Electronic Measurement of Medication Adherence

Drug Research Academy
Copenhagen, Denmark,
29-05-08

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Katholieke Universiteit Leuven, Belgium
1. Measurement of adherence with drug regimens

2. Testing assumptions of Electronic Monitoring
Transplant adherence research
Research & methodological priorities

Measurement:

- Assessment methods should be highly standardized and should be derived from *clear explicit definitions* of the domains to be measured

- To obtain a firmer grip on the best measurement methodologies, it will be necessary to compile and assess the value, appropriateness, reliability and validity of a wide range of possible measurement strategies, both objective and subjective

*DiMatteo et al. Medical Care* 2006; 44; 297-299
*Cuppes et al. Journal Heart Lung Transplant*, 2006; 25:716-25
*De Geest et al., Journal Cardiovascular Nursing* 2005; 55: S85-S95.
*Balkrishnan et al. Clinical Therapeutics* 2007; 29: 1180-1183
Transplant adherence research
Research & methodological priorities

Measurement (Ctn.):

- Multi method approach
  → electronic monitoring, assay, pharmacy refills, self- & collateral report
  → novel assessment strategies, e.g. internet based data collection

- Standardization of measurement and operational definitions
  → Calculate rates adjusting for follow up duration cases/100 persons/y.
  - Need to develop clinically meaningful definition of non-adherence
  - Which patterns/level of adherence are associated with highest risk?
  - How to combine information from different measurement methods?

Osterberg et al., NEJM 2005; 353: 487-97
Cuppes et al. Journal Heart Lung Transplant, 2006; 25:716-25
Balkrishnan et al. Clinical Therapeutics 2007; 29: 1180-1183
Measurement of adherence

A. Direct methods
   - observation
   - assay

B. Indirect methods
   - pill count
   - prescription refill
   - clinical judgment
   - self-report
   - electronic monitoring
Medication Event Monitoring System
MEMS® (Aardex, Zug, CH)
The Helping Hand™
(Medicom, Bang & Olufsen, Denmark)
Med-eMonitor™ System
InforMedix, Rockville, Md. (USA)
Electronic Adherence Packaging
Meadwestvaco Healthcare Packaging
SIMpill

For Pills

“Classic”

“Smart”

kpn

SIMpill

SIMpill Nederland
Advantages and disadvantages of EM

ADVANTAGES

- Insight in medication taking dynamics
- Superior sensitivity
Diagnostic values of single or combined adherence measures using Electronic Monitoring as gold standard in kidney Tx

**CAS 1:** self-reports and/or collateral-reports

**CAS 2:** self-reported and/or collateral-reported and/or non-therapeutic blood assay variability.

*Schafer-Keller et al., Am. J. of Transpl. 2008*
State-of-the-art measurement: triangulation

“Although certain methods of measuring adherence may be preferred in specific clinical or research settings, a combination of measures maximizes accuracy”

Advantages and disadvantages of EM

ADVANTAGES

- Insight in medication taking dynamics
- Superior sensitivity

DISADVANTAGES

- Cost
- Ingestion not proven
- Practical and confidentiality issues (HIV)
- Challenging in large trials for logistic reasons

TO BE TESTED: → Usability
                → Internal and external validity
How to analyze EM data?

**EM-parameters: period prevalence**

- **Taking adherence** = \( \frac{\# \text{ taken doses} \times 100}{\# \text{ prescribed doses}} \)

- **Dosing adherence** = \( \frac{\# \text{ days with correct dosing} \times 100}{\# \text{ days monitored}} \)

- **Timing adherence** = \( \frac{\# \text{ correct interdose intervals}^* \times 100}{\# \text{ openings}} \)

- **Drug holidays**: no medication intake for >24h or more depending on drug measured

* **correct interdose interval** = within +/- 25% of prescribed interval
How to analyze EM data?

Problems

Skewed distribution (J shaped) of the generally used period prevalence parameters

- J-shaped distribution, can not be transformed in normal distribution
- Loss of information as dosing sequence (daily) is lost
How to analyze EM data?

