**KU LEUVEN**

# New tools
# to detect medication
# non-adherence

*The hospital pharmacist and the e-health revolution*

**Jasper Vanhoof,** MScN, PhD-student
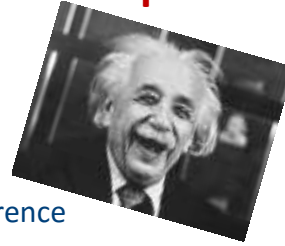
Department of Public Health and Primary Care
Academic Centre for Nursing and Midwifery

**eahp**
european association
of hospital pharmacists

## I have no disclosures related to this presentation

**KU LEUVEN**

# The important thing is **not to stop questioning...**

1. Modern tools are able to reveal non-adherence in all patients: **True** - **False**

2. Skipping medication doses is a more prevalent problem than patients stopping the medication regimen completely: **True** - **False**

3. Adherence measurement should become part of standard practice of all pharmacists: **True** - **False**

**KU LEUVEN**
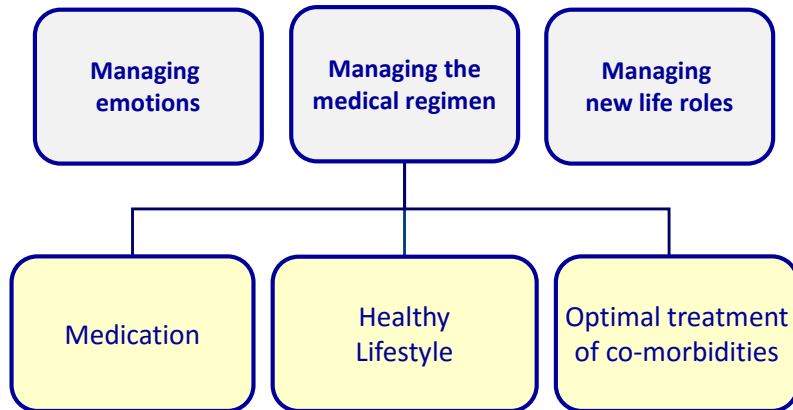
---

# Increasing prevalence of **chronic diseases**



Projected Growth In Population With Chronic Conditions, 2013–25
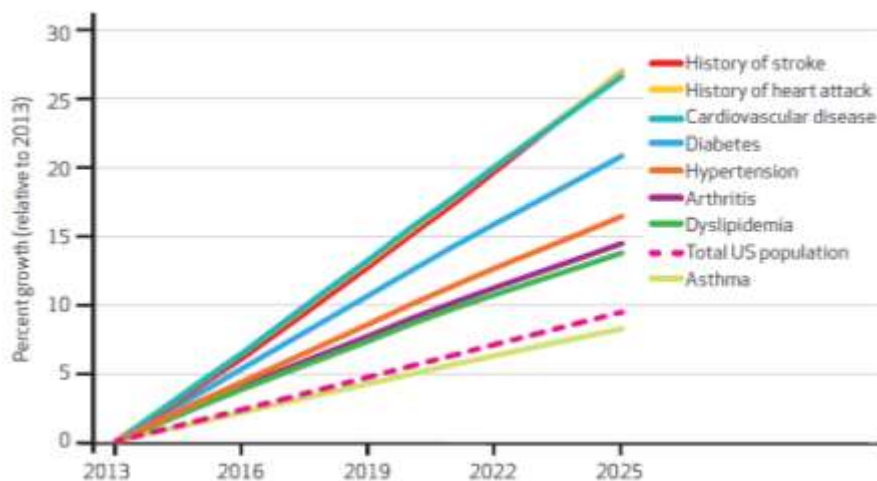
**KU LEUVEN**

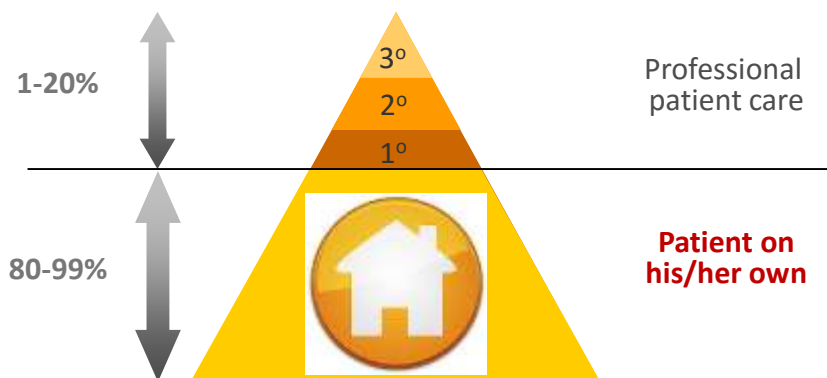Dall. Health Affairs. 2013;32(11):2013-2020

2

24/03/2016

# Treatment after chronic disease onset:
## A complex regimen

| Managing emotions | Managing the medical regimen | Managing new life roles |
|---|---|---|

| Medication | Healthy Lifestyle | Optimal treatment of co-morbidities |
|---|---|---|

**KU LEUVEN**

Lorig KR. Ann Behav Med. 2003;26(1):1-7.

# The hidden healthcare system

1-20%

3º
2º
1º

Professional patient care

80-99%

**Patient on his/her own**

Per Ake Zillen (kidney transplant patient, Sweden):
*"There are 8760 hours in a year; I spent 5 hours within the health care system. The other 8755 hours are my responsibility"*

## Medication taken by kidney Tx patient during one year (>4000 pills)



Ambühl P. Nephrol Dial Transplant 2005; 20:1267

**KU LEUVEN**

## Overview of presentation

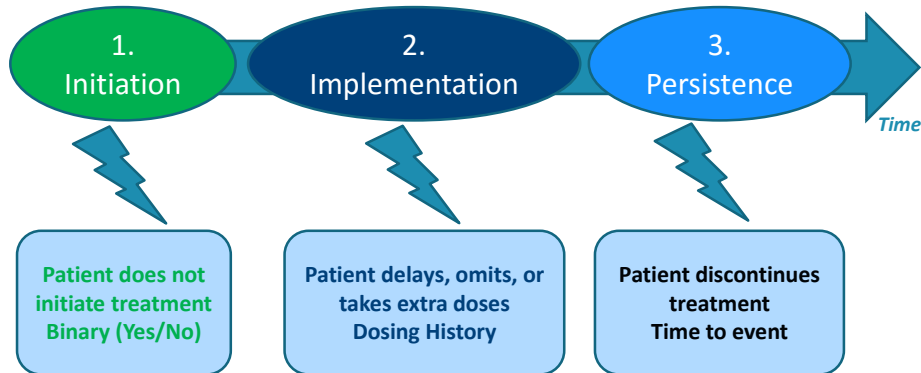| 1 | • What is medication (non-)adherence? |
| 2 | • Criteria to choose (e-)tools for medication adherence measurement |
| 3 | • Which modern methods are available to monitor medication adherence? |

