Observance thérapeutique et la place des nouveaux outils

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‘One year of loyalty to the pills. For what aim? Surviving the pills and the doctor!’

Blister collection of 1 year’s medication of a kidney transplant patient (>4000 pills)

Drug adherence and mortality: A meta-analysis across diseases

Drug adherence to a beneficial drug decreases mortality

<table>
<thead>
<tr>
<th>Study</th>
<th>Beneficial drug therapy</th>
<th>Good adherence to drug therapy</th>
<th>Poor adherence to drug therapy</th>
<th>Odds ratio (random) (95% CI)</th>
<th>Weight (%)</th>
<th>Odds ratio (random) (95% CI)</th>
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<tbody>
<tr>
<td>Coronary Drug Project Research Group 1980⁸⁴</td>
<td>106/708</td>
<td>80/357</td>
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<td>12.11</td>
<td>0.54</td>
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<td>Wei et al 2002⁸⁵</td>
<td>14/272</td>
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<td>2.06</td>
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<td>0.25 to 1.13</td>
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<td>Cotter et al 2004⁶⁰</td>
<td>1/52</td>
<td>1/12</td>
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<td>β blocker heart attack trial (men) 1990⁸²</td>
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<td>0.32</td>
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<td>0.60</td>
<td>0.10 to 2.41</td>
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<td>Canadian amiodarone myocardial infarction arrhythmia trial 1999⁶⁶</td>
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<td>0.46</td>
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<td>San Andres Rebollo et al 2004⁶⁹</td>
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<td>Garcia de Olalla et al 2002⁹¹</td>
<td>156/831</td>
<td>105/368</td>
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<td>0.62</td>
<td>0.47 to 0.83</td>
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<td>Grimwade et al 2005⁹²</td>
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<td>Hogg et al 2002⁹³</td>
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<td>0.45</td>
<td>0.30 to 0.67</td>
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<td>Paterson et al 2000⁹⁴</td>
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<td>1/18</td>
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<td>Physicians health study 1994⁹⁶</td>
<td>89/6608</td>
<td>102/4396</td>
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<td>West of Scotland prevention study 1997⁹¹</td>
<td>66/2435</td>
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<td>7.59</td>
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<td>Howell et al 2004⁹²</td>
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<td>Miura et al 2001⁹⁰</td>
<td>17/218</td>
<td>32/213</td>
<td></td>
<td>3.15</td>
<td>0.48</td>
<td>0.26 to 0.89</td>
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<tr>
<td>Dobbs et al 2004⁹³</td>
<td>9/84</td>
<td>2/17</td>
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<td>0.46</td>
<td>0.90</td>
<td>0.18 to 4.59</td>
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<tr>
<td>Total (95% CI)</td>
<td>17 354</td>
<td>9082</td>
<td></td>
<td>100.00</td>
<td>0.55</td>
<td>0.49 to 0.62</td>
</tr>
</tbody>
</table>

Total events: 832 (good adherence), 898 (poor adherence)
Test for heterogeneity: χ²=14.34, df=18, P=0.71, I²=0%
Test for overall effect: z=1.64, P<0.0001
Comment améliorer la compliance ?

Trois étapes importantes :

* La détection
  * La prévention
  * L’amélioration et le maintien
Definitions

Adherence

Drug prescription

Acceptance

Discontinuation

End prescription

365 days

Time

Compliance (%drug taken)

Persistence (days)
Definitions

Compliance: the quality of execution of the prescribed drug regimen; the extent to which the patient’s dosing history corresponds to the prescribed regimen

Persistence: the length and time between onset and discontinuation

Adherence: includes acceptance, execution and discontinuation. Poor adherence signals that something is or was wrong with the drug regimen; either not accepted, poorly executed and/or discontinued prematurely
Drug adherence problems are characterized by two major patterns!

- Perfect adherence: 100%
- Non-persistence: 70%
- Good persistence but bad execution (drug holydays): 70%

The identification of the problem is crucial since the prevention strategy depends on the type of pattern.
Methods of measuring compliance

• Directly observed therapy
• Blood levels of medicine, biologic marker or metabolite
• Patient questionnaires, patient self-reports, pill counts
• Rates of prescription refills
• Electronic medication monitors
• Patient diaries

Farmer KC. Clin Ther 1999; 21: 1074-1090
Osterberg L, Blaschke T. NEJM  2005; 353: 487-497
Methods of measurement of compliance

Non-invasive methods

Directly observed therapy
Electronic monitoring
Pill count
Drug measurement in body fluids
Biomarker measurement in body fluids

Invasive methods

Patient interview
Patient diary
Adherence questionnaire
Prescription record review

Accuracy

Less accurate
Most accurate
Limits of blood measurements to monitor compliance

<table>
<thead>
<tr>
<th>Mo</th>
<th>Tu</th>
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Blood levels in therapeutic range

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<td>0</td>
<td>0</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>2</td>
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</tbody>
</table>

Blood levels in therapeutic range

Blood levels in therapeutic range
Predictive value of the physician’s opinion on compliance

69 patients, 290 months of treatment

Monitoring of compliance with an electronic device and impression of the physician gathered at the end of each consultation.

