

Patient Medication Adherence: Measures in Daily Practice

Beena Jimmy, Jimmy Jose

Received: 03 Feb 2011 / Accepted: 09 Apr 2011

© OMSB, 2011

Abstract

Adherence to therapies is a primary determinant of treatment success. Failure to adherence is a serious problem which not only affects the patient but also the health care system. Medication non adherence in patients leads to substantial worsening of disease, death and increased health care costs. A variety of factors are likely to affect adherence. Barriers to adherence could be addressed as patient, provider and health system factors, with interactions among them. Identifying specific barriers for each patient and adopting suitable techniques to overcome them will be necessary to improve medication adherence. Health care professionals such as physicians, pharmacists and nurses have significant role in their daily practice to improve patient medication adherence.

Medications adherence is defined by the World Health Organization as "the degree to which the person's behavior corresponds with the agreed recommendations from a health care provider."¹ Though the terms adherence and compliance are synonymously used adherence differs from compliance. Compliance is the extent to which a patient's behavior matches the prescriber's advice.² Compliance implies patient obedience to the physician's authority,³⁻⁵ whereas adherence signifies that the patient and physician collaborate to improve the patient's health by integrating the physician's medical opinion and the patient's lifestyle, values and preferences for care.⁶⁻⁸

There are several types of non adherence but most often the categorization is indisputable, and there is a degree of overlap. The first is known as primary non adherence, in which providers write prescription but the medication is never filled or initiated. This type is commonly called non fulfillment adherence.⁹

A second type of non adherence is called non persistence in which patients decide to stop taking a medication after starting it, without being advised by a health professional to do so. Non persistence is rarely intentional and happens when patients and providers miscommunication about therapeutic plans. Unintentional non adherence arises from capacity and resource limitations that prevent patients from implementing their

decisions to follow treatment recommendations (e.g. problems of accessing prescriptions, cost, competing demands etc) and sometimes involves individual constraints (e.g. poor inhaler technique, problems remembering doses etc). Whilst intentional non adherence arises from the beliefs, attitudes and expectations that influence patients' motivation to begin and persist with the treatment regimen.¹⁰

A third type of non adherence is known as non conforming, this type includes a variety of ways in which medication are not taken as prescribed, this behavior can range from skipping doses, to taking medications at incorrect times or at incorrect doses, to even taking more than prescribed.

Rate of adherence is usually reported as the percentage of the prescribed doses of the medication actually taken by the patient over a specified period.¹¹ The extent of non-adherence varies widely, and in different studies it has been recorded as low as 10 percent and as high as 92%.¹² Extensive review of the literature reveal that in developed countries adherence to therapies averages 50%.^{13,14} Approximately half of this non-adherence is intentional, whilst the remainder occurs because patients are either unaware that they are not taking medications as prescribed or the regimen is just too complex.¹⁵ Adherence rates are typically higher among patients with acute conditions, as compared against those with chronic conditions.¹⁶⁻¹⁸ Studies reveal that patients with chronic illnesses take only ~50% of medications prescribed for those conditions.^{18,19}

The consequence of non adherence is waste of medication, disease progression, reduced functional abilities, a lower quality of life, increased use of medical resources such as nursing homes, hospital visits and hospital admissions.^{19,20} Economic studies reveal that poor adherence to prescribed regimens can result in serious health consequence which is supported by various studies. For instance in a study conducted by Anon, it was shown that the risk of hospitalization was more than double in patients with diabetes mellitus, hypercholesterolemia, hypertension, or congestive heart failure who were non adherent to prescribed therapies compared with a general population.²¹ Studies conducted among Chronic Obstructive Pulmonary Disease patients have shown that poor adherence to drug therapy and disease management leads to emergency hospitalization.^{22,23}

Medication non adherence can have negative consequences not only for the patient but also for the provider, the physician, and even

Beena Jimmy, Jimmy Jose ✉
 Department of Pharmacy Practice
 School of Pharmacy, College of Pharmacy and Nursing,
 University of Nizwa, Birkat Al Mouz, Nizwa-616, Sultanate of Oman
 E-mail: jimmy_jose2001@yahoo.com, jimmy.jose@unizwa.edu.om

the medical researchers who are working to establish the value of the medication on the target population. The potential burden of medication non adherence outcomes on health care delivery makes it an important public health concern.^{13,24,25} Hence, helping people take their medicine appropriately would be a better achievement to avoid higher risk of severe relapses, antibiotic resistance, and preventable hospitalizations.

