COMMENTARY

Pharmacoadherence: A new term for a significant problem

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In 2003, the World Health Organization declared nonadherence to medical treatment a major public health concern, particularly among patients with chronic conditions.[1] Research has found that adherence to long-term treatment regimens associated with chronic conditions is problematic,[2-6] with nonadherence rates in the longer-term regimens ranging from 20% to 82%.[7-11] Patient adherence to medical treatment regimens has been shown to be directly associated with health outcomes,[12] with poor adherence or nonadherence contributing to increased morbidities and mortalities.[13] Unfavorable outcomes associated with nonadherence also result in annual health care costs of approximately $100 billion.[14] What exactly, though, are we referring to when we discuss the concept of adherence?

Adherence refers to the extent to which an individual's behavior regarding a medical treatment regimen corresponds with the agreed-on recommendations of a health care professional.[15] Distinct in meaning from the term "compliance" in the health care lexicon, "adherence" indicates collaboration between the patient and the health care professional,[16-18] whereas "compliance" suggests obedience to the health care professional.[16,19-23]

Several factors influence the assessment of adherence to medical treatment, including the type of treatment or behavior (e.g., medication, diet, exercise, appointments), the population studied (e.g., condition, disease), and the method used to measure adherence (e.g., observation, patient interview). Owing to the multiple influences involved in determining adherence, rates of adherence (or nonadherence) and meanings associated with those rates vary widely. Given the complex nature of adherence within a medical context, it may be useful to narrow down the concept to adherence subtypes. One such subtype is medication adherence, which we will coin as "pharmacoadherence." Thus, the objectives of this article are to introduce and define a new term, pharmacoadherence, as a subtype of adherence. In addition, we wish to explore the measures available to assess pharmacoadherence and to provide an overview of the strategies and interventions that have been developed to improve pharmacoadherence.

Defining pharmacoadherence

The term pharmacoadherence denotes adherence solely associated with medication-taking behavior, narrowing the focus considerably to a patient's practice of taking a prescribed medication, which includes the collaboration component necessary to distinguish adherence from compliance. We offer the following formal definition of pharmacoadherence: the extent to which a patient follows a given therapeutic medication regimen as agreed on in partnership with a health care professional.

Measures of pharmacoadherence

Pharmacoadherence can be measured directly, indirectly, and subjectively. Direct measures such as biochemical assays (e.g., serum concentrations) provide evidence that a medication has been administered. Indirect measures (e.g., pill counts, refill records), on the other hand, provide evidence merely suggesting that a medication has been consumed or taken. Both direct and indirect measures are considered objective. The third category, subjective measures (e.g., self-reports), provide testimony from the patient that medication has or has not been taken. Neither indirect nor subjective measures offer definitive proof that a medication has been administered, which is a limitation of each. The types of measures available within each of the three categories, as well as their advantages and disadvantages, are described in Table 1.[3,17,18,24-51] The measure selection process to assess

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Table 1.
Attributes of Measures of Pharmacoadherence

