EPID 765

Pharmacoepidemiology

Lesson 13:
Adherence
Persistence

Some slides adopted
from Alan Brookhart

A Note on Terminology

- Medication compliance and persistence are two different constructs.
- Medication compliance (synonym: adherence) refers to the degree or extent of conformity to the recommendations about day-to-day treatment by the provider with respect to the timing, dosage, and frequency. It may be defined as "the extent to which a patient acts in accordance with the prescribed interval, and dose of a dosing regimen."
- Medication persistence refers to the act of continuing the treatment for the prescribed duration. It may be defined as "the duration of time from initiation to discontinuation of therapy."
- No overarching term combines these two distinct constructs
- PS: compliance term abandoned since it blames patient (lopsided)

Cramer JA, et al. Medication Compliance and Persistence: Terminology and Definitions. Value Health 2008;11: 44-7.

Do Most Stakeholders Benefit From Good Adherence/Persistence?

- Patients
  - But stopping due to insidious side-effects may prevent ADR (e.g., rhabdomyolysis)
- Physicians
- Insurance companies
  - But long-term benefit offset by short term cost (e.g., treatment of high blood pressure)
- Pharmacies
- Pharmaceutical companies
- Society (public health)

The Potential Consequences of Nonadherence

- >100,000 deaths per year in U.S.
- Of all medication-related hospital admissions in the United States, 1/3 to 2/3 are due to poor medication adherence
- Total cost estimates range from $100 billion to $300 billion
- Cave: assumptions and causal contrasts!

Haynes, R. B., D. W. Taylor, et al., Eds. (1979). Compliance in Health Care. Baltimore, Johns Hopkins University Press
Blackwell B. Drug therapy: patient compliance. N Engl J Med 1973;289:249-52.
DiMatteo, Variations in patients' adherence to medical recommendations: a quantitative review of 50 years of research. Med Care 2004;42:197-9.
McDonnell PJ, Jacobs MR. Hospital admissions resulting from preventable adverse drug reactions. Ann Pharmacother 2002; 36:1331-6.

Why We Need to Study Adherence and Persistence

- Quantify magnitude
- Understand determinants
- Target interventions
- Advance nonexperimental study design and analysis

What do we know

- Many papers on
  - **Low** adherence/persistence with chronic preventive treatments
  - **Patient groups at risk of becoming** nonpersistent (people of lower education, socioeconomic status, depressed patients)
  - **Predictors of nonpersistence** (medication regimen complexity, cost, clinical need)
  - **Consequences** of nonpersistence but most of questionable validity (cave: tomato effect)

What do we not know

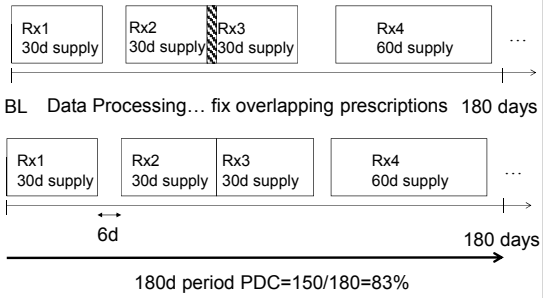
- Very little is known about
  - **Why** patients stop specific treatments
  - **How** to predict nonpersistence at the patient level
  - **How** to validly assess consequences of nonpersistence
  - **What** interventions will cause meaningful improvements
  - **What** are reasonable causal contrasts (i.e., not: 100% vs. 0% adherence!)

Table 1. **Methods of Measuring Adherence.**

Test	Advantages	Disadvantages
Direct methods		
Directly observed therapy	Most accurate	Patients can hide pills in the mouth and then discard them; impractical for routine use
Measurement of the level of medicine or metabolite in blood	Objective	Variations in metabolism and "white-coat adherence" can give a false impression of adherence; expensive
Measurement of the biologic marker in blood	Objective; in clinical trials, can also be used to measure placebo	Requires expensive quantitative assays and collection of bodily fluids
Indirect methods		
Patient questionnaires, patient self-reports	Simple; inexpensive; the most useful method in the clinical setting	Susceptible to error with increases in time between visits; results are easily distorted by the patient
Pill counts	Objective, quantifiable, and easy to perform	Data easily altered by the patient (e.g., pill dumping)
Rates of prescription refills	Objective; easy to obtain data	A prescription refill is not equivalent to ingestion of medication; requires a closed pharmacy system
Assessment of the patient's clinical response	Simple; generally easy to perform	Factors other than medication adherence can affect clinical response
Electronic medication monitors	Precise; results are easily quantified; tracks patterns of taking medication	Expensive; requires return visits and downloading data from medication vials
Measurement of physiologic markers (e.g., heart rate in patients taking beta-blockers)	Often easy to perform	Marker may be absent for other reasons (e.g., increased metabolism, poor absorption, lack of response)
Patient diaries	Help to correct for poor recall	Easily altered by the patient
When the patient is a child, questionnaire for caregiver or teacher	Simple; objective	Susceptible to distortion