What influences medication adherence?

Non-adherence is a very common phenomenon in all patients with drug taking behavior. Complexity of adherence is the result of an interplay of a range of factors including patient views and attributes, illness characteristics, social contexts, access and service issues.^{13,26-28}

Barriers to the effective use of medicines specifically include poor provider-patient communication, inadequate knowledge about a drug and its use, not being convinced of the need for treatment, fear of adverse effects of the drug, long term drug regimens, complex regimens that require numerous medications with varying dosing schedules,²⁹ cost and access barriers.^{11,30,31}

It has also been observed that patient non adherence varies between and within individuals, as well as across time, recommended behaviors and diseases.³² Adherence to drug therapy varies with patient age group also. In children, adherence to drug therapy is affected due to their dependence on an adult care giver. The literature concerning adherence reports in elderly patients reports that compliance rates range roughly from 38%-57% with an average rate of less than 45%.^{33,34}

A major reason for non adherence is higher patient-physician discordance leading to decreased patient satisfaction.³⁵⁻⁴⁰ Studies report that 40-60% of patients could not correctly report what their physicians expected of them 10-80 minutes after they were provided with the information.^{41,42} Yet another study reported that over 60% of patients interviewed immediately after visiting their doctors misunderstood the directions regarding prescribed medications.⁴³

Non adherence can also occur when the medication regimen is complex which could include improper timing of drug administration, or administration of numerous medications at frequent or unusual times during the day. These patient behavioral factors may or may not be perceived by the physician and results in decreased therapeutic outcome. Most deviations in taking medication occur as omission of doses (rather than additions) or delays in the timing of doses.^{44,45}

Patients most often become non-compliant for chronic diseases, like hypertension, where they do not have any unpleasant symptoms even without strict compliance to medication regimen. Estimates of medication non adherence illustrates that the non adherence percentage is greatest when the patients are symptom-free.⁴³ Seventy seven percent of patients demonstrated high degrees of compliance with their medication regimen when the treatment was designed to cure a disease and only 63% of patients

complied when treatment was aimed at prevention. However, when medication was to be taken over a long period, compliance rates dropped dramatically to around 50% for either prevention or cure.³³

One major factor that influences adherence is the patient's ability to read and understand medication instructions. Patients with low literacy may have difficulty understanding instructions; this ultimately results in decreased adherence and poor medication management.⁴⁶ Gender, personality, and cultural factors may influence adherence-compliance rates. For instance, women may be better at adhering to their medication regimens than men. This may be particularly so for drugs those treat behavioral health conditions, such as antidepressant medications.⁴⁷ On the contrary some studies show that none of the common demographic factors such as age, marital status, living alone, sex, race, income, occupation, number of dependents, intelligence, level of education or type of personality have been consistently related to non compliance.⁴⁸

Methods to improve medication adherence

The effectiveness of a treatment depends on both the efficacy of a medication and patient adherence to the therapeutic regimen. Patients, health care providers, and health care systems, all have a role to improve medication adherence. A single method cannot improve medication adherence, instead a combination of various adherence techniques should be implemented to improve patient's adherence to their prescribed treatment. A systematic approach that could be instituted in improving medication adherence is as follows:

1) Level of prescribing:

- ✦ **Introduce a collaborative approach with the patient at the level of prescribing**
Whenever possible, involve patients in decision making regarding their medications so that they have a sense of ownership and they are partners in the treatment plan.
- ✦ **Simplify medication taking**
Use the most possible simplified regimen based on patient characteristics at the first level of drug use.

2) Communicating with the patient:

- ✦ **Explain key information when prescribing/ dispensing a medicine**
Address the key information about the drugs (what, why, when, how, and how long).
- ✦ **Inform the common side effects and those that patient should necessarily know** (Patients would be more worried and lead

to non adherence due to side effects that was not cautioned to them in advance by health care professionals)

♦ **Use medication adherence improving aids**

Provide medication calendars or schedules that specify the time to take medications, drug cards, medication charts or medicine related information sheets or specific packaging's such as pill boxes, 'unit-of-use' packaging, and special containers indicating the time of dose.