Measure	Advantages	Disadvantages	Comments
Direct measures			
Direct observation[18,24-26]	Objective, highly specific, not invasive	Feasibility issues, labor intensive (e.g., training observers), vulnerable to Hawthorne effect, not practical in clinic or outpatient setting	Considered most precise measure; works better in hospital or research setting or when medication is administered by health care professional
Serum drug concentrations[25,27-32]	Objective, may be part of standard care, direct assessment of whether patient has taken medication	Snapshot of behavior (not a day-to-day measure), affected by factors other than pharmacoadherence (e.g., metabolism, drug–drug or drug–food interactions, poor absorption), cost, invasive	No standard method for determining the correlation between drug levels and pharmacoadherence; determination of pharmacoadherence should be made on a case-by-case basis[29]
Biological markers or tracers (e.g., bromide, phenobarbitone)[25,26,29,31,33,34]	Objective, direct assessment of whether patient has taken medication	Snapshot of behavior (not a day-to-day measure), affected by factors other than pharmacoadherence (e.g., metabolism, drug–drug or drug–food interactions, poor absorption), cost, invasive	Most effective with markers or tracers that have long half-life; steady-state concentration will not be reached until drug has been ingested on regular basis for a certain period of time
Indirect measures			
Electronic monitoring[3,24,27-29,35-41]	Objective, indicates times and dates of bottle opening (and therefore provides real-time tracking and detects poor pharmacoadherence to dosing schedule), detects overestimation in other measures, detects pill dumping, not invasive	Cost, not effective when pillboxes or liquid medications used, can malfunction and lose data, may interfere with personal pharmacoadherence strategies (e.g., pillboxes, daily decanting), device may be bulky and inconvenient to patient, may cause distress among patients (due to obviousness of pharmacoadherence surveillance), relies on assumption that medication removed from bottle has been consumed	Considered best available pharmacoadherence measure to date; increased sensitivity to poor pharmacoadherence (compared with self-reports and pill counts)
Pill counts (includes medication weighing)[24,26,27,29,34,42-46]	Objective, inexpensive, not invasive	Time-consuming, computations involved may be complex, relies on assumption that medications not counted have been consumed, tends to overestimate pharmacoadherence[a]	Unannounced pill counts correlate highly with electronic monitors; higher sensitivity and specificity than self-reports
Refill records[3,25-27,29,30,43,47-50]	Objective, convenient, standardized data, identifies patients who fail to refill medication(s), not invasive, inexpensive	Possible misinterpretation of use when changes are made to dosage, relies on assumption that filled prescriptions are consumed, assumes all sources of medication are captured, patterns of poor pharmacoadherence not detectable, only useful for long-term medications, increased complexity when using records from multiple pharmacies	Correlated to electronic monitors in some studies; correlated with clinical outcomes and other adherence behaviors (e.g., keeping health care appointments); considered most accurate estimate of pharmacoadherence in large populations; more likely to identify nonpharmacoadherent patient than self-report

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Table 1 (*continued*)

Measure	Advantages	Disadvantages	Comments
Surrogate clinical parameters (e.g., blood pressure, blood glucose levels, low-density-lipoprotein cholesterol levels)[18,26,43]	May be assessed as part of standard care	Influenced by other variables (e.g., patient's physical state, adequacy of medication), problems regarding reliability and validity	Considered poor substitute for more direct measures
Clinical outcomes (e.g., pain management)[26,43]	May be assessed as part of standard care	Influenced by variables other than medication adherence (e.g., physical therapy), problems regarding validity and reliability	Considered poor substitute for more direct measures
Subjective measures			
Self-reports (e.g., diaries, standardized questionnaires, interviews, visual analogue scales)[3,18,24,26-30,43,44,46,50,51]	Simple, quick, inexpensive, avoids sophisticated methodology and equipment, may provide information that explains variation in pharmacoadherence patterns and clinical response to medication therapy	Overestimates pharmacoadherence, low sensitivity; patients may provide socially acceptable responses; limited patient recall (impact of time); diaries may be burdensome, may not be returned, or may be returned incomplete; tends to be done around time of clinic visit when pharmacoadherence generally increases (introducing bias into results)	Independent predictor of clinical outcomes; correlated with electronic measures in some studies; patient reports of poor pharmacoadherence (as opposed to reports of good pharmacoadherence) are generally valid; generally considered unreliable
Clinician assessment[18,29,31,32]	Simple, quick, inexpensive, avoids sophisticated methodology and equipment	May be influenced by interactions with patients and by patient therapeutic outcomes	Clinician reports of poor pharmacoadherence (as opposed to reports of good pharmacoadherence) are generally valid; independent predictor of clinical outcomes; commonly fails to identify nonpharmacoadherent patients
Assessment by others (e.g., caregivers, significant others, research personnel)[17,31]	Simple, quick, inexpensive, avoids sophisticated methodology and equipment	Affected by amount of time spent with patient and level of involvement in patient's care (e.g., accuracy of assessment may decrease if significant other has only limited involvement in patient's treatment regimen)	Used and studied less frequently than other measures of pharmacoadherence

[a]Research suggests that unannounced home-based pill counts may be more accurate compared with scheduled and office-based pill counts.[45]

pharmacoadherence generally depends on several factors, including setting (e.g., outpatient clinic), time, cost, and available resources.