**KU LEUVEN**

# **Taxonomy** on medication adherence

<u>Medication Adherence</u>: The process by which patients take their medications as prescribed

| 1. Initiation | 2. Implementation | 3. Persistence |
|---|---|---|

*Time*

**Patient does not initiate treatment Binary (Yes/No)**

**Patient delays, omits, or takes extra doses Dosing History**

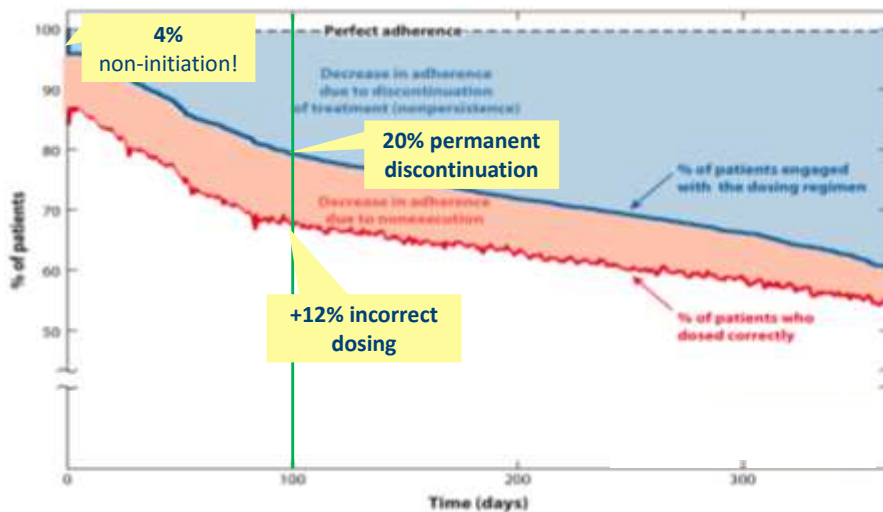**Patient discontinues treatment Time to event**

**KU LEUVEN**

Vrijens. Br J Clin Pharmacol 2012;73:691 - 705

# **Non-persistence: more common than implementation problems!**

16,907 participants from 95 clinical studies

**4% non-initiation!**

**20% permanent discontinuation**

**+12% incorrect dosing**

Perfect adherence

Decrease in adherence due to discontinuation of treatment (nonpersistence)

Decrease in adherence due to nonexecution

% of patients engaged with the dosing regimen

% of patients who dosed correctly

% of patients

Time (days)

Blaschke. Annu Rev Pharmacol Toxicol 2012;52:275 - 301

# Overview of presentation

| | |
|---|---|
| **1** | • What is medication (non-)adherence? |
| **2** | • Criteria to choose (e-)tools for medication adherence measurement |
| **3** | • Which modern methods are available to monitor medication adherence? |

**KU LEUVEN**
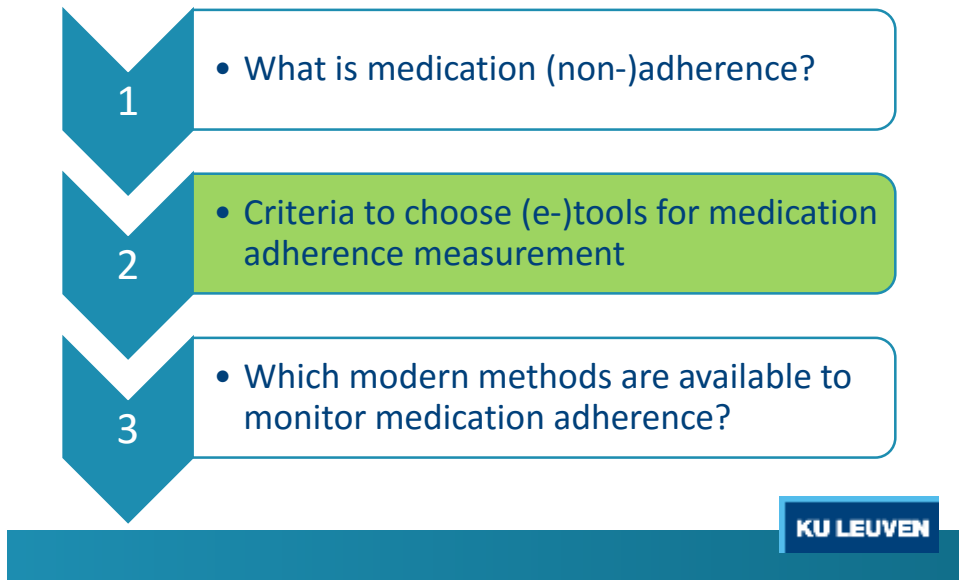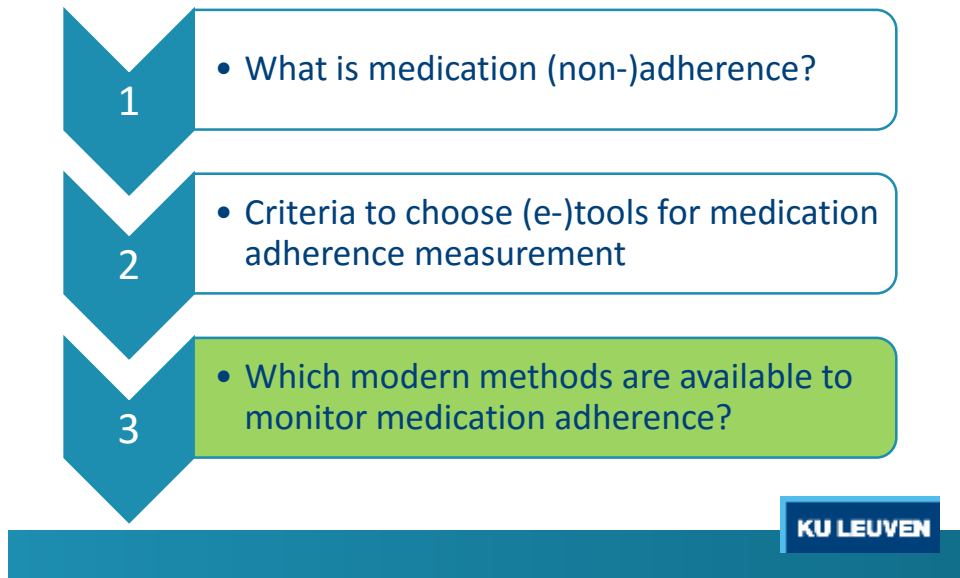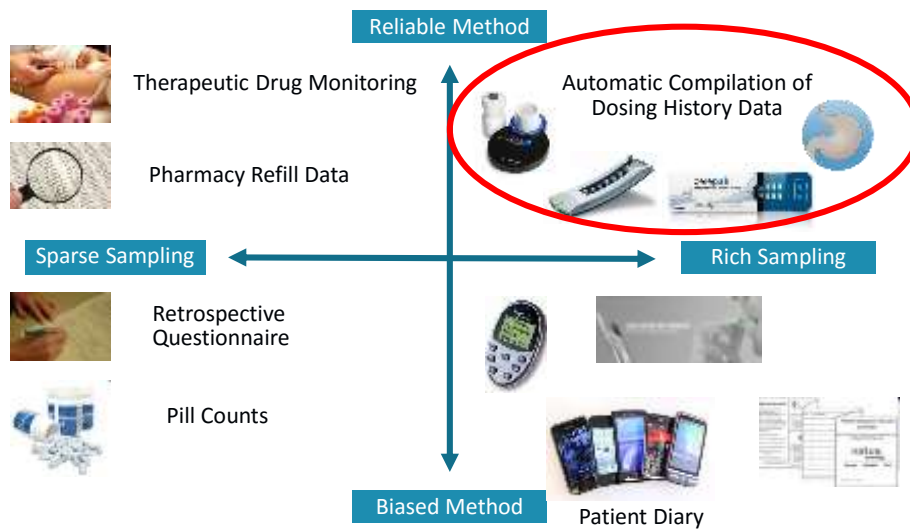
# Some questions to be considered

