Medication Adherence: How Much is Enough?

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Definition of Non-Adherence

Non-Adherence is present when the actual treatment a subject receives is different from the nominal (intended) assignment.
But...

• Adherence is not a dichotomous variable (“adherent” vs “non-adherent”)
• No single metric (e.g., percent of prescribed doses taken) can adequately describe actual patterns of adherence
• TIME is an important component of describing adherence
• *We need to have and use a common taxonomy for describing adherence*
Medication Adherence

The process, over time, by which patients take their medications as prescribed

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

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

3. Persist
   - Patient discontinues treatment
   - Time to event

Vrijens et al., BJCP, 2012.
Each of these 4 patients took 75% of prescribed doses during a 3-month period…!
Each patient took 90% of prescribed doses during a 12-month period...
Persistence: overall, 40% of patients with HIV in a clinical trial will have discontinued treatment by month 12.

(Data obtained from electronic monitoring (EM) of dosing)

Source: http://www.iadherence.com/www/
A Longitudinal illustration of the taxonomy

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

1. Initiate

- **25%** of patients do not initiate a new prescription
- Large differences between:
  - Diseases/Drugs
  - Centers
  - HC systems
  - Drug delivery/practice

2. Implement

- Daily, **15%** of patients do not implement as prescribed
- Patient attributes
- Dosing regimen
  - Once daily: 10%
  - Twice daily: 20%
- Implementation decreases with:
  - Food requirements
  - Complexity of Rx

3. Persist

- During the first year, **40%** of patients have discontinued treatment
- Large differences between:
  - Diseases/Drugs
  - Centers
  - HC systems
  - Drug delivery/practice

METRICS

FACTORS
Key Messages:

• Suboptimal adherence is the rule, rather than the exception, during clinical trials during drug development (as well as in treatment settings)

• The most important problem in adherence is lack of persistence; poor implementation is less problematic, but may be a precursor of discontinuation

• Percent adherence is insufficient to characterize individual patient adherence

• Technology is available to provide accurate, detailed and high fidelity drug dosing histories
“TO MEASURE IS TO KNOW. IF YOU CANNOT MEASURE IT YOU CANNOT IMPROVE IT.”

Sir William Thomson Scottish engineer, mathematician, and physicist, 1824-1907

“WHAT GETS MEASURED, GETS MANAGED.”

Peter Drucker, described as "the founder of modern management"
Adherence Measurement Methods

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

WHY MEASURE ADHERENCE?
INTERVENTIONS TO IMPROVE ADHERENCE

67 RCT identified with electronic compilation of drug dosing histories (1979-2010) N = 9057 patients

Difference in adherence outcome measures by intervention component

- TRT simpl (n=18): p = 0.37
- Cogn-Educ (n=36): p = 0.14
- Behav-Counsel (n=47): p = 0.07
- Soc-Psych (n=13): p = 0.50
- EM-feedback (n=22): p = 0.02
- Tech rem (n=20): p = 0.22
- Tech equip (n=11): p = 0.59
- Rewards (n=4): p = 0.44

Percent number of studies with significant intervention effect

- 70.6% of 17 studies that reported p-value
- 64.3% of 28 studies
- 55.6% of 36 studies
- 37.5% of 8 studies
- 77.8% of 18 studies
- 46.7% of 15 studies
- 66.7% of 9 studies
- 50.0% of 2 studies

A SPECIFIC EXAMPLE: WORSENING REGIMEN EXECUTION, THEN COMPLETE DISCONTINUATION
INDIVIDUAL EXAMPLE OF A SUCCESSFUL INTERVENTION

Here's where a new intervention is needed

Intervention by the physician or the nurse

Here’s where a new intervention is needed
Super Learner Analysis of Electronic Adherence Data Improves Viral Prediction and May Provide Strategies for Selective HIV RNA Monitoring

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Mark J. van der Laan, PhD,* Honghu Liu, PhD,¶¶¶ and David R. Bangsberg, MD, MPH##
But: How Much Adherence is Enough?
IT DEPENDS…. 

• On the patient’s pattern(s) of missing doses
• On the drug(s) being used
  – The dose of drug
  – Their half-lives and the intersubject variability
  – Their duration of action
  – Their forgiveness
Patterns of Patient Dosing
Impact of Poor Adherence: Efficacy and Safety Issues

Periodic loss of effectiveness & emergence of drug resistance (HIV-HCV)

Occasional toxicity

Successful Projection of the Time Course of Drug Concentration in Plasma During a 1-Year Period From Electronically Compiled Dosing-Time Data Used as Input to Individually Parameterized Pharmacokinetic Models

Bernard Vrijens, Eric Tousset, Richard Rode, Richard Bertz, Steve Mayer, and John Urquhart

Journal of Clinical Pharmacology, 2005;45:461-467
EM enables long term projections of drug exposure

PK projection assuming perfect intake (steady state)
PK projection based on electronic monitoring

Last reported dose by the patient

Observed concentration

Vrijens & al., Journal of Clinical Pharmacology, 2005
55% of residual PK variability is explained by EM

Vrijens et al. – IAS Paris 2003
IT DEPENDS....

- On the drug(s) being used
  - The dose of drug
  - Their half-lives and the intersubject variability
  - Their duration of action
  - Their forgiveness
Drug factors:
Forgiveness
Duration of action
Forgiveness can be defined as how long drug action continues at therapeutically effective levels after a last-taken dose or The post-dose duration of effective action minus its recommended dosing interval.
Drug factors:
Duration of action

_An example using HIV PIs_
Estimation of the comparative therapeutic superiority of QD and BID dosing regimens, based on integrated analysis of dosing history data and pharmacokinetics

Laetitia Comté · Bernard Vrijens · Eric Tousset · Paul Gérard · John Urquhart
Pharmacokinetic projections of representative patients during a QD or BID dosing regimen assuming that the patients maintain pharmacokinetic steady state. The y-axis shows the concentration of PI as a function of time. The consequences of missing one QD or three BID doses are illustrated. The time to reach a critical concentration of 1000 ng/ml is 42.3 h and 47.2 h, respectively, for a BID and a QD regimen when the drug is lopinavir/ritonavir.

*Slide courtesy of Bernard Vrijens, AARDEX and Pharmionic Research Centre, Visé, Belgium*
How frequent are those errors?

The cumulative percentage of QD and BID patients with dosing intervals greater than 36 h

73% QD
54% BID

Slide courtesy of Bernard Vrijens, AARDEX and Pharmionic Research Centre, Visé, Belgium
What can we do to improve adherence?
A Systems View for Changes

Healthcare Professionals
1. Better collaboration between HCPs
2. Measure adherence & provide feedback
3. Review medications at hospital discharge
4. Manage polypharmacy & synchronize refills (pharmacists)
5. Build Medication taking Habit Strategies
6. Schedule follow-up

Healthcare/Prescribing policy
1. Raise awareness
2. Support education of HCP
3. Promote integrated care models
4. Make prescription & dispensing data bases available to HCP
5. At TRT failure, check adherence before escalation
6. Incentivize performance
7. Support research in adherence-related sciences
8. Data policy for adherence measures

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

Pharma Industry
1. Optimize drug development and identify the most effective dose
2. Think individualized therapies rather than one dose fits all
3. Move from selling a chemical pill to providing a system improve the “package”

Family and Caregivers
1. Special attention to kids, adolescents, and elderly
2. Caution with depression and associated diseases
3. Ask help from patient associations

B. Vrijens, personal view
Questions and Discussion?

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