♦ **Provide behavioral support**

Collaborate with patient to incorporate the medication regimen into his/her daily regimen (essential in those on complex drug regimens, those having unintentional difficulties in adherence e.g. elderly)

3) During follow ups:

♦ **Schedule appropriate follow up**

Monitoring the medication adherence should also be a criteria while scheduling patient follow up

♦ **Assess adherence during consequent follow ups**

Measure adherence by various methods which may be dependent on patient as well as drug characteristics. Check the effectiveness of medication adherence aids used, if any. This should be done by physicians as well as pharmacists.

♦ **Identify difficulties and barriers related to adherence**

♦ **Address the problems**

♦ **Inform the patients accordingly how the problems have been addressed**

Patient involvement in decision making is essential in improving medication adherence. It is vital for health care providers to identify the underlying causes of patient non adherence to determine appropriate interventional strategy.

One of the major reasons that patients become non adherent is because they forget to take their medications. Results of a study conducted showed that 49.6% of patients mentioned forgetfulness as one of the major non-intentional reasons for non adherence.⁴⁹ Forgetfulness can be taken care by reminders i.e. through directly mailed letters, telephone, e-mails, text messages to cellular phones and alarms; even though it may not be practically possible in all work settings. Involving the patient's care givers would be an additional way of combating non adherence due to forgetfulness.

Medication non adherence may also occur because patients perceive it to be unnecessary or because of their fears and beliefs related to adverse effects of drugs. Hence, providing clear medication related information to patients is essential to improve adherence that includes addressing the key information of what, why, when, how and how long. Patient medication counseling can be supplemented by providing detailed written information about

medications. Succinct written instructions which include drug cards, medication charts or any written material in a plastic sheet or laminated sheet also helps in improving adherence especially for elderly patients who find it difficult to comprehend much of the information which is provided during medication counseling.

Patients' fears and concerns about adverse drug reactions can be alleviated by educating patients regarding common side effects of the drugs which they are taking, how to prevent an adverse drug reaction, if possible, and also convincing the patient of the need for treatment.

Complexity of drug regimen is found to negatively affect medication adherence. Modification will have to be made to medication regimens to reduce the frequency of administration, and/or reduce the number of different medications, and if applicable, to replace with combination products. This method often calls for patient's cooperation, thus highlights patient participation in disease management.

Patient-health care professional, especially patient-physician or patient-pharmacist communication is central to optimizing patient adherence.⁵⁰

Methods to measure adherence

Various methods have been reported and are in use to measure adherence. The methods available for measuring adherence can be broken down into direct and indirect methods of measurement.

Direct methods include direct observed therapy, measurement of the level of a drug or its metabolite in blood or urine and detection or measurement of a biological marker added to the drug formulation, in the blood. Direct approaches are one of the most accurate methods of measuring adherence but are expensive. Moreover, variations in metabolism and "white coat adherence" can give a false impression of adherence.¹¹

Indirect methods include patient questionnaires, patient self reports, pill counts, rates of prescription refills, assessment of patient's clinical response, electronic medication monitors, measurement of physiologic markers, as well as patient diaries.

Each method has its own advantages and disadvantages and no method is considered as the gold standard.^{51,52} The simplest way of measuring adherence is from the patient's self report.^{53,54}

Assessing children's adherence can be done by asking the help of a care giver (school nurse or teacher). Among the various methods questioning the patient, patient diaries and assessment of clinical response are all methods that are relatively easy to use, but questioning the patient can be susceptible to misrepresentation and tends to result in the health care provider overestimating the patient's adherence.

Pill counts i.e. counting the number of pills that remain in the patient's medication bottles or vials is a common method to measure adherence. Though this method is simple, it has many disadvantages that the patients can switch medicines between bottles and may even discard pills before hospital visits in order to appear to be following the regimen.⁵⁵⁻⁵⁷ Hence, this is not an

ideal measure of adherence. Furthermore, this method does not provide information on dose timing and drug holidays, where the medication has to be omitted on 3 or more sequential days, both of which help to determine clinical outcomes.

Rates of refilling prescriptions are an accurate measure of overall adherence in a closed pharmacy system (health maintenance organization countries with universal drug coverage) since refills are measured at several points in that time.⁵⁸⁻⁶⁰

Electronic monitors capable of recording and stamping the time of opening bottles, dispensing drops (eye drops) or activating canister (metered dose inhaler for asthma) can also give a measure of adherence. The disadvantage with this method is that the measure of adherence is not accurate as the patients may open the container and not take the medication, take the wrong amount of medication or take multiple doses out of the container at the same time (or place multiple doses in another container).