1. Which aspect of medication adherence do you want to assess?
2. In which context do you want to assess adherence?
   - Routine clinical care
   - Trial setting: Phase 1 ➔ 4 – 5
   - Cohort studies / Registries
3. What is the purpose of the adherence assessment?
   - Observational
   - Intervention     *... or a combination?*
4. What type of data is most suitable?
   - Objective or subjective data
   - Rich or sparse data
5. Which tools does the patient want to use?
6. Which resources do you have available?

# Overview of presentation

| | |
|---|---|
| **1** | • What is medication (non-)adherence? |
| **2** | • Criteria to choose (e-)tools for medication adherence measurement |
| **3** | • Which modern methods are available to monitor medication adherence? |

KU LEUVEN

# Adherence measurement methods



Reliable Method

Therapeutic Drug Monitoring

Automatic Compilation of Dosing History Data

Pharmacy Refill Data

Sparse Sampling ← → Rich Sampling

Retrospective Questionnaire

Pill Counts

Biased Method

Patient Diary

Vrijens. J Antimicr Chemoth. 2005;55:616-627

KU LEUVEN

# Electronic Monitoring (EM)

## Integrating measurement and immediate analysis (& Feedback)

### Medication Event Monitoring System

### Aardex Adherence Platform

MEMS® Cap

Electronic Dosepak

Helping Hand®

Cerepak®

Aardex Modeling and Simulation Center

medAmigo

medAmigo Customer Interface

**Usability/Feasibility issues**
- Technical failure
- Accuracy (measurement error)?
- Usability problems
- Ingestion is not proven
- Often only 1 drug to monitor

**Feedback: Option for behavioral intervention!!!!**

KU LEUVEN

Demonceau. Drugs. 2013;73:545-562; Denhaerynck. BMC Med Res Meth. 2008;8(5):1-11;
Courtesy of B. Vrijens of MedWestVaeco & Univ. of Liege; De Bleser. Sensors. 2010;10:1535-1552

---

Frontiers in PHARMACOLOGY

ORIGINAL RESEARCH ARTICLE
published: 13 March 2013
doi: 10.3389/fphar.2013.00028

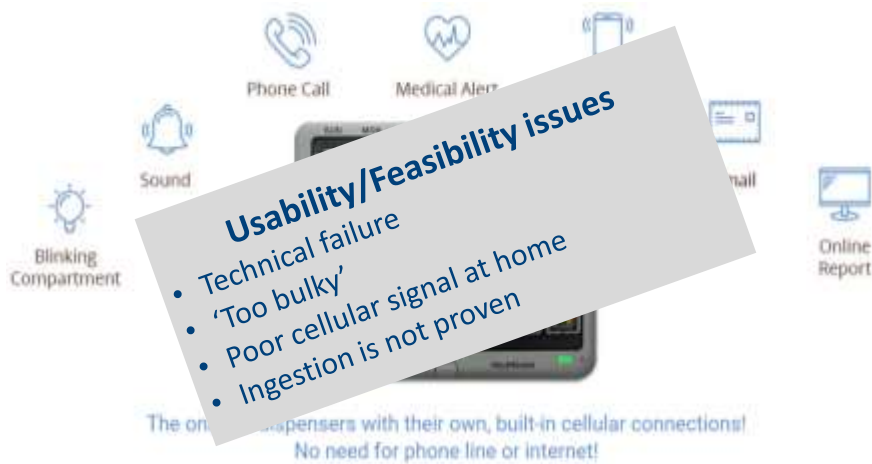## Polymedication Electronic Monitoring System (POEMS) – a new technology for measuring adherence

**Usability/Feasibility issues**
- Resource intense
- Ingestion is not proven

Arnet. Front in Pharmac. 2013;4(26):1-6

KU LEUVEN

# Medminder (multiple dosing system)



Phone Call  Medical Alert  Sound  Blinking Compartment  Online Report

**Usability/Feasibility issues**
- Technical failure
- 'Too bulky'
- Poor cellular signal at home
- Ingestion is not proven

The on... ...spensers with their own, built-in cellular connections!
No need for phone line or internet!

