New tools to detect medication non-adherence

The hospital pharmacist and the e-health revolution

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I have no disclosures related to this presentation
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

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**Increasing prevalence of chronic diseases**

[Graph showing projected growth in population with chronic conditions, 2013-25]

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

The hidden healthcare system

1-20%  3°  2°  1°  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)

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?
Medication Adherence: The process by which patients take their medications as prescribed

1. Initiation
   - Patient does not initiate treatment
     Binary (Yes/No)

2. Implementation
   - Patient delays, omits, or takes extra doses
     Dosing History

3. Persistence
   - Patient discontinues treatment
     Time to event

Non-persistence: more common than implementation problems!

16,907 participants from 95 clinical studies

4% non-initiation!

20% permanent discontinuation

+12% incorrect dosing


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?

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?

Adherence measurement methods

- Reliable Method
  - Therapeutic Drug Monitoring
  - Pharmacy Refill Data

- Biased Method
  - Retrospective Questionnaire
  - Pill Counts

- Sparse Sampling

- Rich Sampling
  - Automatic Compilation of Dosing History Data
  - Patient Diary

Electronic Monitoring (EM)

Integrating measurement and immediate analysis (& Feedback)

Medication Event Monitoring System
Aardex Adherence Platform

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!!!!


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

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

Medminder (multiple dosing system)

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

Proteus Raisin Technology towards a new gold standard?

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**

- **Sparse Sampling**
  - Therapeutic Drug Monitoring
  - Pharmacy Refill Data
  - Retrospective Questionnaire
  - Pill Counts

- **Rich Sampling**
  - Automatic Compilation of Dosing History Data

- **Biased Method**
  - Patient Diary


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**iPhones with capsule photo application**

A Simple, Novel Method for Assessing Medication Adherence

Capsule Photographs Taken With Smartphones

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

First pilot work to test reliability and accuracy in small samples

Pal. Drug and Alcoh Depend. 2015; 146,e60
**Adherence measurement methods**

- **Sparse Sampling**: Therapeutic Drug Monitoring, Pharmacy Refill Data
- **Rich Sampling**: Automatic Compilation of Dosing History Data, Patient Diary

**Biased Method**: Retrospective Questionnaire, Pill Counts

**Reliable Method**: Pharmacy Refill Data

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**Pharmacy Refill Data**

- Did the patient visit the pharmacy to collect his medication over time?
- Gives objective information of overall adherence and patient discontinuation.

**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!**

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**Adherence measurement methods**

**Sparse Sampling**
- Therapeutic Drug Monitoring
- Pharmacy Refill Data
- Retrospective Questionnaire
- Pill Counts

**Rich Sampling**
- Automatic Compilation of Dosing History Data
- Patient Diary

**Reliable Method**
- Biased Method

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**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)

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

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**
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
**Adherence measurement methods**

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

**Reliable Method**

**Biased Method**


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**Home fingerprick sampling**

- Minimally invasive
- Small volume
- Difference between capillary and venous blood is within clinically acceptable limits

**Usability/Feasibility issues**

- Suboptimal sample collection techniques?
- Delays in sample delivery?
- Extreme conditions during shipment?
- Send data electronically?

Mean adherence across diseases

<table>
<thead>
<tr>
<th>Illness</th>
<th>Mean (%)</th>
<th>Random effects 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV</td>
<td>88.3</td>
<td>(78.9; 95.2)</td>
</tr>
<tr>
<td>Arthritis</td>
<td>81.2</td>
<td>(71.9; 89.0)</td>
</tr>
<tr>
<td>Cancer</td>
<td>79.1</td>
<td>(73.9; 84.2)</td>
</tr>
<tr>
<td>Cardiovascular diseases</td>
<td>76.6</td>
<td>(73.4; 80.8)</td>
</tr>
<tr>
<td>End-stage kidney disease</td>
<td>70.0</td>
<td>(56.8; 81.6)</td>
</tr>
<tr>
<td>Lung disease</td>
<td>68.8</td>
<td>(61.2; 76.2)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>67.5</td>
<td>(58.5; 75.8)</td>
</tr>
</tbody>
</table>

Mean adherence to medication across 17 illnesses: 79.4%


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 group

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


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 Jwersen-Bergmann, Dr. rer. nat.,*
Martina Steinbeck, Prof. Dr. med.,† and Hilke Andreesen-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
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”

Medication nonadherence =
“Deviation from the prescribed medication regimen sufficient to influence adversely the regimen’s intended effect”

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


**Automatic Compilation of Dosing History Data (Electronic Monitoring)**

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

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**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
### Proteus Raisin System for Adherence Monitoring

- **PRS** is a novel technology for monitoring treatment adherence in transplant patients.
  - It uses a tiny ingestible micro-sensor (IEM) of 1x1x 0.45 mm that can be combined with a drug.
  - The IEM consists of an integrated circuit coated with thin layers of Cu and Mg forming a biogalvanic battery in presence of water.
  - 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)**

<table>
<thead>
<tr>
<th>Sub-clinical approach</th>
<th>Clinical approach</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direct methods</td>
<td>Observation</td>
</tr>
<tr>
<td></td>
<td>Assay</td>
</tr>
<tr>
<td>Indirect methods</td>
<td>- Pill count</td>
</tr>
<tr>
<td></td>
<td>- Pharmacy refill</td>
</tr>
<tr>
<td></td>
<td>- Clinical judgement</td>
</tr>
<tr>
<td></td>
<td>- Electronic monitoring</td>
</tr>
<tr>
<td></td>
<td>- Self-report</td>
</tr>
</tbody>
</table>

A combination of measures will maximize accuracy

# Direct methods of measuring

<table>
<thead>
<tr>
<th>Test</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Directly observed therapy</td>
<td>Most accurate</td>
<td>- Patient can discard pills</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Impractical for routine use</td>
</tr>
<tr>
<td>Level of medicine or metabolite in blood</td>
<td>Objective</td>
<td>- Variations in metabolism</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- “White coat” adherence</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Depending on half-life of drug and drug-drug interactions</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- No info on timing of intake</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Expensive</td>
</tr>
<tr>
<td>Biological marker in blood</td>
<td>Objective</td>
<td>- Expensive</td>
</tr>
</tbody>
</table>

# Indirect methods of measuring

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

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Factors **hindering** a healthy lifestyle: Beyond patient factors

Health care policy
  (macro level)

Healthcare setting
  (meso level)

Community and provider
  (micro level)

Patient level
Understanding the **drivers of non-adherence**: a multifaceted problem

Examples of **risk factors**

<table>
<thead>
<tr>
<th>Socio-economic</th>
<th>Condition related</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low socio-economic status</td>
<td>Depression</td>
</tr>
<tr>
<td>Low literacy</td>
<td>Cognitive problems</td>
</tr>
<tr>
<td>Poor</td>
<td>Higher co-morbidity</td>
</tr>
<tr>
<td></td>
<td>Substance abuse</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment related</th>
<th>Patient related</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complex, lifelong treatment</td>
<td>Poor health beliefs</td>
</tr>
<tr>
<td>Side effects</td>
<td>Busy lifestyle</td>
</tr>
<tr>
<td>Number of daily doses</td>
<td></td>
</tr>
</tbody>
</table>
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!
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