Strategies to improve pharmacoadherence

Based on the literature, a model of four major factors that influence pharmacoadherence—motivation, knowledge, skills, and access—was developed.[52] The core of the model, patient motivation, incorporates patient beliefs, values, attitudes, and willingness to follow the dosing regimen. This model suggests that the likelihood of patients' pharmacoadherence is increased by factors that (1) improve their access to medication, (2) enhance their knowledge and skills concerning medication regimens and disease states, and (3) increase their motivation to adhere to medication regimens. A literature search of MEDLINE (PubMed) restricted by language only (English) was conducted to identify those intervention studies that address the factors associated with pharmacoadherence using combinations of the following search terms: "adherence," "medication adherence," and "intervention." The literature search produced multiple studies, with pharmacoadherence interventions generally categorized as technical, educational, behavioral, affective, or multimodal.

Technical interventions address the medication regimen itself rather than external factors that influence a patient's medication-taking behavior. Successful technical interventions have included simplifying the dosing regimen and schedule and the use of tools such as pillboxes.[2,53] For example, it was found that single daily dose regimens were linked with significantly greater pharmacoadherence than that of multiple daily dose regimens.[54]

Educational interventions focus on teaching and providing knowledge related to the patient's medical condition and medication regimen. Some examples of this approach are notifying patients of medication-related adverse effects, distributing medication information in booklets or leaflets, and offering structured individual education sessions.[2,55] For instance, an educational intervention consisting of an informative booklet, group and individual instruction sessions, and a self-management plan was found to improve pharmacoadherence.[56]

Behavioral interventions attempt to modify a patient's medication-taking behaviors through the use of cues, reminders, and reinforcements.[2,53] For example, a telephone-linked reminder system was found to increase pharmacoadherence among elderly adults,[57] and monetary reinforcers plus the use of personalized cues for remembering dose administration times were found to improve pharmacoadherence in HIV-infected patients.[58]

Affective interventions attempt to improve pharmacoadherence by addressing a patient's emotional needs and social support systems.[59] Interventions in this category include family therapy and intensive individual counseling.[59,60] For example, an intervention designed to promote HIV treatment adherence through the development of peer support relationships (i.e., each participant acts as both a peer advocate for adherence and a recipient of peer advocacy efforts) resulted in a 90% average pharmacoadherence rate for patients by the end of the study period.[61]

Multimodal interventions use strategies from two or more of the four major categories—technical, educational, behavioral, affective—identified to address and improve pharmacoadherence. For example, an intervention consisting of individual counseling, detailed information about a medication regimen, an individually tailored medication schedule, telephone support, and regular clinic visits was found to have moderate effects on improving pharmacoadherence.[62] The results of a meta-analysis indicate that combining interventions that include behavioral, educational, and affective components was most successful in improving pharmacoadherence,[63] a finding that is generally consistent with systematic reviews of pharmacoadherence interventions.

Several systematic reviews of pharmacoadherence interventions conducted in recent years provide a cohesive overview of the effects of various intervention strategies. In 2002, McDonald and colleagues[64] published a review of randomized controlled trials (RCTs) of pharmacoadherence interventions. An update of this review was conducted in 2005 by Haynes and colleagues.[65] In both studies, <50% of interventions were associated with improvements in pharmacoadherence; however, the majority of interventions that were associated with improvements in pharmacoadherence also demonstrated improvements in clinical outcomes. The majority of effective interventions combined the use of technical, educational, behavioral, and affective intervention strategies. Virtually none of the RCTs examined had a follow-up of greater than two years, and thus the sustained impact of successful interventions is unknown.

A systematic review of RCTs of interventions to improve pharmacoadherence in chronic conditions found that a higher percentage of behavioral interventions demonstrated improvements in pharmacoadherence as compared with educational or combination interventions.[55] Other studies, however, are consistent with the findings of McDonald et al.[64] and Haynes et al.[65] regarding the success of multimodal interventions as compared with other types of interventions. For example, a review of antipsychotic pharmacoadherence interventions found that the great-

est improvements were observed in eight studies that employed combinations of behavioral, educational, and affective strategies, while solely educational interventions produced the least improvement.[59] Similarly, Vergouwen et al.[66] found that 9 of 11 collaborative care interventions that incorporated behavioral, educational, and affective components significantly improved pharmacoadherence to antidepressant therapy. A review of interventions to improve pharmacoadherence among older adults found that multimodal interventions tailored to address age-related adherence barriers were most effective in promoting pharmacoadherence.[67]