**KU LEUVEN**

Foster. BMC Nephrol. 2014;15:139; www.medminder.com
McGillicuddy. JMIR Res Protoc. 2013;2(2):e32

# Proteus Raisin Technology
## towards a ... ...standard?



Proteus

**Usability/Feasibility issues (n = 20)**
- Gastrointestinal symptoms (n = 2)
- Inadequate mobile telephone service (n = 4)
- Acceptance??
- Skin intolerance (n = 7)

Eisenberger. Transplantation 2013;96(3):245 - 250

# Adherence **measurement** methods

Reliable Method

Therapeutic Drug Monitoring

Automatic Compilation of
Dosing History Data

Pharmacy Refill Data

Sparse Sampling

Rich Sampling

Retrospective
Questionnaire

Pill Counts

Biased Method

Patient Diary

**KU LEUVEN**

Vrijens. J Antimicr Chemoth. 2005;55:616-627
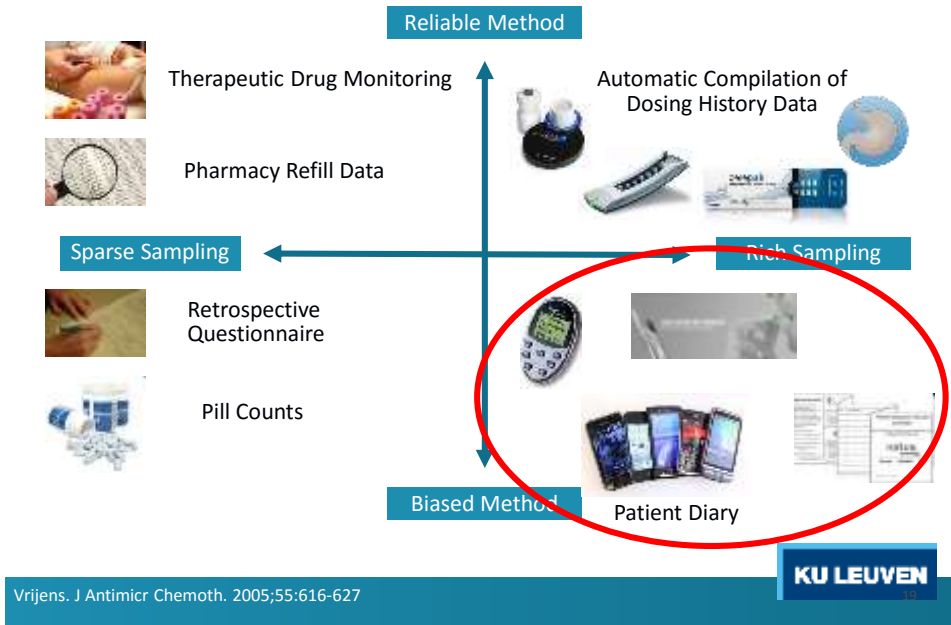
# **iPhones** with capsule photo application

A Simple, Novel Method for Assessing
Medication Adherence

Capsule Photographs Taken With C        phones

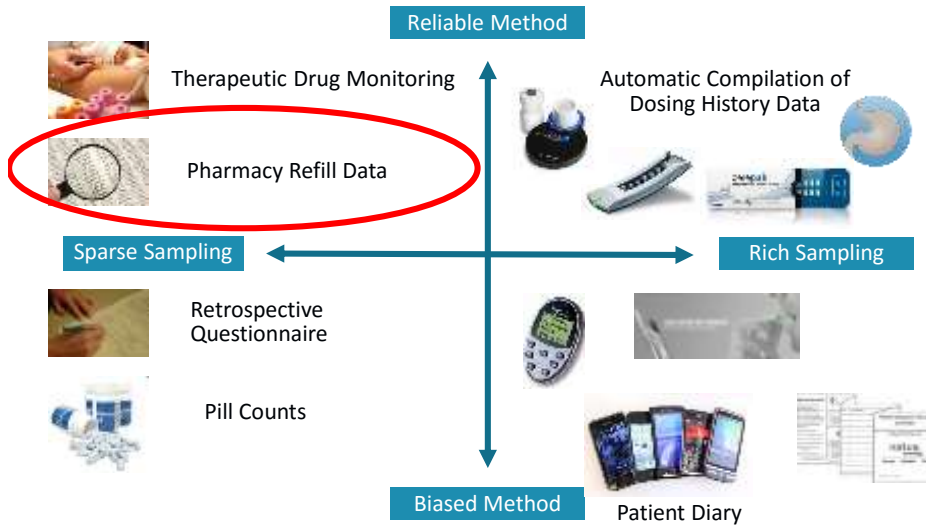**Usability/Feasibility issues**
- Access to smartphone?
- High patient burden?
- True benefit over diary?

First pilot work to test reliability and accuracy in small samples

**KU LEUVEN**

Galloway. J Addict Med. 2011;5:170-174; Dayer. J Am Pharm Assoc. 2003;53(2):172-181
Pal. Drug and Alcoh Depend. 2015; 146,e60

## Adherence **measurement** methods



Reliable Method

Therapeutic Drug Monitoring

Automatic Compilation of Dosing History Data

Pharmacy Refill Data

Sparse Sampling → Rich Sampling

Retrospective Questionnaire

Pill Counts

Biased Method

Patient Diary

Vrijens. J Antimicr Chemoth. 2005;55:616-627

**KU LEUVEN**

---

## Pharmacy **Refill** Data

- Did the patient visit the pharmacy to collect his medication o...

- Gives objecti... **overall** adhere... patient discont...

*Usability/Feasibility issues*
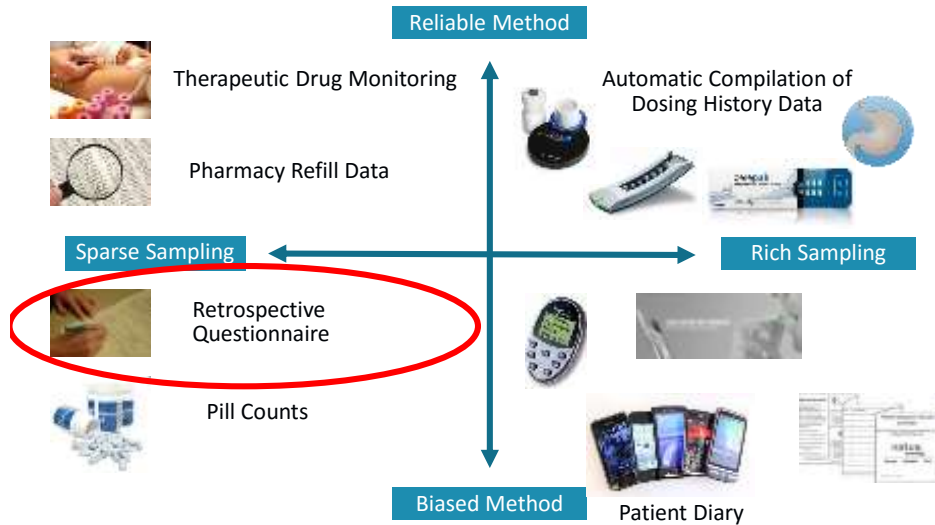- Requires a closed pharmacy system
- Collecting medication ≠ ingestion

→ Patient visit can be ideal situation for follow-up conversation (and adherence intervention)
→ Pharmacist as adherence manager!?