Conclusion

Patient medication non adherence is a major medical problem globally. There are many inter related reasons for the same. Though patient education is the key to improving compliance, use of compliance aids, proper motivation and support is also shown to increase medication adherence. Health care professionals should identify practically possible strategies to improve medication adherence within the limits of their practice eventually enhancing therapeutic outcome. It should be a multidisciplinary approach that needs to be carried out with the support of all those who are involved in medication use.

Acknowledgements

The authors reported no conflict of interest and no funding was received for this work.

References

- Dobbels F, Van Damme-Lombaert R, Vanhaecke J, De Geest S. Growing pains: non-adherence with the immunosuppressive regimen in adolescent transplant recipients. *Pediatr Transplant* 2005 Jun;9(3):381-390.
- Horne R. Compliance, adherence, and concordance: implications for asthma treatment. *Chest* 2006 Jul;130(1 Suppl):65S-72S.
- Agras WS. Understanding compliance with the medical regimen: the scope of the problem and a theoretical perspective. *Arthritis Care Res* 1989 Sep;2(3):S2-S7.
- Noble LM. Doctor-patient communication and adherence to treatment. In: Myers LB, Midence K, eds. *Adherence to treatment in medical conditions*. Harwood Academic Publishers, 1998.p.51-82.
- Carr AJ, Donovan JL. Why doctors and patients disagree. *Br J Rheumatol* 1998 Jan;37(1):1-4.
- Spiro H. Compliance, adherence, and hope. *J Clin Gastroenterol* 2001 Jan;32(1):5.
- Di Matteo MR. Adherence to treatment. In: Feldman MD, Christensen JF, eds. *Behavioral medicine in primary care. A practical guide*. Stamford, Connecticut: Appleton and Lange, 1997.p.136-140.
- Roter DL, Hall JA, Merisca R, Nordstrom B, Cretin D, Svarstad B. Effectiveness of interventions to improve patient compliance: a meta-analysis. *Med Care* 1998 Aug;36(8):1138-1161.
- Gellad WF, Grenard J, McGlynn EA. A review of barriers to medication adherence: A frame work for driving policy options. Available at http://www.rand.org/pubs/technical_reports/2009/RAND_TR765.pdf. Accessed on June 10, 2010.
- Horne R, Weinman J, Barber N, Elliott RA, Morgan M. *Concordance, adherence and compliance in medicine taking: a conceptual map and research priorities*. London, National Co-ordinating Centre for NHS Service Delivery and Organisation NCCSDO; 2005.
- Osterberg L, Blaschke T. Adherence to medication. *N Engl J Med* 2005 Aug;353(5):487-497.
- Grahame-Smith DG, Aronson JK. *Oxford Textbook of Clinical Pharmacology and Drug Therapy*. 3rd Edition. Oxford University Press, USA. 2002.
- World Health Organization. 2003. Adherence to long term therapies: evidence for action [online]. Available at http://www.who.int/chronic_conditions/en/adherence_report.pdf. Accessed on June 06, 2010.
- Carter S, Taylor D, Levenson R. 2005. A question of choice- compliance in medicine taking. From compliance to concordance. 3rd ed. London: Medicines Partnership. Available at: www.medicines-partnership.org/research-evidence/major-reviews/a-question-of-choice. Accessed on June 10, 2010.
- Ley P. *Communicating with patients: improving communication, satisfaction and compliance*. Cheltenham, Stanley Thornes Pub Ltd. 1997.
- Jackevicius CA, Mamdani M, Tu JV. Adherence with statin therapy in elderly patients with and without acute coronary syndromes. *JAMA* 2002 Jul;288(4):462-467.
- Cramer J, Rosenheck R, Kirk G, Krol W, Krystal J; VA Naltrexone Study Group 425. Medication compliance feedback and monitoring in a clinical trial: predictors and outcomes. *Value Health* 2003 Sep-Oct;6(5):566-573.
- Haynes RB, McDonald HP, Garg AX. Helping patients follow prescribed treatment: clinical applications. *JAMA* 2002 Dec;288(22):2880-2883.
- Col N, Fanale JE, Kronholm P. The role of medication noncompliance and adverse drug reactions in hospitalizations of the elderly. *Arch Intern Med* 1990 Apr;150(4):841-845.
- Sullivan S, Kreling D, Hazlet T. Noncompliance with medication regimens and subsequent hospitalizations: A literature analysis and cost of hospitalization estimate. *J Res Pharmaceut Econ* 1990;2:19-33.
- Anon. Poor medication adherence increases healthcare costs. *PharmacoEconomics and Outcomes News*. 2005;480:5.
- Fuso L, Incalzi RA, Pistelli R, Muzzolon R, Valente S, Pagliari G, et al. Predicting mortality of patients hospitalized for acutely exacerbated chronic obstructive pulmonary disease. *Am J Med* 1995 Mar;98(3):272-277.
- Garcia-Aymerich J, Barreiro E, Ferrero E, Marrades RM, Morera J, Antó JM. Patients hospitalized for COPD have a high prevalence of modifiable risk factors for exacerbation (EFRAM study). *Eur Respir J* 2000 Dec;16(6):1037-1042.
- Sokol MC, McGuigan KA, Verbrugge RR, Epstein RS. Impact of medication adherence on hospitalization risk and healthcare cost. *Med Care* 2005 Jun;43(6):521-530.
- National Council on Patient Information and Education. *Enhancing prescription medicine adherence: a national action plan*. August 2007. Available at: http://www.talkaboutrx.org/documents/enhancing_prescription_medicine_adherence.pdf Accessed on June 5, 2010.
- Haynes RB, McKibbon KA, Kanani R. Systematic review of randomised trials of interventions to assist patients to follow prescriptions for medications. *Lancet* 1996 Aug;348(9024):383-386.
- Haynes RB, Devereaux PJ, Guyatt GH. Physicians' and patients' choices in evidence based practice. *BMJ* 2002 Jun;324(7350):1350.
- Cox K, Stevenson F, Britten N, Dundar Y. A Systematic Review of Communication between Patients and Health Providers about Medicine-taking and Prescribing. GKT Concordance Unit, Kings College, 2003.
- Leupkar RV. Patient adherence: A "risk factor" for cardiovascular disease. The Framington Study. *JAMA* 1971;215:1617-1625.
- Tarn DM, Heritage J, Paterniti DA, Hays RD, Kravitz RL, Wenger NS. Physician communication when prescribing new medications. *Arch Intern Med* 2006 Sep;166(17):1855-1862.