The general findings of the systematic reviews discussed here suggest that the most effective pharmacoadherence interventions are those that include combination or multimodal techniques. The advantage of multimodal interventions is that they address multiple barriers to pharmacoadherence on multiple levels. However, there are also drawbacks or limitations to combination interventions. Their reproducibility is difficult to predict, and intervention outcomes may vary depending on the patient population.[68] Often, studies do not evaluate multimodal interventions to determine the most effective or critical components and eliminate extraneous or superfluous techniques that distract from the primary strategies.[55,68,69] In addition, the effect sizes of combination interventions vary with regard to changes in pharmacoadherence and clinical outcomes; variability in effect sizes related to clinical outcomes has also been noted for other categories of interventions.[64,65,68,70] Kripalani and colleagues[55] further suggest that clinical outcomes can-

Table 2.
Summary of American Psychological Association Recommendations To Promote Adherence to a Medication Regimen[72]

Recommendation	Example
Explain the medication regimen	Educational materials In-depth discussions with patients, including asking patients open-ended questions to ensure patient understands what medication is for and how to take it
Tailor the medication regimen to the patient's lifestyle and daily routine	Develop dosing schedule around patient's primary daily activities such as work or school (e.g., a once-daily medication that could be taken before or after school or work) Develop dosing schedule around a daily event such as breakfast (e.g., take medication before breakfast each morning) Provide patient with container that allows convenient organization of daily medication Provide patient with convenient medication containers that are easily transportable (if medications must be taken away from home)
Establish collaborative relationship with patient, and facilitate patient interaction with other pharmacy staff	Be available to address patient concerns regarding medication Assist patient in developing strategies to maintain adherence Provide patient with alternative pharmacist contact who can offer advice/answer questions on medication regimen if you are not available
Identify and address individual barriers to adherence	Ask patients what things lead to nonadherence to medication, and work with patient to develop strategies to address these challenges (e.g., setting an alarm to sound when it is time to take medication if a patient identifies forgetfulness as a barrier to adherence)
Refer special-needs patients to appropriate services	Identify patients with substance abuse and/or mental health issues and refer patients to support services
Promote self-efficacy	Provide positive reinforcement to pharmacoadherence successes; something as simple as offering words of encouragement can be extremely beneficial to the patient's confidence regarding his or her ability to follow a long-term medication regimen
Create and maintain an environment conducive to pharmacoadherence	Collaborate with other health care professionals (e.g., physician, home health nurse) involved in the patient's care to communicate the patient's level of pharmacoadherence and to strategize on promoting or improving pharmacoadherence

not be consistently linked to changes in pharmacoadherence. Finally, the cost and time involved in conducting multimodal interventions may limit their utility in clinical practice. Despite these limitations, combination or multimodal interventions have consistently demonstrated the most promise in addressing poor pharmacoadherence. Health care professionals and researchers would do well to focus on designing, implementing, assessing, and then finely tuning multimodal interventions to maximize pharmacoadherence and to promote adaptation and application of effective interventions to diverse patient populations.

The American Public Health Association proposed a four-step approach to promote adherence to medications that may also be useful for health care professionals.[71] First, an assessment of factors influencing adherence should be conducted and barriers identified. Next, the health care professional should establish a therapeutic alliance with the patient to facilitate the development of a medication adherence plan. Third, multiple measures should be used to assess the patient's level of medication adherence. Finally, multiple interventions should be conducted that target the barriers identified in the first step.

The American Psychological Association (APA) has also addressed the issue of adherence, noting that to be adherent to a medication regimen, patients must (1) have a basic comprehension of their regimen (e.g., how often and how much medication should be taken), (2) have confidence that they can follow the regimen, (3) remember to take their medication, (4) incorporate their medication regimen into daily routines, and (5) maintain adherence to their medication regimen in the face of changes in daily routine.[72] To further assist health care professionals in promoting adherence, APA provided recommendations that include several elements of the adherence interventions identified as effective in the literature (Table 2).

Summary

We defined pharmacoadherence as the extent to which a patient follows a given therapeutic medication regimen as agreed on in partnership with a health care professional. Rates of pharmacoadherence among the general patient population are variable, with the World Health Organization estimating an average rate of 50%.[1,7] Given the critical interplay between pharmacoadherent behaviors, health outcomes, and health care costs, it is important to have a clear understanding of what the term pharmacoadherence really means as well as reliable and valid assessment measures and effective interventions to target deficits in pharmacoadherence. Future research should continue to refine measures of assessment and intervention protocols to improve pharmacoadherence.