**Importance of open and non-judgemental communication!**

Osterberg. New Eng J Med 2005;353:487-497

**KU LEUVEN**

# Adherence **measurement** methods



Reliable Method

Therapeutic Drug Monitoring

Automatic Compilation of
Dosing History Data

Pharmacy Refill Data

Sparse Sampling

Rich Sampling

Retrospective
Questionnaire

Pill Counts

Biased Method

Patient Diary

**KU LEUVEN**

Vrijens. J Antimicr Chemoth. 2005;55:616-627

# What are good self-report **instruments?**

***Criteria to be taken into consideration:***

✓ Easy to complete

✓ Easy to score and interpret

✓ Showing good reliability and validity



   1) Measuring **specific components** of medication adherence

   2) Able to **detect minor deviations** from the prescribed regimen

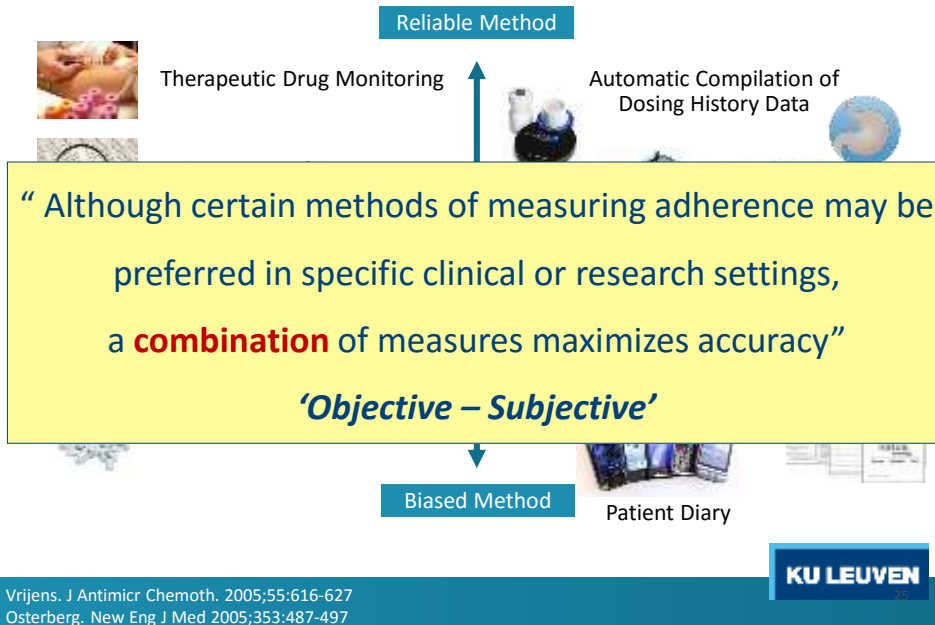   3) **Sensitive to change** (e.g. over time; after intervention)

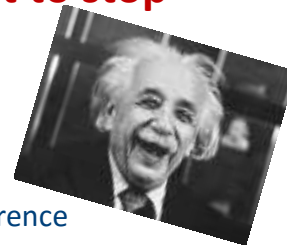**Interview is preferred over patient self-report**

**KU LEUVEN**

Dobbels. Transplantation. 2010;90:205-219; Nguyen. Br J Clin Pharmacol. 2013;77(3):427-445

# Adherence **measurement** methods

Reliable Method

Therapeutic Drug Monitoring

Automatic Compilation of Dosing History Data

" Although certain methods of measuring adherence may be

preferred in specific clinical or research settings,

a **combination** of measures maximizes accuracy"

*'Objective – Subjective'*

Biased Method

Patient Diary

**KU LEUVEN**

Vrijens. J Antimicr Chemoth. 2005;55:616-627
Osterberg. New Eng J Med 2005;353:487-497

# The important thing is **not to stop questioning...**

1. Modern tools are able to reveal non-adherence in all patients: True - **False**

2. Skipping medication doses is a more prevalent problem than patients stopping the medication regimen completely: True - **False**

3. Adherence measurement should become part of standard practice of all pharmacists: **True** - False

**KU LEUVEN**

# Take home messages!

- Monitoring medication adherence is crucial in chronically ill patients

- The choice of measurement method should depend on context, purpose, type of data, resources **AND** user perspective

- Many (electronic) measurement methods are available, yet need to be further tested

- Communication with patients should always be open and non-judgemental

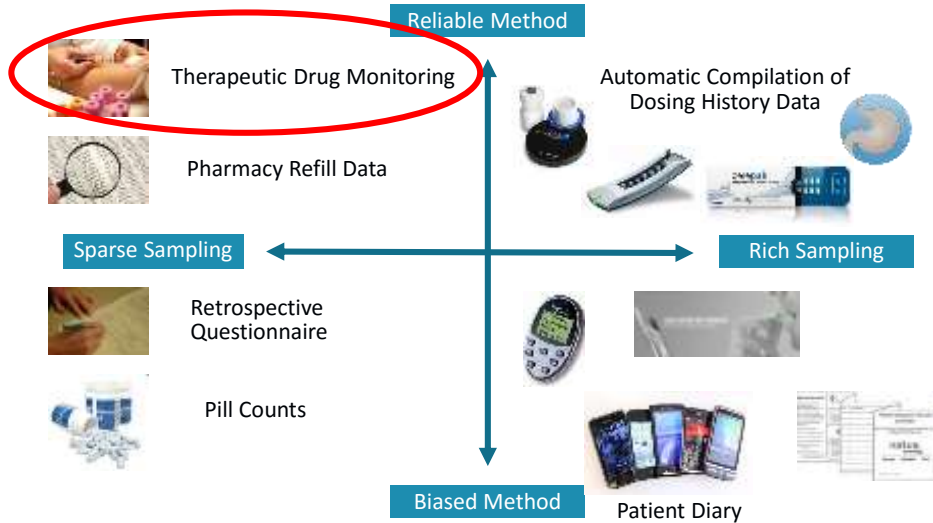- To get a comprehensive view on medication adherence, a combination of methods is recommended

jasper.vanhoof@med.kuleuven.be

**KU LEUVEN**

# Adherence **measurement** methods



- Reliable Method
- Therapeutic Drug Monitoring
- Automatic Compilation of Dosing History Data
- Pharmacy Refill Data
- Sparse Sampling
- Rich Sampling
- Retrospective Questionnaire
- Pill Counts
- Biased Method
- Patient Diary

**KU LEUVEN**

Vrijens. J Antimicr Chemoth. 2005;55:616-627

# Home **fingerprick** sampling



**Usability/Feasibility issues**
- Suboptimal sample collection techniques?
- Delays in sample delivery?
- Extreme conditions during shipment?
- Send data electronically?

- Mini...ly invasive
  ...e
  ...tween
  ...renous
  ...clinically
  ...mits
  ...erence assessment?

