Compliance with treatment in hypertension

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Submitted: 12 November 2008
Accepted: 29 November 2009

Arch Med Sci 2009; 5, 2A: S 359–S 365

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Abstract

Among the several factors responsible for suboptimal control rates in hypertension, patient adherence, i.e. patient compliance, and persistence have been identified as two of the main causes. Patient compliance, or synonymously, patient adherence, is the extent to which a person's behavior – taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a healthcare provider, whereas medication persistence represents the accumulation of time from initiation to discontinuation of therapy. Persistence is measured in terms of time, whereas medication adherence is reported in terms of the percentage of prescribed doses taken per defined period of time. When monitored electronically, patients have been shown to be fully compliant (50-60% of total), i.e. those who follow at least 80% of the prescribed regimen; partially compliant (30-40% of total), i.e. patients with periods of poor adherence or "drug holidays"; or non-compliant (5-10% of total), i.e. those with levels of compliance less than 80% of the prescribed treatment. Compliance is a multidimensional phenomenon determined by the interplay of five sets of factors: patient related, condition related, therapy related, health system related, and social/economic related. Compliance is assessed by electronic monitoring devices, pharmacy refill rates, pill counts, and pharmacological methods. Compliance can be improved by patient education, simplifying the dosage regimen, selecting drugs that are well tolerated, patient self-monitoring, involving family members, electronic pill cap monitors, "alarm clocks", computer based reminder systems, and remote home monitoring systems.

Key words: compliance, persistence, adherence.

Introduction

Despite the well-known beneficial effects of lowering high blood pressure, an important contributor to overall cardiovascular risk, the control of hypertension is far from being optimal, not only in the developing world but also in the developed countries [1-3]. Among the several factors responsible for suboptimal control rates in hypertension, patient adherence, i.e. patient compliance, and persistence have been identified as two of the main causes [4-6]. It is not enough that patients take their medications regularly; they must also continue to do so in the long term in chronic diseases such as hypertension to avoid cardiovascular morbidity and mortality.

Definition and epidemiology

Described by the World Health Report 2003 as "the single most important modifiable factor that compromises treatment outcome across diseases", patient compliance, or synonymously, patient adherence, is the extent to which a person's behavior – taking medication, following a diet, and/or executing lifestyle changes – corresponds with agreed recommendations from a healthcare provider, whereas medication persistence represents the accumulation of time from initiation to discontinuation of therapy (Figure 1) [7, 8]. The WHO Report emphasized the need to differentiate adherence from compliance, the main difference being that adherence requires the patient's agreement to the recommendations, while most authors believe the two terms should be used synonymously [6, 7, 9].

Persistence is measured in terms of time, whereas medication adherence is reported in terms of the percentage of prescribed doses taken per defined period of time. Medication adherence is a dynamic parameter that varies over time. It has been demonstrated that medication-taking behaviour often improves during a scheduled clinic visit and presents a decrease immediately after the physician's appointment, named as "white coat compliance pattern" [10].

When monitored electronically, patients have been shown to be fully compliant (50-60% of total), i.e. those who follow at least 80% of the prescribed regimen; partially compliant (30-40% of total), i.e. patients with periods of poor adherence or "drug holidays"; or non-compliant (5-10% of total), i.e. those with levels of compliance less than 80% of the prescribed treatment [11, 12].

It is estimated that adherence rates are approximately 50%, with a great variation ranging between 0 and 100% [13]. In a quantitative review, there was reported a mean adherence rate of 76.6% to medical recommendations for cardiovascular disease [14]. As demonstrated in this review and other studies, adherence not only to medical treatment but also to lifestyle advice is inadequate [15]. While physicians claim that 70% of their patients adhere to treatment, 81% of patients claim they always take their medication [16].

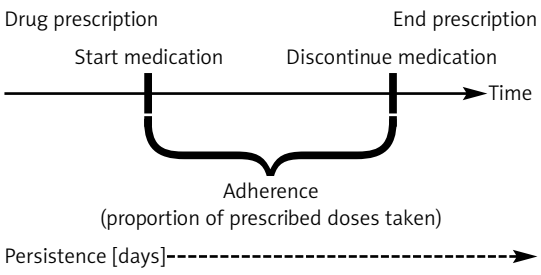

Figure 1. The patient compliance (adherence)

Persistence with antihypertensive therapy is also far from being optimal. It has been demonstrated that persistence decreased in the first 6 months after the start of the antihypertensive treatment and declined in the next 4 years [17]. Compliance and persistence rates decrease substantially after 12 months. Throughout 10 years of follow-up, more men than women used antihypertensive therapy continuously; however, for both men and women, persistence decreased over time.