References

1. World Health Organization. Adherence to long-term therapies. Evidence for action. 2003. www.emro.who.int/ncd/Publications/adherence_report.pdf (accessed 2007 Jun 20).
2. Van Dulman S, Sluijs E, van Dijk L et al. Patient adherence to medical treatment: a review of reviews. *BMC Health Serv Res.* 2007; 7:55.
3. Modi AC, Lim CS, Yu N et al. A multimethod assessment of treatment adherence for children with cystic fibrosis. *J Cyst Fibros.* 2006; 5:177-85.
4. Balfour L, Kowal J, Silverman A et al. A randomized controlled psycho-education intervention trial: improving psychological readiness for successful HIV medication adherence and reducing depression before initiating HAART. *AIDS Care.* 2006; 17:830-8.
5. Kruse W, Weber E. Dynamics of drug regimen compliance: its assessment by microprocessor-based monitoring. *Eur J Clin Pharmacol.* 1990; 38:561-5.
6. Luscher TF, Vetter H, Siegenthaler W et al. Compliance in hypertension: facts and concepts. *J Hypertens.* 1985; 3:3-9.
7. DiMatteo MR. Variations in patients' adherence to medical recommendations. A quantitative review of 50 years of research. *Med Care.* 2004; 42:200-9.
8. Cramer JA, Mattson RH, Prevey ML et al. How often is medication taken as prescribed? *JAMA.* 1989; 261:3273-7.
9. De Klerk E, van der Linden S. Compliance monitoring in NSAID drug therapy in ankylosing spondylitis, experiences with an electronic monitoring device. *Br J Rheumatol.* 1996; 35:60-5.
10. Simoni JM, Frick PA, Huang B. A longitudinal evaluation of a social support model of medication adherence among HIV-positive men and women on antiretroviral therapy. *Health Psychology.* 2006; 25:74-81.
11. DeGeest S, Borgermans L, Gemoets H et al. Incidence, determinants, and consequences of subclinical noncompliance with immunosuppressive therapy in renal transplant recipients. *Transplantation.* 1995; 59:340-7.
12. DiMatteo M, Giordani P, Lepper H et al. Patient adherence and medical treatment outcomes. *Med Care.* 2002; 40:794-811.
13. Simpson SH, Eurich DT, Majumdar SR et al. A meta-analysis of the association between adherence to drug therapy and mortality. *BMJ.* 2006; 333:15.
14. Berg JS, Dischler J, Wagner DJ et al. Medication compliance: a healthcare problem. *Ann Pharmacother.* 1993; 27:S1-24.
15. Sabate E. Adherence to long-term therapies: evidence for action. Geneva: World Health Organization; 2003:1-211.
16. Lutfey KE, Wishner WJ. Beyond "compliance" is "adherence." *Diabetes Care.* 1999; 22:635-9.
17. Velligan DI, Lam YF, Glahn DC et al. Defining and assessing adherence to oral antipsychotics: a review of the literature. *Schizophr Bull.* 2007; 32:724-42.
18. Bennett Johnson S. Methodological issues in diabetes research. *Diabetes Care.* 1992; 15:1658-67.
19. Stimson GV. Obeying doctor's orders: a view from the other side. *Soc Sci Med.* 1974; 8:97-104.
20. Chatterjee JS. From compliance to concordance in diabetes. *J Med Ethics.* 2006; 32:507-10.
21. Barber N. Should we consider noncompliance a medical error? *Qual Saf Health Care.* 2002; 11:81-4.
22. Huffman MH. Compliance, health outcomes, and partnering in PPS. Acknowledging the patient's agenda. *Home Healthc Nurs.* 2005; 23:23-8.
23. Schechter CB, Walker EA. Improving adherence to diabetes self-management recommendations. *Diabetes Spectrum.* 2002; 15:170-5.
24. Farmer KC. Methods for measuring and monitoring medication regimen adherence in clinical trials and clinical practice. *Clin Ther.* 1999; 21:1074-90.
25. Partridge AH, Avorn J, Wang PS et al. Adherence to therapy with oral antineoplastic agents. *J Natl Cancer Inst.* 2002; 94:652-61.
26. Hill J. Adherence with drug therapy in the rheumatic diseases. Part two: measuring and improving adherence. *Musculoskeletal Care.* 2005; 3:143-56.
27. Liu H, Golin CE, Miller LG et al. A comparison study of multiple measures of adherence to HIV protease inhibitors. *Ann Intern Med.* 2001; 134:968-77.