**KU LEUVEN**

Yonan. Clin Transplant. 2006;20(2):221-225; Hooper. Nat Clin Pract Nephr. 2009;5:E1;
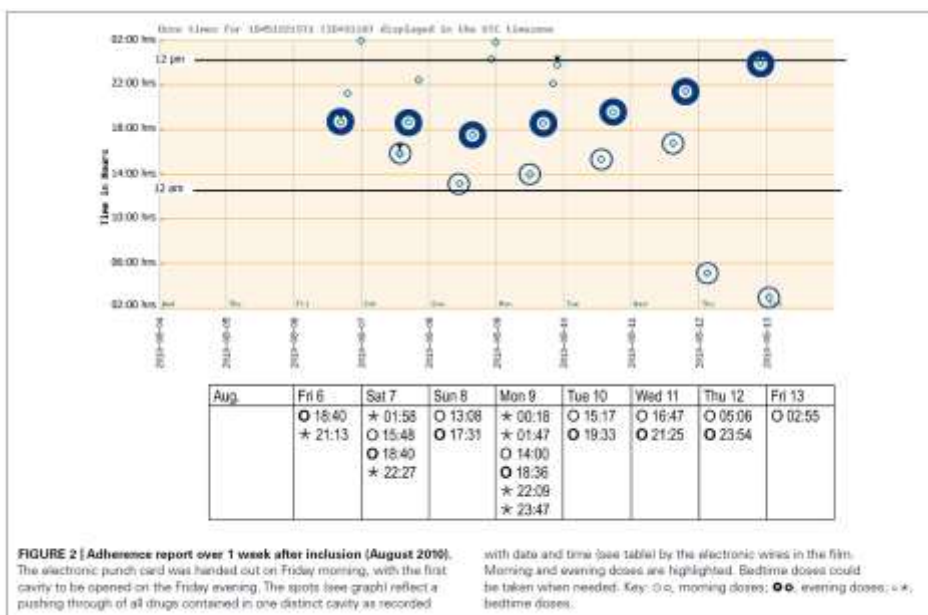Dickerson. Pediatr Transplant. 2015;19:101-106; Wilhelm. Clin Pharmacokinet. 2014;53(11):961-973

# Mean adherence across diseases

| Illness | Mean (%) | Random effects 95% CI |
|---|---|---|
| HIV | 88.3 | (78.9; 95.2) |
| Arthritis | 81.2 | (71.9; 89.0) |
| Cancer | 79.1 | (75.9; 84.2) |
| Cardiovascular diseases | 76.6 | (73.4; 79.8) |
| End-stage kidney disease | 70.0 | (56.8; 81.6) |
| Lung disease | 68.8 | (61.1; 76.2) |
| Diabetes | 67.5 | (58.5; 75.8) |

**Mean adherence to medication across 17 illnesses: 79.4%**

**KU LEUVEN**

DiMatteo. Med Care. 2004;42(3):200-209



FIGURE 2 | Adherence report over 1 week after inclusion (August 2010). The electronic punch card was handed out on Friday morning, with the first cavity to be opened on the Friday evening. The spots (see graph) reflect a pushing through of all drugs contained in one distinct cavity as recorded with date and time (see table) by the electronic wires in the film. Morning and evening doses are highlighted. Bedtime doses could be taken when needed. Key: ○ ○, morning doses; ● ●, evening doses; ★ ★, bedtime doses.

**KU LEUVEN**

Arnet. Front in Pharmac. 2013;4(26):1-6

## Packing interventions to increase medication adherence: systematic review

- 52 Reports (N=22 858)

- Selection criteria

  - Pill-boxes or blister packaging interventions

  - Primary study characteristics reliably coded

  - Outcomes reliably coded

- **Results**

**71% adherent in treatment- 63% adherent among control grou**

**Interventions most effective with blister packs and when were delivered in pharmacies. Intervention less effective with elder and those with cognitive impairment.**

**KU LEUVEN**

Conn et al. Current Medical Research & Opinion 2014; 31: 145-160.

---

## Segmental **hair analysis** of hair samples

### Analysis of Cyclosporin A in Hair Samples From Liver Transplanted Patients

*Alexander Müller, Dr. rer. nat.,\* Hilke Jungen,\* Stefanie Iwersen-Bergmann, Dr. rer. nat.,\* Martina Sterneck, Prof. Dr. med.,† and Hilke Andresen-Streichert, Dr. rer. nat.\**



- N = 15 liver transplant patients
- CsA can be detected in patients' hair samples.
- Relation of CsA trough blood concentrations and hair concentrations.
- No correlation between CsA hair concentrations and CsA doses
- Hair analysis might be useful for the long-term follow-up of liver transplant patients to detect substantial nonadherence

Müller. Ther Drug Monit. 2013;0:1-9

**KU LEUVEN**

# **Definition** of adherence

**Adherence =**

"The extent to which the person's behavior (taking medications, following a recommended diet and/or executing lifestyle changes) corresponds with the **agreed** recommendations from a health care provider"[1]

**Medication nonadherence =**

"Deviation from the prescribed medication regimen sufficient to influence adversely the regimen's intended effect"[2]

**KU LEUVEN**

**1.** Sabate. World Health Organization, 2003; **2.** Fine. Am J Transplant. 2009;9:35-41

## Intentional vs non-intentional non-adherence

- **Intentional non-adherence:**
  Refers to patients consciously choosing not to skip or alter dosages or stop taking the medication overall driven often by inadequate health beliefs such as conviction that drugs are toxic or beliefs that medications are not effective.

- **Un-intentional non-adherence:**
  Refers to situations where non-adherence it is not deliberate and is mostly related to forgetfulness

Clifford et al. J Psychosom Res 2008; 64: 41–46
Wroe A. J Behav Med 2001; 25(4): 355-372
Griva et al. Ann. Behv. Med. 2012 Aug;44(1):85-93