**Solution:** time series analysis

- Adherence = day with (1) or without (0) a missed dose or wrong time
- Logistic regression built on this dichotomous binary sequence
- Taking into account that data within patients are assumed to be correlated, but data from different patients are independent
  → random intercepts logistic regression analysis
- Transform the original EM data into an analyzable database
<table>
<thead>
<tr>
<th>date</th>
<th>hour</th>
<th>patient number</th>
<th>monitor</th>
<th>interval</th>
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<th>tim</th>
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</table>
1. Measurement of adherence with drug regimens

2. Testing assumptions of Electronic Monitoring
Electronic monitoring

• Electronic monitoring (EM) of medication intake behavior is in use for many years now

• Compared to the investment in the technological development of EM, little investment has been done in the methodological domain
Internal and external validity EM

Unbiased EM assessment requires fulfillment of internal and external validity assumptions:

1) EM equipment functions correctly
2) all EM-bottle openings correspond to the actual intake of the prescribed dose
3) EM does not influence a patient’s normal adherence behavior
4) EM does not bias the representativeness of the sample

Denhaerynck et al., BMC Medical Research Methodology 2008, 8:5
Assumptions

<table>
<thead>
<tr>
<th>Assumption</th>
<th>1. EM equipment functions correctly</th>
</tr>
</thead>
<tbody>
<tr>
<td>Processes violating this assumption?</td>
<td>Non-functioning EM system technology</td>
</tr>
<tr>
<td>Registration failures</td>
<td>2. All EM-bottle openings correspond to actual intake of the prescribed dose</td>
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<tr>
<td>Too many registrations</td>
<td>Correct intake of prescribed drugs from a non-EM source (e.g., after having removed the prescribed dose from the EM bottle)</td>
</tr>
<tr>
<td>1.a</td>
<td>Opening of the EM bottle without ingestion or with ingestion occurring at a later time</td>
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<td>2.a</td>
<td>Ingestion of a dose larger or smaller than dose prescribed</td>
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<tr>
<td>2.b</td>
<td>Interference with other adherence strategies (e.g., pill organizer)</td>
</tr>
<tr>
<td>2.c</td>
<td>Intervention effect of starting EM</td>
</tr>
<tr>
<td>2.d</td>
<td>3.b</td>
</tr>
<tr>
<td>3.b</td>
<td>3.c</td>
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<tr>
<td>3.d</td>
<td>4. Use of EM does not bias the sample representativeness</td>
</tr>
<tr>
<td>Refusal to participate</td>
<td>Loss of data</td>
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</tbody>
</table>

Denhaerynck et al., BMC Medical Research Methodology 2008, 8:5
Assumptions

1. EM equipment functions correctly
2. All EM-bottle openings correspond to actual intake of the prescribed dose
3. EM does not influence typical adherence behavior
4. Use of EM does not bias the sample representativeness

Processes violating this assumption?
- Non-functioning EM system technology
- Correct intake of drugs from a non-EM source (e.g., removed the prescribed dose from the EM bottle)
- Interference with other adherence strategies (e.g., pill organizer)
- Refusal to participate

Effect of the violation
- Too many registrations
- Registration failures
- Underestimation of non-adherence
- Overestimation of non-adherence

(Denhaerynck et al., paper submitted)
Assumptions

1. EM equipment functions correctly
2. All EM-bottle openings correspond to actual intake of the prescribed dose
3. EM does not influence typical adherence behavior
4. Use of EM does not bias the sample representativeness

Processes violating this assumption?
- Non-functioning EM system technology
- Interference with other adherence strategies (e.g., pill organizer)
- Intervention effect of starting EM
- Refusal to participate
- Drop-out
- Loss of data
- Registration failures

Effect of the violation
- Overestimation of non-adherence
- Underestimation of non-adherence

Denhaerynck et al., BMC Medical Research Methodology 2008, 8:5
**Assumptions**

1. EM equipment functions correctly
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**Processes violating this assumption?**
- Non-functioning EM system technology
- Interference with other adherence strategies (e.g., pill organizer)
- Intervention effect of starting EM
- Refusal to participate
- Drop-out data

**Effect of the violation**
- Overestimation of non-adherence
- Underestimation of non-adherence

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Denhaerynck et al., BMC Medical Research Methodology 2008, 8:5
Testing the assumptions

Assumption 1: Technology functions correctly
→ Prevalence of non-functioning systems & measurement error

Assumption 2: Correspondence registration-intake
→ - Prevalence of non-adherence to the EM-system
  - Prevalence of reported incongruencies between decanting and intake

Assumption 3: No EM-influence on usual behavior
→ Testing an increase of non-adherence after EM start

Assumption 4: Sample representativeness
→ Screening for differences between participants and refusers/drop-outs