31. Rodondi N, Peng T, Karter AJ, Bauer DC, Vittinghoff E, Tang S, et al. Therapy modifications in response to poorly controlled hypertension, dyslipidemia, and diabetes mellitus. *Ann Intern Med* 2006 Apr;144(7):475-484.
32. Sewitch MJ, Dobkin PL, Bernatsky S, Baron M, Starr M, Cohen M, et al. Medication non-adherence in women with fibromyalgia. *Rheumatology (Oxford)* 2004 May;43(5):648-654.
33. Sackett DL, Snow JC. The magnitude of compliance and non compliance. IN Haynes NRB, Taylor DW, Sackett DL, eds. *Compliance in Health Care*. Baltimore: John Hopkins University Press; 1979:11-22.
34. Dunbar J. Issues in assessment. In: Cohen NSJ. ed. *New directions in Patient Compliance*. New York: Lexington Books, 1979.p.41-57.
35. Haynes RB, Taylor DW, Snow JC, Sackett DL. Annotated and indexed bibliography on compliance with therapeutic and preventive regimens. In: Haynes RB, Taylor DC, Sackett DL, eds. *Compliance in health care*. Baltimore: Johns Hopkins University Press, 1979.p.337-474.
36. Francis V, Korsch BM, Morris MJ. Gaps in doctor-patient communication. Patients' response to medical advice. *N Engl J Med* 1969 Mar;280(10):535-540.
37. Sherbourne CD, Hays RD, Ordway L, DiMatteo MR, Kravitz RL. Antecedents of adherence to medical recommendations: results from the Medical Outcomes Study. *J Behav Med* 1992 Oct;15(5):447-468.
38. Würtemberger G, Hütter BO. Health-related quality of life, psychological adjustment and compliance to treatment in patients on domiciliary liquid oxygen. *Monaldi Arch Chest Dis* 2000 Jun;55(3):216-224.
39. Oermann CM, Swank PR, Sockrider MM. Validation of an instrument measuring patient satisfaction with chest physiotherapy techniques in cystic fibrosis. *Chest* 2000 Jul;118(1):92-97.
40. Weingarten SR, Stone E, Green A, Pelter M, Nessim S, Huang H, et al. A study of patient satisfaction and adherence to preventive care practice guidelines. *Am J Med* 1995 Dec;99(6):590-596.
41. Svarstad B. Physician-patient communication and patient conformity with medical advice. In: Mechanic D, ed. *The Growth of Bureaucratic Medicine*. New York: John Wiley & Sons Inc; 1976.
42. Ley PN, Spellman MS. *Communication with the Patient*. London: Staples Press; 1967.
43. Meichenbaum D, Turk DC. *Facilitating Treatment Adherence: A Practitioner's Guidebook*. New York: Plenum Publishing Corp; 1987.
44. Burnier M. Long-term compliance with antihypertensive therapy: another facet of chronotherapeutics in hypertension. *Blood Press Monit* 2000;5(Suppl 1):S31-S34.
45. Paes AH, Bakker A, Soe-Agnie CJ. Impact of dosage frequency on patient compliance. *Diabetes Care* 1997 Oct;20(10):1512-1517.
46. Praska JL, Kripalani S, Seright AL, Jacobson TA. Identifying and assisting low-literacy patients with medication use: a survey of community pharmacies. *Ann Pharmacother* 2005 Sep;39(9):1441-1445.