**KU LEUVEN**

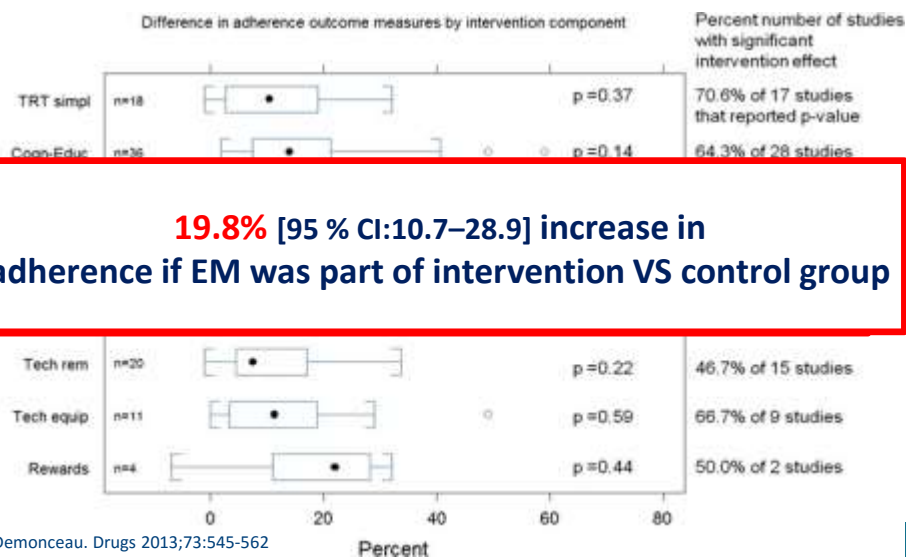# Automatic Compilation of Dosing History Data (Electronic Monitoring)
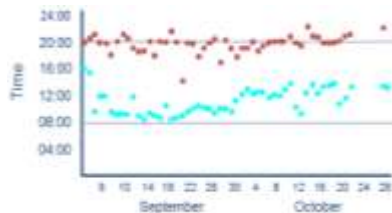


- "Gold Standard"
- Measures taking and timing of intake
- Assess adherence continuously
- Superior reliablity and validity compared to other methods

**KU LEUVEN**

Meadwestvaco.com

# Meta analysis: EM Adherence Studies

**79 Studies testing 87 Interventions (N = 5237 patients)**



**19.8%** [95 % CI:10.7–28.9] **increase in adherence if EM was part of intervention VS control group**

Demonceau. Drugs 2013;73:545-562

More on the electronic detection of package entry

| | MEMS cap | Helping Hand | Dosepak Reusable electronic | Cerepak |
|---|---|---|---|---|
| Device |  |  |  |  |
| Recorded events | Package monitors and tracks the open/close of the drug container | Package monitors and tracks the removal of the blister from Helping Hand | Package monitors and tracks the open/close of the inner card fold over panel | Package monitors and tracks the removal of pill from the blister |
| Logistics Production | Manufacturing, distribution, inventory remains exact same<br><br>Standard HDPE bottles | Manufacturing, distribution, inventory remains exact same<br><br>Initiation cost to adapt the device to the blister | Manufacturing, distribution, inventory remains exact same<br><br>Electronics are integrated with package downstream of manufacturing | Electronics and traces are integrated during manufacturing<br><br>Drastic Increase in manufacturing complexity and costs |
| Logistics Delivery and use | Caps and packaging are shipped separately<br><br>Typically: One cap is used during the monitored period.<br><br>Specialty Pharmacy, Clinical Site staff, patient instructed to screw the MEMS cap on the drug container | Helping Hands and packaging are shipped separately<br><br>Typically : One Helping Hand is used during the monitored period.<br><br>Specialty Pharmacy, Clinical Site staff, patient instructed to slip the blister in the Helping Hand and to replace it when the blister is empty | Electronics and Packaging are shipped separately<br><br>Typically : One reusable electronic is used during the monitored period.<br><br>Staff attaches Electronic Module to Dosepak<br>Staff instructs patients on how to detach electronics from "old" Dosepak after last dose taken and reattach it to "new" Dosepak | Electronically enabled packages are shipped<br><br>Several electronically enabled blister are used during the monitored period.<br><br>Staff instructs patients to keep the blisters after their use<br><br>Need to merge data from several devices |
| Cost | + | + | ++ | ++++ |
| Remarks | | | | Increase in cost for little added value.<br>Adapted to complex regimens (e.g. Hep C) or titration in clinical trial |

## Proteus Raisin System for Adherence Monitoring

- PRS is a novel technology for monitoring treatment adherence in transplant patients.

   o It uses a tiny ingestible micro-sensor (IEM) of 1x1x 0.45 mm that can be combined with a drug.

   o The IEM consists of an integrated circuit coated with thin layers of Cu and Mg forming a biogalvanic battery in presence of water.

   o After ingestion the IEM becomes activated for a few minutes once in contact with gastric electrolytes and communicates within the body fluids to a battery-powered, unmedicated adhesive skin patch sensor (process similar to EKG)
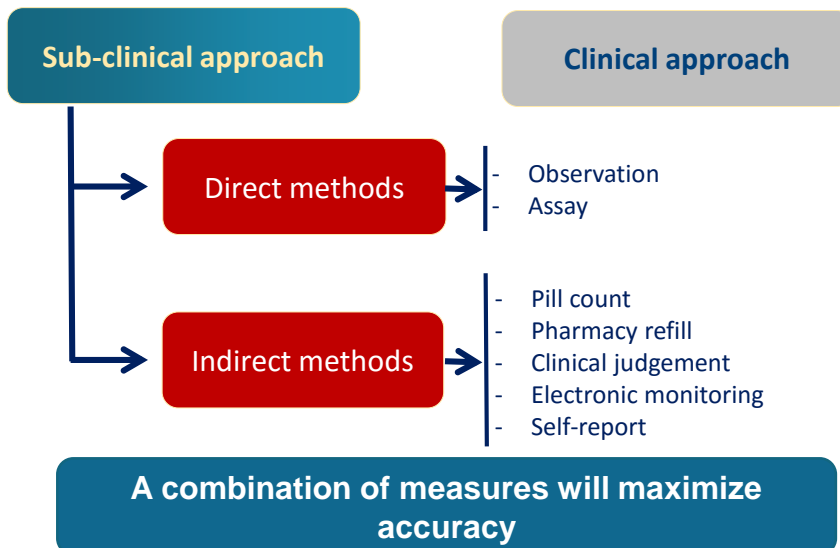
# How to "catch" non-adherent patients?



