome drug resistance

www.nih.gov/precision-medicine-initiative-cohort-program
Innovative Clinical Trials for adult, pediatric cancers … Adherence matters!

40% of children had <95% adherence leading to a 2.7 fold increase in relapse rate (N=600)

"… we must not lose sight of the fact that precision medicine also applies to optimizing known effective therapy"
Addressing adherence is key to avoid treatment escalation & needless combination therapies.

1. Poor adherence
2. Disease progression
3. More complex treatments
4. Treatment failure

Circle flow: Poor adherence → Disease progression → More complex treatments → Treatment failure → Poor adherence
Variable adherence creates drug-specific issues of efficacy, safety, & drug resistance

Occasional toxicity

Adherence is Key to Therapeutic Success

“Drugs don’t work in patients who don’t take them.”

– C. Everett Koop, former US Surgeon General
Medication adherence: ABC Taxonomy

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

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.

Daily, 15% of patients do not implement as prescribed.

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

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


Adherence based on self-report and pill count not reliable

Reliability of adherence data should be improved

No covariate can have a larger impact than not taking the drug

Adherence data could provide valuable information for both efficacy and safety

More attention should be paid to adherence data in regulatory review

Jiang Liu & Yaning Wang; ACDRS, September 13, 2012

Memorandum of FDA Advisory Cte meeting, April 16, 2012

Adherence Measurement Methods

Sparse Sampling
- Retrospective questionnaire
- Pill Counts

Rich Sampling
- Patient diary
- Electronic compilation of dosing history data
- Therapeutic drug monitoring
- Pharmacy refill data

Reliable

Biased

Each of these 6 patients took the same percentage (81%) of prescribed doses.
Hi-Fidelity measurement of drug exposure using electronic monitoring of adherence

Medication Event Monitoring Systems (MEMS) & smart packages: <3% Discrepancies Between Projected and Observed Concentrations

Vrijens B et al., J of Clinical Pharmacol, 2005, 45: 461-467

MEMS Bibliometry

703 peer-reviewed publications
53K journal citations
117 h-index

February 2016, Google Scholar.
The importance of continuous assessment of drug exposure

Two examples of long term PK projection based on electronic capture of dosing times

- Measured trough concentrations

Vrijens B et al., J of Clinical Pharmacol. 2005, 45: 461-467
Probing the time-course of drug exposure

Consequences of medication non-adherence

A Initiate

Drugs don’t work in patients who do not initiate them

B Implement

Drugs work partially or may create harm in patients who implement a dosing regimen sporadically

C Persist

Drugs stop working in patients who discontinue them

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

- **Increased risk of toxicity**
- **Periodic loss of effectiveness**

Concentration vs. Dosing time (Day)
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

The struthian approach is no longer an option!
Adherence un-informed clinical development

What is the best dosing regimen?

Drug development

- Phase I
- Phase II
- Phase III

Market

Formulation

- Adherence?
- PK/PD

Efficacy

Safety

Compensate for diluted efficacy

Unexpected adverse drug reactions (ADRs)

Highest Safe Dose*

*based on small, controlled, (adaptive) designs
Promising drug that could have been …

**Drug Development**

Failed clinical trials due to lack of efficacy

30% attrition

Increased risk of toxicity due to an overestimated dose

30% attrition

**Medical Practice**

Risk of post-approval dose reduction

1 in 5: >50% dose reduction\(^1,2\)

Short persistence: high churn rates

50% non-persistence during the 1st year of treatment

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Three critical factors to achieve and maintain a successful treatment

- **Concentration**
- **Increased risk of toxicity**
- **Periodic loss of effectiveness & resistance**

**Dosing regimen (dose & internal)**

**Biological variability (PK/PD)**

**Patient adherence variability**

**Time**

**Concentration**
Adherence-informed clinical trials

Opportunities

Time Savings

• Better informed benefit/risk and developmental decisions
• Shorter time to set the optimal regimen

Cost Savings

• Greater efficacy and lower variability (increased power/decreased sample size)
• Fewer post-approval dose-reductions

Improved Therapies

• More informative safety
• More effective dosing regimens

The changing pharma model

- One dose fits all

- One dose does not fit all
  - Need knowledge at point of care
    - Precision medicine
    - Personalized therapy
    - Individualized treatment
    - Patient-centered care
    - m-health / e-health

Key is being “on treatment”

- Initiation &
- Persistence

Proportion of Days Covered

PDC >80%

Medication Adherence is a vital sign to measure and manage
Adherence management is becoming part of care pathways.

When a treatment is not working, think non-adherence!
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”

**EU-sponsored research**

Patients’ awareness of their adherence patterns changes behavior.

Focused discussion between a pharmacist and patient based on reliable and detailed adherence data.

Example of a successful intervention:

EU-sponsored study confirms that showing patients their own dosing errors is the most effective means to improve adherence.

Demonceau et al, Drugs; April 2013.