Causes of non-compliance:

- Compliance is a multidimensional phenomenon determined by the interplay of five sets of factors:
  - patient related,
  - condition related,
  - therapy related,
  - health system related,
  - social/economic related.

Patient related factors associated with poor compliance

Among patient characteristics that may influence adherence, demographic factors such as age, gender and race may play a role. Although the role of age is controversial, elderly people being more adherent than younger ones in some studies and less compliant in others, age is not an independent predictor of compliance with treatment [13, 18, 19]. In general, younger patients have a tendency to stop their medication due to the feeling of well-being, whereas older patients discontinue due to adverse effects [20]. Although women have been found to be less adherent than men in some studies, they are generally more adherent to their antihypertensive treatment [18-20]. Evidence has suggested that depression may reduce medication adherence and is a modifiable factor [19]. Patient's motivation and physician-patient relationship, namely an open and trusting partnership, are important determinants of patient compliance.

Condition related

Being asymptomatic for a considerable time and due to the fact that patients are unaware of the long-term complications of hypertension, there exists a risk for hypertensive patients to be poor compliers. Rate of progression or severity of the disease and availability of the drugs are also among the condition related factors [7].

Social/economic related

Lower socioeconomic status, i.e. cost of treatment, is a big consideration – particularly relevant in the developing world [7]. Level of education and unemployment are also important risk factors for poor adherence [7].

Health system related

Health system related issues, such as delivery of care, financing and providing proper pharmaceutical management also play an important role in the promotion of adherence [7].

Therapy related

Drug intolerability or side effects, treatment turbulence or frequent changes in antihypertensive medication, initial choice of drug therapy, complexity of the treatment regimen, frequency of daily dosage, number of concurrent medications either for accompanying cardiovascular diseases or else high costs of treatment effects are therapy-related factors which have a great influence on poor adherence [8, 17, 21].

Side effects associated with antihypertensive drugs are important particularly among younger patients and elderly hypertensives under multidrug treatment [8, 20, 22]. The solution to this important problem could be the prescription of antihypertensive drugs with favourable tolerability profile which are well tolerated or a fixed-combination treatment strategy as advocated by most hypertension guidelines to achieve target blood pressure values [23]. One other advantage of fixed-dose combination treatment would be the simplification of treatment, a crucial factor to improve compliance and persistence [24]. Data from several analyses have shown that patients on antihypertensive treatment with favourable tolerability and once daily dosing had greater medication persistence rates at 1 year than those treated with other classes of antihypertensive agents [19, 24].

Impact on blood pressure control and cardiovascular outcomes

Compliance with antihypertensive therapy improves BP control (<140/90 mm Hg), thus preventing the risk of adverse cardiovascular outcomes. It has been well established that patients whose hypertension is uncontrolled are more likely to have target organ damage and higher long-term cardiovascular risk when compared to those with good control of blood pressure [25].

Economic consequences of poor compliance with antihypertensive therapy

Discontinuing or switching antihypertensive therapy is associated with a significant cost burden. A retrospective analysis has demonstrated that poor adherence causes an average loss of 3.5 work days per year [26]. It has also been shown that poorly compliant patients incurred an additional annual cost of $873 per patient [27].

Non-compliance and poor persistence are significant burdens in the treatment of hypertension that lead to:

- suboptimal BP control,
- suboptimal CV protection,
- high economic burden.

Improved adherence can lead to higher rates of treatment success, fewer diagnostic procedures, fewer hospitalizations, and lower mortality rates.

Assessment of compliance

In recent years, research efforts have focused on the use and evaluation of methods for measuring adherence. There are many methods that one can use to determine whether an individual has been taking the prescribed pills as directed. Table I compares various feasible methods used to measure adherence to antihypertensive medication.

Self report

Research has shown that the simple, direct question, "Have you missed any pills in the last week?" has a 50% specificity and 87% sensitivity for adherence at least over the week [28]. More elaborate questioning systems and several multi-item questionnaires have been developed with the explicit aim of ascertaining antihypertensive medication adherence [12]. In an effort to facilitate the identification of barriers to adequate compliance, Morisky et al. [29] developed a multi-item scale to assess patient adherence to blood pressure medication regimens in the outpatient setting. For several of these self-report tools, high reliability and validity have been reported [30, 12].