**"What gets measured, gets managed"**
**(Peter Drucker)**

# Starting point: Measurement of non-adherence (medication as example)

**Sub-clinical approach**   **Clinical approach**

**Direct methods**
- Observation
- Assay

**Indirect methods**
- Pill count
- Pharmacy refill
- Clinical judgement
- Electronic monitoring
- Self-report

**A combination of measures will maximize accuracy**

Osterberg. New Eng J Med 2005;353:487-497

# **Direct** methods of measuring

| Test | Advantages | Disadvantages |
|---|---|---|
| Directly observed therapy | Most accurate | - Patient can discard pills<br>- Impractical for routine use |
| Level of medicine or metabolite in blood | Objective | - Variations in metabolism<br>- "White coat" adherence<br>- Depending on half-life of drug and drug-drug interactions<br>- No info on timing of intake<br>- Expensive |
| Biological marker in blood | Objective | - Expensive |

**KU LEUVEN**

# **Indirect** methods of measuring

| Test | Advantages | Disadvantages |
|---|---|---|
| Pill count | Easy to perform | - Pill dumping |
| Prescription refill | Easy to obtain | - Not equivalent of ingestion<br>- Closed pharmacy system required |
| Clinical judgement | Easy to perform | - Covert behavior not easy to detect |
| Electronic monitoring | Precise, continuous<br>Tracks dynamics of taking medication (taking, timing, dosing) | - Expensive<br>- Ingestion not proven |
| Self-report | Simple<br>Inexpensive | - Overestimates adherence<br>- Recall bias |

**KU LEUVEN**

# What are good self-report instruments?
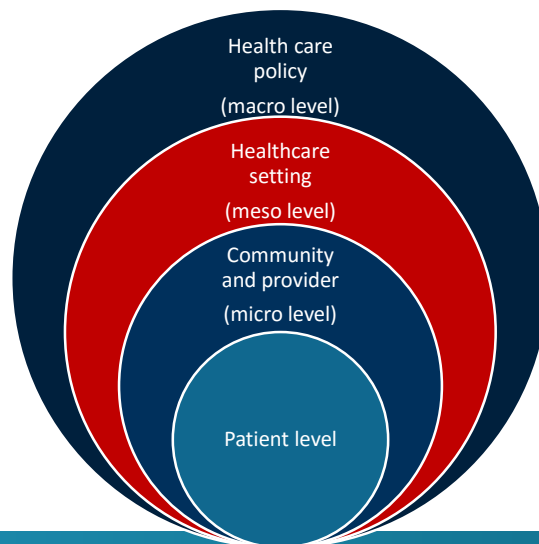
*Systematic review on questionnaires that are:*

✓ Easy to complete

✓ Easy to score and interpret

✓ Showing good reliability and validity

1) Measuring both **taking and regularity** of medication intake

2) Able to **detect minor deviations** from the prescribed regimen
   taking less than 95% of the tablets
   deviation of > 2 hours from the prescribed timing

3) **Sensitive to change** (e.g. over time; after intervention)

- Basel Assessment of Adherence Scale for Immunosuppressants (BAASIS)
- Transplant Adherence Questionnaire (TAQ)

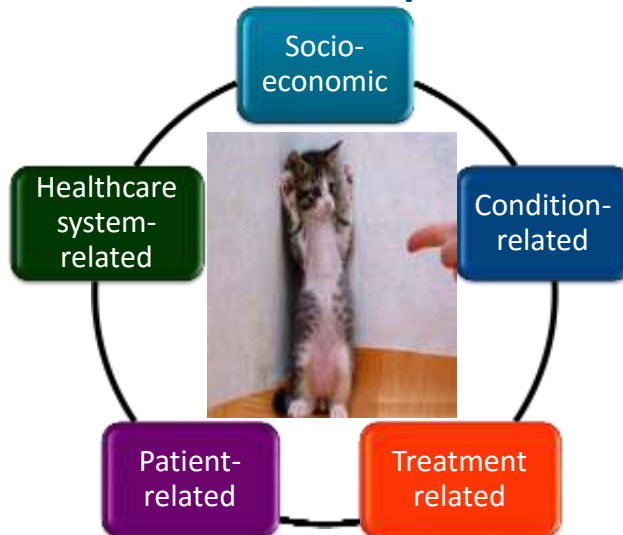**Available for free after registering at transplant360.com**

Dobbels. Transplantation. 2010;90:205-219

# Factors hindering a healthy lifestyle: Beyond patient factors

Health care policy (macro level)

Healthcare setting (meso level)

Community and provider (micro level)

Patient level

KU LEUVEN

## Understanding the drivers of non-adherence: a multifaceted problem



Socio-economic

Condition-related

Healthcare system-related

Patient-related

Treatment related

Sabate. WHO. 2003: http://whqlibdoc.who.int/publications/2003/9241545992.pdf

**KU LEUVEN**

## Examples of risk factors

| Socio-economic | Condition related |
|---|---|
| ...io-economic status | Depression |
| ...illiteracy | Cognitive problems |
| | Higher co-morbidity |
| Poor | Substance abuse |

| Treatment related | ...ient related |
|---|---|
| Complex, lifelong treatment | Forg... |
| Side effects | Health belie... |
| Number of daily doses | Busy lifestyle |
| Frequent changes in medications | |

NEED FOR A COMPREHENSIVE BUT PRAGMATIC APPROACH

**KU LEUVEN**

# Take home messages!

- Actively involving patients and focusing on skills development, rather than on passively educating them, is a promising pathway

- Self-management support should be needs-driven and contain a 'system approach', involving patients, partners and an interdisciplinary team

- Still a lot of room for improvement with regard to Tx self-management intervention research

- Self-management support training should become part of the core curriculum of all healthcare professionals!

Table 1  Comparison of different electronic monitoring methods

| | Electronic detection of package entry | Smart ingestible sensor (pill) | Photographic documentation of drug intake | Electro |
|---|---|---|---|---|
| Requires drug reformulation | No | Yes; need to reestablish acceptable stability parameters | No | No |
| Level of patient involvement | Low; requires the patient to take medications out of the package | High; requires skin patch maintenance | High; requires the patient to take and transmit a picture of each drug intake | High; requi to timely re |
| Safety-related issues | No | Yes; skin reactions to transdermal patch[36-38], unresolved long-term safety | No | No |
| Applicable to a wide variety of formulations | Yes; oral medications, injectables, pumps, topical formulations, and so on | No; limited to solid oral medications | Yes; may become challenging if administration requires two hands | Yes; oral me injectables, formulation |
| Reliability | High; susceptible to false-positive detection (<3%) | High; susceptible to false-negative detection (3–5%) | Medium; makes patient's routine more complex | Medium; m routine mo |
| Patient intrusiveness | Low | High | High | High |
| Patient acceptability | High | Low[37] to medium[36] | Medium | Medium |

**?**

Evaluation of an electronic diary for improvement
of adherence to interferon beta-1b in patients
with multiple sclerosis: design and baseline
results of an observational cohort study

evaluate the effect of using electronic and paper diaries on treatment adherence to interferon beta-1b in patients with a first clinical isolated syndrome (CIS) or relapsing-remitting multiple sclerosis (RRMS).
**More women chose a paper diary**

Zettl et al. BMC Neurology 2013, 13:117

Figure 2 Picture of the digital diary.

**KU LEUVEN**

GNURF    AHAJOKES.COM

Is prototype design and testing really necessary?