Sensitivity of the doctors opinions: 35 %
Specificity of the doctors opinions: 91 %
Probability of low compliance when predicted: 35 %
Electronic drug monitoring devices

Helping Hand™ and IDAS II electronic blister card and dispenser (Bang & Olufsen Medicom a/s)

Med-ic® electronic compliance monitor (Information Mediary Corp)

MEMS® electronic event monitoring (Aardex Ltd)

MEMS®: www.aardex.ch
The electronic monitoring system: MEMS

MEMS:
Medication
Event
Monitoring
System

MEMS®: www.aardex.ch
Patient 1: The perfect patient!

Chronology report:
Arrows indicate days on which medication was not taken
Patient 2: discontinued treatment after 60 days!

Chronology report:
Arrows indicate days on which medication was not taken
Patient 3: several doses missed, drug holiday!

Chronology report:
Arrows indicate days on which medication was not taken

Patient 4: only few doses missed, irregular time!

Chronology report:
Arrows indicate days on which medication was not taken

The 4 patients: adherence/compliance is a dynamic process

[Graphs showing dosing time over time for Patients 1 to 4, with annotations for discontinued treatment.]
ALL of those 4 patients are 79% « compliant »!

Color code:
- 2 doses
- 1 doses
- 0 doses
- >2 doses
Long-term compliance monitoring in an hypertensive patient

Compliance is a dynamic process!
Drug persistence across the therapeutic fields

Data collected from various studies performed with the MEMS device

B. Vrijens, Pharmionics, Abstract
Proportion of patients having experienced a drug holiday (>3 days)

Data collected from various studies performed with the MEMS device
Compliance rates by dosing frequency

P. Ruud, AHJ, 1995

Percent Compliance

n = 7-11 studies

QD  BID  TID  QID

Compliance rates by dosing frequency
Compliance to the morning and evening dose of an AT₁ receptor blocker in hypertensive patients

Würzner et al, J Hypertens, 2001
White coat compliance in hypertensive patients

Compliance (%)

- 1st week
- 2nd week
- 3rd week
- 4th week
- day -3
- day -2
- day -1

before consultation

Bochud M et al, J Hypertens, 2003, abstract
Monitoring of compliance improves BP control

Blood pressure (mmHg)

<table>
<thead>
<tr>
<th>Date</th>
<th>Losartan 50</th>
<th>Torasemide 10</th>
<th>Felodipine 10</th>
<th>Metoprolol 100</th>
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</tbody>
</table>

Measured compliance (%)

84%
95%
95%
95%
Electronic monitoring of compliance in resistant hypertension

Burnier M, J Hypertens, 2001
Monitoring of compliance in uncontrolled hypertensive patients

Uncontrolled office BP (n = 69)

Objective monitoring of compliance

Target BP achieved < 140/90 mmHg
23/69 (33.3%)
Group 1

Target BP not achieved BP improved
23/69 (33.3 %)
Group 2

Target BP not achieved BP not improved
23/69 (33.3%)
Group 3

Bertholet et al, J Clin Hypertens, 2000
Changes in blood pressure during the monitoring of compliance in hypertensive patients

Bertholet et al, J Clin Hypertens, 2000
Electronic monitoring of drug adherence improves blood pressure control in hypertension: a randomized, controlled study

Valérie Santschi (1), Christiane Ruffieux (2), Olivier Bugnon (1), Michel Burnier (3)

(1) Policlinique Médicale Universitaire, Lausanne, Switzerland
(2) Institute of Social and Preventive Medicine, Lausanne, Switzerland
(3) Dept of Nephrology and Hypertension consultation, Lausanne, Switzerland
Objective

To evaluate whether having the ability to monitor drug adherence with an electronic system (Medication Event Monitoring System, MEMS®) improves the physician’s ability to lower BP <140/90 mmHg in treated uncontrolled hypertensive patients.
Design of the study