28. Butler JA, Peveler RC, Roderick P et al. Measuring compliance with drug regimens after renal transplantation: comparison of self-report and clinician rating with electronic monitoring. *Transplantation.* 2004; 77:786-9.
29. Miller LG, Hays RD. Measuring adherence to antiretroviral medications in clinical trials. *Hiv Clin Trials.* 2000; 1:36-46.
30. Smith SR, Wahed AS, Kelley SS et al. Assessing the validity of self-reported medication adherence in hepatitis C treatment. www.theannals.com/cgi/reprint/aph.1K024v1 (accessed 2007 Jun 11).
31. Byerly MJ, Thompson A, Carmody T et al. Validity of electronically monitored medication adherence and conventional adherence measures in schizophrenia. *Psychiatr Serv.* 2007; 58:844-7.
32. Rand CS, Wise RA. Measuring adherence to asthma medication regimens. *Am J Respir Crit Care Med.* 1994; 149:569-76.
33. Braam RL, van Uum SH, Russel FG et al. Bromide as a marker to measure adherence to drug therapy. *Eur J Clin Pharmacol.* 2006; 62:285-90.
34. Dunbar J. Adherence measures and their utility. *Control Clin Trials.* 1984; 5:515-21.
35. Hearnshaw H, Lindenmeyer A. What do we mean by adherence to treatment and advice for living with diabetes? A review of the literature on definitions and measurements. *Diabet Med.* 2005; 23:720-8.
36. Wagner GJ, Ghosh-Dastidar B. Electronic monitoring: adherence assessment or intervention? *HIV Clin Trials.* 2002; 3: 45-51.
37. Wagner GJ, Rabkin JG. Measuring medication adherence: are missed doses reported more accurately than perfect adherence? *AIDS Care.* 2000; 12:405-8.
38. Wendel CS, Mohler MJ, Kroesen K et al. Barriers to use of electronic adherence monitoring in an HIV clinic. *Ann Pharmacother.* 2001; 35:1010-5.
39. Lee J, Krusek J, Greene P et al. Assessing medication adherence by pill count and electronic monitoring in the African American Study of Kidney Disease and Hypertension (AASK) pilot study. *Am J Hypertens.* 1996; 9:719-25.
40. Choo PW, Rand CS, Inui TS et al. Validation of patient reports, automated pharmacy records, and pill counts with electronic monitoring of adherence to antihypertensive therapy. *Med Care.* 1999; 37:846-57.
41. Wetzels GE, Schouten JS, Dirksen CD et al. Electronic monitoring of adherence as a tool to improve blood pressure control. *Am J Hypertens.* 2007; 20:119-25.
42. Jasti S, Siega-Riz AM, Cogswell ME et al. Correction for errors in measuring adherence to prenatal multivitamin/mineral supplement use among low-income women. *J Nutr.* 2006; 136:479-83.
43. Schlenk EA, Dunbar-Jacob J, Engberg S. Medication non-adherence among older adults. *J Gerontol Nurs.* 2004; 30:33-43.
44. Lee JK, Grace KA. How should we measure medication adherence in clinical trials and practice? *J Am Pharm Assoc.* 2006; 46:420,423.
45. Kalichman SC, Amaral CM, Stearns H et al. Adherence to antiretroviral therapy assessed by unannounced pill counts conducted by telephone. *J Gen Intern Med.* 2007; 22:1003-6.
46. Grosset KA, Bone I, Reid JL et al. Measuring therapy adherence in Parkinson's disease: a comparison of methods. *J Neurol Neurosurg Psychiatry.* 2006; 77:249-51.
47. Hess LM, Raebel MA, Conner DA et al. Measurement of adherence in pharmacy administrative databases: a proposal for standard definitions and preferred measures. *Ann Pharmacother.* 2006; 40:1280-8.
48. Steiner JF, Prochazka AV. The assessment of refill compliance using pharmacy records: methods, validity, and applications. *J Clin Epidemiol.* 1997; 50:105-16.
49. Fairley CK, Permana A, Read TR. Long-term utility of measuring adherence by self-report compared with pharmacy records in a routine clinic setting. *HIV Med.* 2005; 6:366-9.
50. Prado JC Jr., Krupek E, Mion D Jr. Validity of four indirect methods to measure adherence in primary care hypertensives. *J Hum Hypertens.* 2007; 21:579-84.