Denhaerynck et al., BMC Medical Research Methodology 2008, 8:5
Debeler et al., work in progress, Katholieke Universiteit Leuven, Belgium
Deschamps et al., JAIDS 2006; 43: 247-249.
Assumption 1: Technology functions correctly

249 MEMS: 1 cap gradually lost its capacity to record bottle openings (=0.4%)
Assumption 2: Correspondence registration-intake (n=249)

Denhaerynck et al., BMC Medical Research Methodology 2008, 8:5
Measurement: data quality control

<table>
<thead>
<tr>
<th>Date/Heure</th>
<th>Description du problème</th>
<th>Pour quelle raison?</th>
<th>Qu’est-ce que vous avez fait?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exemple: 30.10.00 20.00 h</td>
<td>Je n’ai pas pris les médicaments</td>
<td>Je suis sortis pour dîner avec des amis</td>
<td>J’ai pris les médicaments à 23h seulement</td>
</tr>
</tbody>
</table>

- **Hour**: I went out for dinner with friends
- **Medication not taken**: I took the medication at 11 pm

*Denhaerynck et al., BMC Medical Research Methodology 2008, 8:5*
**Measurement**: data quality control

**Adherence to the EM system (BAAREM):**

**Self-reported EM bottle use**

- EM system always used as
- Instructed?
- Yes
- No
- Sometimes
- Never

**Yellow paper**

- Complete notes
- Some notes
- No notes

**Adherent**

- Adherent
- Minor NA

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*Denhaerynck et al., BMC Medical Research Methodology 2008, 8:5*
Assumption 2: Correspondence registration-intake (n=249)

- 62% of patients noted discrepancies on form between actual intake
  - decanting earlier than taking
  - taking medication from other supply
  - phantom openings

→ 2.4 adjustments on average per patient

- 57 (20%) patients fully or partly non-adherent to EM guidelines

Denhaerynck et al., BMC Medical Research Methodology 2008, 8:5
Assumption 2: Correspondence registration-intake (n=249)

- 9.2% of patients defined periods of non-adherence to EM guidelines leading to censored days
  - Including these data decreased the dosing adherence from 96.3% to 92.9%
  → overestimation of non-adherence

Denhaerynck et al., BMC Medical Research Methodology 2008, 8:5
Assumption 3: No EM-influence on usual behavior

- **Step 1:**
  - Preparing a database including adherence information for each prescribed intake moment

- **Step 2:**
  - Testing if there is a EM intervention effect; i.e. testing if non-adherence increases after starting EM

*Denhaerynck et al., BMC Medical Research Methodology 2008, 8:5*
Assumption 3: No EM-influence on usual behavior

Step 2:
The binary adherence data was used as response variable in a multiple random intercepts logistic regression analysis

- Including fixed effects
  - Time since EM start (exposure)
  - Bottle size
  - Researcher including the patients
  - Patient’s perception: intervention effect or not

- Including ‘patient’ as a random effect

Denhaerynck et al., BMC Medical Research Methodology 2008, 8:5
### Assumption 3: Results mixed models

<table>
<thead>
<tr>
<th>Outcome variable</th>
<th>Parameter</th>
<th>Estimate</th>
<th>Standard error</th>
<th>DF</th>
<th>t-value</th>
<th>p-value</th>
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</thead>
<tbody>
<tr>
<td>Omitted intakes</td>
<td>Random-intercepts variance</td>
<td>3.1497</td>
<td>0.5438</td>
<td>235</td>
<td>5.79</td>
<td>&lt;.0001</td>
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<td></td>
<td>Intercept</td>
<td>-4.9259</td>
<td>0.4626</td>
<td>235</td>
<td>-10.65</td>
<td>&lt;.0001</td>
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<td><strong>Exposure</strong></td>
<td><strong>0.0084</strong></td>
<td><strong>0.0019</strong></td>
<td><strong>235</strong></td>
<td><strong>4.48</strong></td>
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<td>Influence perception</td>
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<td>0.0004</td>
<td>235</td>
<td>-1.14</td>
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<td>Bottle size</td>
<td>0.1498</td>
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<td>235</td>
<td>0.43</td>
<td>0.6645</td>
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<td>Interviewer 1 vs. interviewer 4</td>
<td>0.2571</td>
<td>0.3766</td>
<td>235</td>
<td>0.68</td>
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<td>Interviewer 2 vs. interviewer 4</td>
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<td>Interviewer 3 vs. interviewer 4</td>
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<td>235</td>
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<td>Intake variability</td>
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<td>2.7994</td>
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<td>Intercept</td>
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<td><strong>Exposure</strong></td>
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<td><strong>0.0020</strong></td>
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<td><strong>5.49</strong></td>
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<td>Influence perception</td>
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<td>Interviewer 1 vs. interviewer 4</td>
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<td>0.3337</td>
<td>235</td>
<td>0.70</td>
<td>0.4844</td>
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<td>Interviewer 2 vs. interviewer 4</td>
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<td>0.1042</td>
<td>0.3704</td>
<td>235</td>
<td>0.28</td>
<td>0.7787</td>
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</tbody>
</table>