Each of the 4 patients took 75% of prescribed doses during a 3-month period

“What Can Be Measured Can Be Managed”

–Deming, WE

Elements to change patients’ behavior

Training

- EDUCATION knowledge
- MOTIVATION self-efficacy

Package

MANAGEMENT OF ADHERENCE

Goals

- MEASUREMENT awareness

Measurement is also the cornerstone for medication habit building

The habit loop has 3 stages

1. **Cue**
2. **Routine**
3. **Reward**

To design or improve a patient’s habit of adhering to medications, the first step is making the patient *aware* of the habit by:

1. Analyzing the habit loop
2. Write down plans and goals
3. Measure & assess achievements

There is not one formula but hundreds!


There is not one solution to manage medication adherence: it’s hard work!

There is not one solution to manage medication adherence: it’s hard work!

Overview of assessment methods of adherence in ambulatory patients

### Direct methods (PK/PD)
- Requires sampling after prescription
- Sampling is too sparse
- Subject to white coat adherence

### Self-report
- Desirability bias
- Recall bias
- Desirability bias

### Pill counts
- Easily censored by patient
- Only an aggregate summary
- Easily censored by patient

### Prescription & refill databases
- Gold standard if both databases combined
- Only an aggregate summary
- Gold standard but retrospective

### Electronic monitoring
- Gold standard in CT; needs activation
- Gold standard
- Gold standard in CT; needs patient engagement

*Vrijens B, Heidbuchel H, Europace, 17(8):1317-8, 2015*
Packaging is an under-used opportunity to manage effectively medication adherence

E-prescription and pharmacy refill data

Calendared blisters and package activated adherence programs: self-measure

Dosing regimen IMPLEMENTATION and habit building

Smart packages – dosing history data

- In clinical trials & research
- At treatment initiation in specialty pharmacy
- At treatment failure
- When an implementation problem is suspected

Patient Adherence is a Big Systems Problem With Many Elements

**Healthcare Professionals**
1. Better collaboration between HCPs
2. Adherence measure & feedback
3. Think continuity of care
4. Manage polypharmacy
5. Build Medication taking Habit Strategies

**Regulators & Healthcare policy**
1. Raise awareness
2. Support education of HCPs
3. Incentivize performance
4. Promote integrated care models
5. At treatment failure, check adherence before dose escalation
6. Set-up the regulatory framework for individualized therapy
7. Data policy for adherence measures
8. Support research in adherence-related sciences

**Pharma Industry**
1. Optimize drug development
2. Think individualized therapies rather than one dose fits all
3. Move from selling a chemical pill to providing a system
4. Improve the package

**Patients**
1. Empowerment
2. Self-management
3. Adopt new care models and monitoring technologies

**Family and Carers**
1. Special attention to elderly, adolescents, and children
2. Caution with depression and associated diseases
3. Patient associations

B. Vrijens, personal view for Belgian stakeholders meeting, June 2014
High-Fidelity measurement of medication adherence is the **missing link** in precision medicine

LONGER-TERM GOALS

Create a research cohort of **> 1 million American volunteers** who will share genetic data, biological samples, and diet/lifestyle information, all linked to their electronic health records if they choose.

Pioneer a **new model for doing science** that emphasizes **engaged participants**, **responsible data sharing**, and **privacy protection**.

Research based upon the cohort data will:

- Advance **pharmacogenomics**, the right drug for the right patient at the right dose
- Identify new targets for **treatment and prevention**
- Test whether **mobile devices** can encourage healthy behaviors
- Lay **scientific foundation** for precision medicine for **many diseases**

Now that we have the **ABC taxonomy**, … let’s state the **123 conclusions**

1. **The Problem**
   - Poor adherence to treatments for chronic diseases is a long-neglected worldwide problem of striking magnitude
   - Its consequences are: biased clinical study results, poor outcomes of drug treatment, emergence of drug resistance, added costs of health-care

2. **The Opportunity**
   - The advent of uniquely powerful medicines and reliable means to measure adherence bring patient nonadherence into clear view
   - Achieving satisfactory adherence may have far greater impact than any other maneuver to improve medical treatments

3. **The Action**
   - Health systems must evolve to meet the challenge of achieving satisfactory adherence to therapeutic drug regimens
   - Patient-tailored and measurement-guided intervention are required to achieve sufficient adherence to therapeutic drug regimens
Thank you for your attention

20th ESPACOMP meeting will be held in Lisbon, Portugal, on the 18th and 19th November 2016
www.ESPACOMP.eu
Optimizing Drug Development: Towards the Future

Drug development

- Manage Adherence to Medications
  - Maximize drug exposure
  - Estimate method effectiveness (full efficacy)

- Get more insights into Patient Adherence in the Population of interest
  - Initiation / Implementation / persistence
  - Study drug’s forgiveness
  - Go beyond ITT analysis
  - Individualize therapy

- Provide appropriate solutions for treatment individualization & patient adherence
  - Not necessarily the same than in drug development
  - Go beyond the pill and secure appropriate comparative effectiveness

Medical Practice

- Initial Licence
- Full Licence

Selected subset of the population

Close the Adherence Gap

Total Population Size

Adapted from Vrijens & Urquhart, CPT, 2014