51. Mannheimer SB, Mukherjee R, Hirschhorn LR et al. The CASE adherence index: a novel method for measuring adherence to antiretroviral therapy. *AIDS Care.* 2006; 18:853-61.
52. Chisholm MA. Enhancing patients' adherence to medication therapy. *Clin Transplant.* 2002; 16:30-8.
53. Heneghan CJ, Glasziou P, Perera R. Reminder packaging for improving adherence to self-administered long-term medications. *Cochrane Database Syst Rev.* 2006; 25:CD005025.
54. Iskedjian M, Einarson TR, MacKeigan LD et al. Relationship between daily dose frequency and adherence to antihypertensive pharmacotherapy: evidence from a meta-analysis. *Clin Ther.* 2002; 24:302-16.
55. Kripalani S, Yao X, Haynes RB. Interventions to enhance medication adherence in chronic medical conditions. *Arch Intern Med.* 2007; 167:540-50.
56. Gallefoss F, Bakke PS. How does patient education and self-management among asthmatics and patients with chronic pulmonary disease affect medication? *Am J Respir Crit Care Med.* 1999; 160:2000-5.
57. Friedman RH, Kazis LE, Jette A et al. A telecommunication system for monitoring and counseling patients with hypertension. Impact on medication adherence and blood pressure control. *Am J Hypertens.* 1996; 9:285-92.
58. Rigsby MO, Rosen MI, Beauvais JE et al. Cue-dose training with monetary reinforcement: pilot study of an antiretroviral adherence intervention. *J Gen Intern Med.* 2000; 15:841-7.
59. Dolder CR, Lacro JP, Leckband S et al. Interventions to improve antipsychotic medication adherence: review of recent literature. *J Clin Psychopharmacol.* 2003; 23:389-99.
60. Kirscht JP, Kirscht JL, Rosenstock IM. A test of interventions to increase adherence to hypertensive medical regimens. *Health Educ Q.* 1981; 8:261-72.
61. Broadhead H, Heckathorn DD, Altice FL et al. Increasing drug users' adherence to HIV treatment: results of a peer-driven intervention feasibility study. *Soc Sci Med.* 2002; 55:235-46.
62. Knobel H, Carmona A, López JL et al. Adherence to very active antiretroviral treatment: impact of individualized assessment. *Enferm Infecc Microbiol Clin.* 1999; 17:78-81.
63. Roter DL, Hall JA, Merisea R et al. Effectiveness of interventions to improve patient compliance: a meta-analysis. *Med Care.* 1998; 36:1138-61.
64. McDonald HP, Garg AX, Hayner RB. Interventions to enhance patient adherence to medication prescriptions. *JAMA.* 2002; 288:2868-79.
65. Haynes R, Yao X, Degani A et al. Interventions to enhance medication adherence. *Cochrane Database Syst Rev.* 2005; 19:CD000011.
66. Vergouwen AC, Bakker A, Katon WJ et al. Improving adherence to antidepressants: a systematic review of interventions. *J Clin Psychiatry.* 2003; 64:1415-20.
67. Van Eijken M, Tsang S, Wensing M et al. Interventions to improve medication compliance in older patients living in the community. *Drugs Aging.* 2003; 20:229-40.
68. Higgins N, Regan C. A systematic review of the effectiveness of interventions to help older people adhere to medication regimens. *Age Ageing.* 2004; 33:224-9.
69. Hamilton GA. Measuring adherence in a hypertension clinical trial. *Eur J Cardiovasc Nurs.* 2003; 2:219-28.
70. Haynes RB, McKibbon KA, Kanani R. Systematic reviews of randomized trials of interventions to assist patients to follow prescriptions for medications. *Lancet.* 1996; 348:383-6.
71. American Public Health Association. Adherence to HIV treatment regimens. Recommendations for best practices. 2004. www.apha.org/NR/rdonlyres/A030DDB1-02C8-4D80-923B-7EF6608D62F1/0/BestPracticesnew.pdf (accessed 2007 Jun 20).
72. American Psychological Association. Testimony of the American Psychological Association submitted to the U.S. Senate Committee on Labor and Human Resources on the subject of adherence to HIV/AIDS drug therapy. 1997. www.apa.org/ppo/issues/paids.html (accessed 2007 Jun 20).