*Denhaerynck et al., BMC Medical Research Methodology 2008, 8:5*
Assumption 3: Results additive model

Smoothened nonlinear regression lines

Day of exposure to the EM bottle

Outcome measure

- Dose omission
- Intake variability
Assumption 3: Bias in view of non-adherence prevalences

- Dosing adherence using all 90 days: 96.7%
- Dosing adherence excluding the first 35 days: 96.3%
  - a slight underestimation of non-adherence
  - Could maybe be worse when
    - Non-adherence is higher
    - When monitoring less than 3 months

*Denhaerynck et al., BMC Medical Research Methodology 2008, 8:5*
Assumption 3: Additional analyses

Post hoc test: Stronger effect in patients acknowledging an intervention effect (p=0.003)
Use of Electronic Monitoring Induces a 40-Day Intervention Effect in HIV Patients

FIGURE 1. Intervention effect of EM in HIV patients with or without a self-reported intervention effect. Patients reporting an intervention effect attributable to EM use (dotted line) initially have a lower nonadherence level than patients without a self-reported intervention effect (solid line). Moreover, the rise in nonadherence is more pronounced in patients self-reporting an intervention effect.
**Assumption 4:** EM use does not bias sample representativeness

1. Screening for differences in non-EM measured adherence, demographic, and clinical variables
   - Between study refusers and participants
   - Between EM-part refusers and participants
   - Between non-adherers with the EM guidelines vs adherers

2. Adapting p-values for multiple testing using the q-value method

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*Denhaerynck et al., BMC Medical Research Methodology 2008, 8:5*
**Assumption 4:** EM use does not bias sample representativeness

<table>
<thead>
<tr>
<th>Groups</th>
<th>Subgroups</th>
<th>Variable</th>
<th>Probability</th>
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</thead>
<tbody>
<tr>
<td>Refusers</td>
<td>Refusers of the entire study (n=29) vs. participants (n=291)</td>
<td>Systolic blood pressure</td>
<td>0.028; 0.30</td>
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<td></td>
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<td>Gamma-gt</td>
<td>0.004; 0.30</td>
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<tr>
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<td></td>
<td>Graft type</td>
<td>0.032; 0.30</td>
</tr>
<tr>
<td></td>
<td>Refusers of the EM-part (n=65) vs. participants (n=291)</td>
<td>Self-employed</td>
<td>0.010; 0.30</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Use of pill-organiser</td>
<td>0.012; 0.30</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cholesterol</td>
<td>0.026; 0.30</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Years with transplant</td>
<td>0.021; 0.30</td>
</tr>
<tr>
<td>Drop-outs</td>
<td>Nonadherers with the EM guidelines (n=35) vs. adherers (n=249)</td>
<td>Age</td>
<td>0.025; 0.30</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Triglycerides</td>
<td>0.032; 0.30</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Charlson Comorbidity Index</td>
<td>0.034; 0.30</td>
</tr>
</tbody>
</table>

*Denhaerynck et al., BMC Medical Research Methodology 2008, 8:5*
**Assumption 4:** EM use does not bias sample representativeness

1. None of the tested variables was significant after multiple testing correction ($q=0.30$)
2. Alternative adherence measures far from significant even before the correction
   
   → no evidence exists that non-adherers with immunosuppressives have more refusal or dropout

*Denhaerynck et al., BMC Medical Research Methodology 2008, 8:5*
Internal and external validity EM

Unbiased EM assessment requires fulfillment of internal and external validity assumptions:

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Denhaerynck et al., BMC Medical Research Methodology 2008, 8:5
Assumptions should be tested in all future EM studies!!!!!
Announcing the 12th annual European Symposium on Patient Compliance and Persistence

ESPACOMP 2008
5 Sept 2008 - Basel - Switzerland

www.ESPACOMP.eu
www.nursing.unibas.ch

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