A recent study [31] showed that results from a brief self-report tool were associated with timing compliance as a measure of adherence obtained through electronic monitoring (MEMS) in patients taking blood pressure lowering medication. Level 1 of the self report was described as "I always take all of my tablets at the same time of day" and level 6 as "I take hardly any of my blood pressure tablets". A drop to a lower level (that is, from level 1 to level 2 or from level 2 to levels 3-6 combined) was associated with a decrease in timing compliance of 5 percentage points. The self-report tool appears to perform well irrespective of the number of drugs taken. However, the self report has some relevant limitations. It has been shown that self reporting frequently underestimates rates of adherence [32]. Measurement of compliance by questioning the patient leads to over-estimation of the number of tablets taken when compared to an electronic pill counting device [33].

Electronic monitoring devices

Electronic monitoring is recognised as the gold standard of measurement of compliance. The electronic pill counter or MEMS (Medication Event Monitoring System) may be considered as the best

Table I. Feasible methods of measuring medication adherence in outpatient clinical settings (adapted from Krousel-Wood, ref. [12])

	Source of information	Advantages	Disadvantages
Self-reports	Patient completion of survey	• Simple • Economical • Information on social, situational, behavioural factors that affect adherence	• Recall bias • May overestimate compliance • May elicit socially acceptable responses
Electronic adherence monitoring [e.g., Medication Event Monitoring System (MEMS)]	Patient use of system	• Provides information on daily intake and dosing • Provides information enabling analysis of long-term patterns • Potentially captures white-coat adherence	• Medication consumption assumed but not confirmed • Expensive • Can be intrusive (patient must carry it) • Device can fail • Inaccurate if subject to interference by patient or other devices
Pharmacy refill rates	Administrative database	• Objective • Captures amount and frequency of medications obtained by patient • Reflects patient's decision to remain on drug • Provides information on average adherence over time	• Medication consumption assumed but not confirmed • Incomplete data if patient orders by mail, uses several pharmacies, receives free samples • Lag time for data availability
Pill counts	Patient brings medications remaining for time period	• Objective	• Medication consumption assumed but not confirmed • Reliant on patient to bring in pills • May overestimate adherence (e.g., pill dumping/sharing)
Pharmacological methods	Determination of serum and urinary concentrations of drugs	• Objective, higher sensitivity and specificity	• Difficult to use in standard practice

existing system for measurement of compliance [34]. This consists of a standard pill box which has a microprocessor which can register the date and hour of the opening of the container. This allows us to monitor the length of time between doses of drug and the change in compliance with time. There are however several inconveniences such as cost and correlation between opening of the drug container and compliance.

Electronic devices to monitor medication adherence are reported to be highly reliable. Although MEMS has been reported to be acceptable to patients and effective in identifying "white coat compliers" in research studies, limitations to its use in the outpatient setting include cost, device failure, and potential for patients to manipulate the device, resulting in inaccurate measurements [12].

Pharmacy refill rates

Pharmacy refill rates have been used as measures of medication adherence in several studies. It is very important to assess pharmacy records, which are usually highly computerized and lend themselves well to determining when and how many pills were received by a particular patient. Choo et al. [35] reported that pharmacy dispensing records and pill count were each highly correlated with dose-count adherence assessed by electronic monitoring.

Pharmacy refill rate reflects patients' decision to continue with therapy without the influences of pharmaceutical company promotion and sampling to physicians. An important limitation to the use of refill rates in the outpatient setting is the lag time for data availability, which can take 2-6 months depending on country and prescription habits.

Pill counts

In daily practice, a physician can easily assess a patient's adherence by counting the pills remaining in a pill bottle, and comparing this number with the expected consumption. Pill counting systems have also been successfully used. A recent study reported significant correlations between pill count and compliance as measured by MEMS in a clinical study to enhance patient adherence [36]. This method is objective and straightforward in the outpatient setting.

However, there are several limitations of this method. Measurement of compliance by counting remaining pills leads to overestimation of the number of tablets taken when compared to an electronic pill counting device [33]. Problems such as pill dumping or pill sharing may also overestimate adherence.