Osterberg and Blaschke, NEJM 2005

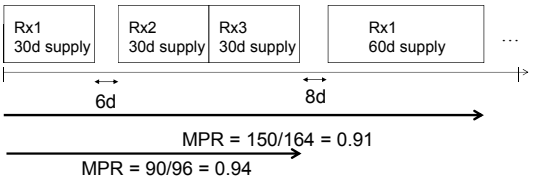
Percentage of Days Covered (PDC)



180d period PDC=150/180=83%

Medication Possession Ratio (MPR)

- MPR is usually defined as the sum of the days supply of medication divided by the number of days between the first fill and the last refill plus the days' supply of the last refill
- Addresses adherence allowing for non-persistence



MPR = 150/164 = 0.91

MPR = 90/96 = 0.94

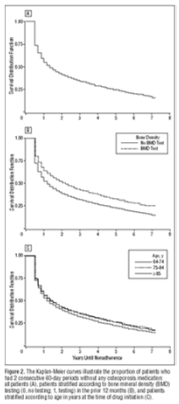
Persistence is very poor

One year after initiating treatment for osteoporosis, 45.2% of the 40,002 patients were not continuing treatment

Compliance With Osteoporosis Medications

Daniel H. Solomon, MD, MPH; Jerry Avorn, MD; Jeffrey N. Katz, MD, MSc; Joel S. Finkelstein, MD; Marilyn Arnold, ScD; Jennifer M. Polinski, MPH; M. Alan Brookhart, PhD

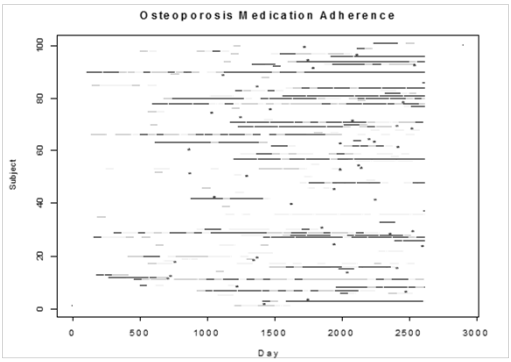
Arch Intern Med. 2005;165:2414-2419



Limitations

- Don't know why patients stop taking meds
  - Side effects
  - Doctors instructions
- Pharmacy refill data
  - "Persistent" patients may not be taking meds
  - Primary nonpersistence
- Informative Censoring
  - Nursing home admission
  - Loss of plan eligibility
  - Death

Dynamics Plot: 100 randomly selected subjects
(blue dash=high adherence, green=medium, yellow=low
black star=censor, red=death



Gaps in Treatment Among Users of Osteoporosis Medications: The Dynamics of Noncompliance

M. Alan Brookhart, PhD, Jerry Avorn, MD, Jeffrey N. Katz, MD, MS, Joel S. Finkelstein, MD, Marilyn Arnold, ScD, Jennifer M. Polinski, MPH, Amanda R. Patrick, MS, Helen Mogun, MS, Daniel H. Solmon, MD, MPH
Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital/Harvard Medical School, Boston, Mass.

The American Journal of Medicine (2007) 120, 251-256

- 60% of patient who stop treatment for 60 days restart within two years
- Use of OP medications appears to be dynamic
- Positive interpretation: Persistence not quite as bad as when looking at first episode only

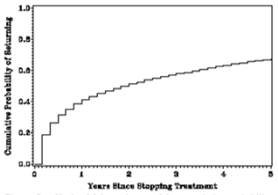


Figure 2 Kaplan-Meier estimate of the cumulative probability of returning to treatment.

Adherence in Effectiveness Research

- Recent studies have reported on effects of persistence on intended outcomes
  - Statins: 50% reduction in risk of AMI
  - Bisphosphonates: reduced risk of fracture

Adherence bias or 'Healthy adherer' effect

- Theory: people adherent/persistent to meds do other things that improve health
- Evidence: adherence to placebo is associated with positive outcomes in RCTs (Simpson, et al. BMJ 2006)
- Related to the 'healthy user' bias
- Implications for the conduct and interpretation of nonexperimental studies of prevention-oriented therapies and health behaviors
- Understudied/ignored

Epidemiology

Statin Adherence and Risk of Accidents
A Cautionary Tale

Colin R. Dormuth, ScD; Amanda R. Patrick, SM; William H. Shrank, MD; James M. Wright, MD, PhD; Robert J. Glynn, PhD, ScD; Jenny Sutherland, BSc; M. Alan Brookhart, PhD

(Circulation. 2009;119:2051-2057.)