47. Ward A, Morgan W. Adherence patterns of health in men and women enrolled in an adult exercise program. *J Cardiac Rehabil*. 1984;4:143-152.
48. Ley P. Doctor-patient communication: some quantitative estimates of the role of cognitive factors in non-compliance. *J Hypertens Suppl* 1985 Apr;3(1):S51-S55.
49. Adisa R, Alutundu MB, Fakeye TO. Factors contributing to nonadherence to oral hypoglycemic medications among ambulatory type 2 diabetes patients in Southwestern Nigeria. *Pharmacy Practice* 2009;7:163-169. internet.
50. Golin CE, DiMatteo MR, Gelberg L. The role of patient participation in the doctor visit. Implications for adherence to diabetes care. *Diabetes Care* 1996 Oct;19(10):1153-1164.
51. Wagner JH, Justice AC, Chesney M, Sinclair G, Weissman S, Rodriguez-Barradas M; VACS 3 Project Team. Patient- and provider-reported adherence: toward a clinically useful approach to measuring antiretroviral adherence. *J Clin Epidemiol* 2001 Dec;54(Suppl 1):S91-S98.
52. Alcoba M, Cuevas MJ, Perez-Simon MR, Mostaza JL, Ortega L, Ortiz de Urbina J, et al; HAART Adherence Working Group for the Province of Leon, Spain. Assessment of adherence to triple antiretroviral treatment including indinavir: role of the determination of plasma levels of indinavir. *J Acquir Immune Defic Syndr* 2003 Jun;33(2):253-258.
53. Walsh JC, Mandalia S, Gazzard BG. Responses to a 1 month self-report on adherence to antiretroviral therapy are consistent with electronic data and virological treatment outcome. *AIDS* 2002 Jan;16(2):269-277.
54. Haynes RB, Taylor DW, Sackett DL, Gibson ES, Bernholz CD, Mukherjee J. Can simple clinical measurements detect patient noncompliance? *Hypertension* 1980 Nov-Dec;2(6):757-764.
55. Rudd P, Byyny RL, Zachary V, LoVerde ME, Mitchell WD, Titus C, et al. Pill count measures of compliance in a drug trial: variability and suitability. *Am J Hypertens* 1988 Jul;1(3 Pt 1):309-312.
56. Pullar T, Kumar S, Tindall H, Feely M. Time to stop counting the tablets? *Clin Pharmacol Ther* 1989 Aug;46(2):163-168.
57. Cramer JA, Mattson RH, Prevey ML, Scheyer RD, Ouellette VL. How often is medication taken as prescribed? A novel assessment technique. *JAMA* 1989 Jun;261(22):3273-3277.
58. Steiner JF, Prochazka AV. The assessment of refill compliance using pharmacy records: methods, validity, and applications. *J Clin Epidemiol* 1997 Jan;50(1):105-116.
59. Lau HS, de Boer A, Beuning KS, Porsius A. Validation of pharmacy records in drug exposure assessment. *J Clin Epidemiol* 1997 May;50(5):619-625.
60. Christensen DB, Williams B, Goldberg HI, Martin DP, Engelberg R, LoGerfo JP. Assessing compliance to antihypertensive medications using computer-based pharmacy records. *Med Care* 1997 Nov;35(11):1164-1170.