MEMS groups
4 networks RPh/GPs

Usual care groups
3 networks RPh/GPs

Treated Hypertensive patients with uncontrolled BP
(≥140/90 mmHg)

34 patients followed for
1 year
Use of MEMS

34 patients followed for
1 year
Without MEMS

Santschi et al, Eur J Int Med
Clinical interest of measuring compliance in clinical practice

A prospective, randomised study in clinical practice with physicians/pharmacists networks in Fribourg/Switzerland

Usual care

7 networks

1 year follow-up

Intervention with MEMS

0  2  4  12 months

Fixed MEMS  MEMS used at the physician’s discretion

Patients: treated hypertensive patients with uncontrolled BP (n=68)
Primary objective: percentage of patients achieving a BP < 140/90 mmHg

Santschi et al, Eur J Int Med
### Results

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Usual care</th>
<th>Intervention</th>
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<tbody>
<tr>
<td>Number of patients</td>
<td>34</td>
<td>34</td>
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<tr>
<td><strong>Demographic</strong></td>
<td></td>
<td></td>
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<tr>
<td>Mean age [range], (years)</td>
<td>71.2 [43-93]</td>
<td>61.4 [44-90]</td>
</tr>
<tr>
<td>Sex (men/women)</td>
<td>19/15</td>
<td>21/13</td>
</tr>
<tr>
<td><strong>Office BP, mean (sem)</strong></td>
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</tr>
<tr>
<td>Systolic (mmHg)</td>
<td>167.0 (2.6)</td>
<td>163.0 (3.2)</td>
</tr>
<tr>
<td>Diastolic (mmHg)</td>
<td>91.6 (2.2)</td>
<td>95.2 (1.7)</td>
</tr>
<tr>
<td><strong>Comorbidities</strong></td>
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<tr>
<td>Smoking</td>
<td>8 (24)</td>
<td>6 (18)</td>
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<tr>
<td>Obesity</td>
<td>13 (38)</td>
<td>17 (50)</td>
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<td>Diabetes</td>
<td>14 (41)</td>
<td>8 (24)</td>
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<td>Dyslipidemia</td>
<td>8 (24)</td>
<td>13 (38)</td>
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<td>Cardiovascular diseases</td>
<td>9 (27)</td>
<td>6 (18)</td>
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<td>Family history of CVD</td>
<td>6 (18)</td>
<td>11 (32)</td>
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<td>Diuretic</td>
<td>24 (71)</td>
<td>21 (62)</td>
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<td>21 (62)</td>
<td>16 (47)</td>
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<td>Ang II receptor blocker</td>
<td>7 (21)</td>
<td>9 (27)</td>
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<td>Calcium antagonist</td>
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<td>Beta-blocker</td>
<td>12 (35)</td>
<td>9 (27)</td>
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<td>Others</td>
<td>1 (3)</td>
<td>1 (3)</td>
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<td><strong>Number of therapies</strong></td>
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<td>7 (21)</td>
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<td>Bitherapy</td>
<td>11 (32)</td>
<td>15 (44)</td>
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<td>Triple therapy or more</td>
<td>16 (47)</td>
<td>12 (35)</td>
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<td><strong>Mean number of antihypertensive drugs [range]</strong></td>
<td>2.5 [1-6]</td>
<td>2.2 [1-4]</td>
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</table>
Percentage of patients achieving the target blood pressure during the study

Proportion of patients with a BP < 140/90 mmHg

Compliance monitoring

Months of follow-up

Baseline 2 4 6 12

Usual care group (n=34) Intervention group (n=34)

P <0.05

(60% of patients monitored)

Santschi et al, Eur J Int Med
Factors associated with the achievement of therapeutic goals (BP <140/90 mmHg) at 4 and 12 months

<table>
<thead>
<tr>
<th>Factors</th>
<th>4 months</th>
<th>12 months</th>
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<tr>
<td></td>
<td>Odd ratio (95% CI)</td>
<td>p-value</td>
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<tr>
<td>Intervention vs. usual care</td>
<td>4.26 (1.07-16.95)</td>
<td>0.04</td>
</tr>
<tr>
<td>Age</td>
<td>0.98 (0.92-1.04)</td>
<td>0.50</td>
</tr>
<tr>
<td>Sex</td>
<td>0.66 (0.19-2.30)</td>
<td>0.51</td>
</tr>
<tr>
<td>Baseline systolic BP</td>
<td>0.99 (0.96-1.03)</td>
<td>0.71</td>
</tr>
<tr>
<td>Baseline diastolic BP</td>
<td>0.98 (0.91-1.04)</td>
<td>0.46</td>
</tr>
</tbody>
</table>

BP: blood pressure; CI: confidence interval

Multivariate analysis adjusted for allocated group, age, sex and baseline blood pressure.