- Research Question: Are patients who are adherent to statins at lower risk of outcomes unlikely to be affected by statin exposure but likely to be related to healthy lifestyle ("negative control")?
- Population: All new users of statins in British Columbia with no evidence of existing heart disease

Accidents…

Results: Accidents

Outcome	More Adherent Event Rate (/ 100 py)	Less Adherent Event Rate (/ 100 py)	Unadjusted Hazard Ratio	95% Confidence Limits for Hazard Ratio	Adjusted Hazard Ratio	95% Confidence Limits for Hazard Ratio
Accident Events:						
Both Sexes (n=141,086)						
Burn	0.28	0.36	0.78	(0.71 - 0.87)	0.88	(0.79 - 0.97)
Fall	0.53	0.54	0.98	(0.90 - 1.06)	0.90	(0.83 - 0.98)
Fracture	2.20	2.38	0.93	(0.89 - 0.96)	0.92	(0.88 - 0.96)
Motor vehicle accident	1.48	2.25	0.66	(0.63 - 0.69)	0.75	(0.72 - 0.79)
Open wound	2.44	2.74	0.89	(0.86 - 0.92)	0.91	(0.88 - 0.95)
Poisoning	0.32	0.41	0.78	(0.71 - 0.86)	0.86	(0.78 - 0.94)
Workplace accident	1.31	2.13	0.62	(0.59 - 0.65)	0.77	(0.74 - 0.81)
All (first occurrence)	**7.38**	**9.39**	**0.79**	**(0.77 - 0.81)**	**0.85**	**(0.83 - 0.87)**

Results: Screening Tests

Outcome	More Adherent Event Rate (/ 100 py)	Less Adherent Event Rate (/ 100 py)	Unadjusted Hazard Ratio	95% Confidence Limits for Hazard Ratio	Adjusted Hazard Ratio	95% Confidence Limits for Hazard Ratio
Screening Events:						
Both Sexes (n=141,086)						
Eye examination	3.58	2.93	1.21	(1.17 - 1.26)	1.08	(1.05 - 1.12)
Fecal occult blood test	8.06	6.14	1.31	(1.27 - 1.34)	1.21	(1.18 - 1.24)
Sigmoidoscopy	0.53	0.49	1.09	(1.00 - 1.18)	1.07	(0.98 - 1.16)
All (first occurrence)	**12.01**	**9.28**	**1.28**	**(1.25 - 1.31)**	**1.17**	**(1.15 - 1.20)**
Females (n=68,403)						
Bone mineral density test	6.74	5.96	1.13	(1.09 - 1.17)	1.10	(1.06 - 1.14)
Pap test	5.27	6.06	0.87	(0.84 - 0.91)	1.03	(0.99 - 1.07)
Screening mammography	3.35	3.32	1.01	(0.96 - 1.06)	1.05	(1.00 - 1.10)
All (first occurrence)	**6.43**	**6.76**	**0.95**	**(0.93 - 0.98)**	**1.07**	**(1.04 - 1.10)**
Males (n=72,683)						
Prostate-specific antigen test	15.63	12.91	1.20	(1.16 - 1.23)	1.07	(1.04 - 1.10)