Santschi et al, Eur J Int Med
Drug adherence with Cinacalcet

Mme AMJ 1963

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<th></th>
<th>déc.04</th>
<th>janv.05</th>
<th>février 05</th>
<th>mars.05</th>
<th>avril 05</th>
<th>mai.05</th>
<th>juin.05</th>
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<td>1114</td>
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<td>1875</td>
<td>884</td>
<td>243</td>
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<td>Ca</td>
<td>2.18</td>
<td>1.93</td>
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<td>1.88</td>
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<td>2.19</td>
<td>1.91</td>
<td>3.21</td>
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<td>5.886</td>
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<td>3.7195</td>
<td>4.1391</td>
<td>3.5908</td>
<td>6.9657</td>
<td>2.2532</td>
<td>2.7018</td>
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Cinacalcet 30 mg, 60 mg, 90 mg

MEMS
iPTH after introduction MEMS (n=7)
Où se situe le problème des médecins ?

- Le médecin n’a pas de sensibilité à la non-compliance, car elle remet fondamentalement en question la confiance dans la relation avec son patient.
- Il n’a pas l’habitude de définir précisément des objectifs thérapeutiques.
- Il ne dispose pas de moyens adéquats pour évaluer la compliance. Sans moyens de mesure, les problèmes ne sont pas détectés et donc pas résolus.
- L’évaluation de l’observance du médecin est surtout fondée sur une impression subjective (respect des dates de consultations, quelques questions au malade sur sa prise médicamenteuse).
Où se situe le problème des pharmaciens ?

• Le pharmacien ne dispose pas non plus de moyens appropriés pour détecter et suivre la compliance (suivre les renouvellements de traitements).
• Il n’a pas connaissance des objectifs thérapeutiques définis par le médecin.
• Il se base aussi sur son jugement pour estimer l’observance du malade (quoique les patients se confient peut-être plus volontiers au pharmacien sur ce sujet).
Compliance monitoring in physician/pharmacist networks

- Physicians
  - Prescription
  - Discussion based on the report
- Patient
  - manage the MEMS
  - Interventions based on the report

Compliance report
‘One year of loyalty to the pills. For what aim? Surviving the pills and the doctor!’

Blister collection of 1 year’s medication of a kidney transplant patient (>4000 pills)

The ultimate case of resistant hypertension

60 year women, hypertensive since the age of 18 y. Well controlled for many years. 3 pregnancies without problems

2004: Hospitalized because of visual problems, BP: 260/150 mmHg

Family history ++
Personal history: Ovarian tumors operated twice
Cystectomy for ? (incontinence ?)

Investigations: Renin/aldo normal
No renal artery stenosis
No vascular lesion in the brain (PICA)
Normal steroid profile
eGFR: 62 ml/min    HVG ++, retinopathy,
Normal dipping
Actual BP: 240/150 mmHg several times
Referred to us with the following treatment:
(January 2006)

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Dosage</th>
<th>Frequency</th>
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<tbody>
<tr>
<td>Furosemide</td>
<td>40 mg</td>
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<tr>
<td>Aldomet</td>
<td>250 mg</td>
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<tr>
<td>Loniten</td>
<td>10 mg</td>
<td>2 x 2</td>
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<tr>
<td>Cardura</td>
<td>4 mg</td>
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</tr>
<tr>
<td>Norvasc</td>
<td>10 mg</td>
<td>1 x 1</td>
</tr>
<tr>
<td>Enatec</td>
<td>20 mg</td>
<td>2 x 1</td>
</tr>
<tr>
<td>Blopress plus 16/12.5</td>
<td>2 x 1</td>
<td></td>
</tr>
<tr>
<td>Tenormin</td>
<td>100 mg</td>
<td>2 x 1</td>
</tr>
<tr>
<td>Aldactone</td>
<td>100 mg</td>
<td>2 cp</td>
</tr>
<tr>
<td>Catapresan</td>
<td>150 scut</td>
<td>4x a day</td>
</tr>
<tr>
<td>Nitroderm TTS 10</td>
<td>1x</td>
<td></td>
</tr>
</tbody>
</table>

31 tablets a day + 4 s-cut injections

What is your next step?