Results: Other Outcomes

Outcome	More Adherent Event Rate (/ 100 py)	Less Adherent Event Rate (/ 100 py)	Unadjusted Hazard Ratio	95% Confidence Limits for Hazard Ratio	Adjusted Hazard Ratio	95% Confidence Limits for Hazard Ratio
Other events, no association expected						
Both Sexes (n=141,086)						
Asthma/COPD hospitalization	0.38	0.42	0.91	(0.83 - 0.99)	0.87	(0.79 - 0.95)
Asthma/COPD outpatient visit	3.29	4.02	0.82	(0.80 - 0.85)	0.87	(0.85 - 0.90)
Bacterial infection	0.43	0.46	0.93	(0.85 - 1.01)	0.91	(0.83 - 0.99)
Deep Vein Thrombosis or other clot	0.58	0.56	1.03	(0.95 - 1.11)	0.98	(0.91 - 1.07)
Dental problem	0.71	1.02	0.69	(0.65 - 0.74)	0.76	(0.72 - 0.81)
Diverticulitis	1.34	1.28	1.04	(0.99 - 1.10)	0.98	(0.93 - 1.03)
Drug dependency	0.17	0.29	0.59	(0.53 - 0.67)	0.73	(0.65 - 0.83)
Food-borne bacterial infection	1.77	2.18	0.81	(0.78 - 0.85)	0.85	(0.82 - 0.89)
Gall stone	0.63	0.78	0.81	(0.75 - 0.86)	0.81	(0.76 - 0.87)
Gastrointestinal bleed	1.71	1.86	0.92	(0.88 - 0.96)	0.90	(0.86 - 0.94)
Gout	1.35	1.44	0.94	(0.89 - 0.99)	0.89	(0.85 - 0.94)
Kidney stone	0.51	0.55	0.93	(0.85 - 1.00)	0.96	(0.89 - 1.04)
Malignant melanoma	0.19	0.14	1.35	(1.16 - 1.58)	1.23	(1.05 - 1.43)
Migraine	0.81	1.20	0.67	(0.63 - 0.71)	0.82	(0.78 - 0.87)
Sexually Transmitted Disease	0.13	0.16	0.82	(0.71 - 0.95)	0.93	(0.80 - 1.09)
Skin infection	3.08	3.41	0.90	(0.87 - 0.93)	0.93	(0.90 - 0.96)
All (first occurrence)	**14.58**	**17.47**	**0.85**	**(0.83 - 0.86)**	**0.87**	**(0.86 - 0.89)**

Discussion

- Patients who adhere to statins
  - More likely to receive a range of prevention-oriented clinical services
  - At decreased risk of accidents and adverse health outcomes

Persistence in Pharmacoepi Outcomes Research

- Discussion point
  - How do we study effects of adherence/persistence?
  - How do we study effects of long-term exposure to preventive medications?
    - Statins (when to stop???)
    - Antidiabetics
    - Antihypertensives

Full Coverage for Preventive Medications after Myocardial Infarction

Niteesh K. Choudhry, M.D., Ph.D., Jerry Avorn, M.D., Robert J. Glynn, Sc.D., Ph.D., Elliott M. Antman, M.D., Sebastian Schneeweiss, M.D., Sc.D., Michele Toscano, M.S., Lonny Reisman, M.D., Joaquim Fernandes, M.S., Claire Spettell, Ph.D., Joy L. Lee, M.S., Raisa Levin, M.S., Troyen Brennan, M.D., J.D., M.P.H., and William H. Shrank, M.D., M.S.H.S., for the Post-Myocardial Infarction Free Rx Event and Economic Evaluation (MI FREEE) Trial

NEJM 2011;365;22: 2088-97.

Table 2. **Medication Adherence during Follow-up.***

Variable	Absolute Adherence†		
	Full Prescription Coverage	Usual Prescription Coverage	Absolute Difference (95% CI)
		percentage points	
All patients§			
ACE inhibitor or ARB	41.1±39.8	35.9±38.1	5.6 (3.4–7.7)
Beta-blocker	49.3±37.5	45.0±36.6	4.4 (2.3–6.5)
Statin	55.1±37.7	49.0±37.3	6.2 (3.9–8.5)
All three medication classes	43.9±33.7	38.9±32.7	5.4 (3.6–7.2)
Patients who filled at least one prescription			
ACE inhibitor or ARB	66.5±29.6	60.8±30.7	5.8 (3.6–8.1)
Beta-blocker	65.0±28.9	61.0±28.9	4.0 (2.1–5.9)
Statin	70.5±27.0	65.0±28.4	5.5 (3.6–7.5)
All three medication classes	67.4±15.5	62.9±26.3	4.5 (2.5–6.4)

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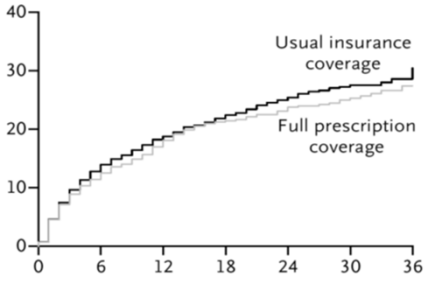
First Fatal or Nonfatal Vascular Event or Revascularization



Conclusion Persistence in Pharmacoepi Outcomes Research

- Increasing adherence/persistence plausibly improves clinical outcomes (cave: tomato)
- Nonexperimental studies of effects of adherence and persistence on clinical outcomes suffer from strong bias
  - Makes adherence look good: usually impossible to separate from true treatment effect
- Valid assessment requires randomization to intervention improving adherence/persistence
- Natural experiments (IVs) may sometimes work
- Effects of intervention likely modest but relevant