Pharmacological methods

Pharmacological measures determine serum and urinary concentrations of drugs or use biological markers integrated into the tablets. Pharmacological methods give percentages of non-compliance which are higher than found by other measures. They are generally thought to have a higher sensitivity and specificity but remain difficult to use in standard practice [33].

Measuring drug metabolites in blood is fraught with error because patients can take the medication only when they are due to be tested [32]. This is known as "white coat adherence". So, even pharmacological methods are not always precise in assessment of compliance with antihypertensive treatment.

Assessment using ancillary properties of drugs

Many physicians are accustomed to using the ancillary pharmacological properties of antihypertensive drugs to estimate adherence to medications. Long-term administration of thiazide-type diuretics often results in increased serum concentrations of uric acid, and this can be used as a surrogate marker for adherence to this important type of antihypertensive drug. α-Blockers and β-blockers are particularly good examples, since they routinely cause an orthostatic BP drop, and at least relative bradycardia, respectively [28].

Methods of improving compliance

A key factor contributing to poor blood pressure control is suboptimal adherence to prescribed therapy. Despite numerous studies conducted over the last 50 years to identify the best method for increasing patient compliance, no single intervention has emerged as superior to the others [12].

In clinical practice, treatment compliance may be as low as 50%, which is much lower than that generally observed in the clinical trial setting, where tighter controls and monitoring reduce non-compliance [5, 37]. Furthermore, in addition to issues regarding compliance with antihypertensive therapy, long-term persistence (remaining on therapy) is also problematic.

Methods of improving adherence to antihypertensive treatment are shown in Table II.

Patient education

A study in 1997 by Bailey et al. [38] showed that 78% wished to know the effects of irregular treatment compliance and 90% wished to know of side effects, 60% wanted to know about possible drug interactions and 82% the causes of arterial hypertension. Providing both written and oral instructions and patient education materials about the medications is recommended.

A recent study has demonstrated that there was a 17.5% absolute increase in blood pressure control in the patient education group [39]. Another study has shown that improvement in the management of hypertension in the "Manage it well!" programme is the consequence of better education [40].

Simplify the dosage regimen

Steps should be taken (if possible) to simplify the regimen: once daily pills that can be taken without regard to meals are generally favoured. Reducing the number of pills (by using combination pills) can be useful. Eisen et al. [34] showed that compliance went from 83.6% for a single daily dose to 59% for a three-times-a-day dosage. The legibility of the prescription is also very important since this

Table II. Methods of improving adherence to medications [5, 28]

- Provide both verbal and written instructions and patient education materials
- Motivate patients to ensure that they adhere to treatment
- Simplify the dosage regimen (minimizing frequency of administration, once-a-day dosing if possible)
- Minimize the number of pills
- Select drugs that are well tolerated
- Be sensitive to cost of pills (attempt to minimize out-of-pocket costs)
- Co-operate with pharmacists and nurses
- Use reminders (manual and computer-based)
- Cue medication consumption with activities of daily living (e.g., caring for teeth)
- Patient self-monitoring
- Involve family and significant others
- Pill organisers
- Electronic pill cap monitors, "alarm clocks"
- Computer based reminder systems, remote home monitoring systems

is generally the only written information given to the patient explaining how he or she should take the treatment.

In a recent meta-analysis of 8 studies and 11,485 observations, Iskedjian et al. [41] reported that the average adherence for once-daily dosing was significantly higher than for multiple daily dosing. Reducing the number of daily doses appears to be effective in increasing adherence to blood pressure-lowering medication and should be tried as a first-line strategy.

Select drugs that are well tolerated

Undesirable effects of treatment are major obstacles to good compliance. The more frequent and handicapping they are, the less motivated the patient.

Several studies show that the level of compliance differs according to the therapeutic class of the antihypertensive. ARBs have the best level of compliance followed by converting enzyme inhibitors, calcium blockers, β-blockers and diuretics [5].

Be sensitive to cost of pills

A potential barrier to medication adherence is the high cost. Attempting to minimize the out-of-pocket costs for pills is useful in two ways. It makes the important point to the patient that the prescriber is trying to save the patient money, and it helps to stabilise resources spent on healthcare.

Generic substitution is an important opportunity to reduce the costs of pharmaceutical care. However, pharmacists and physicians often find that patients and brand-name manufacturers have doubts about the equivalence of the substituted drug. This may be reflected by decreased adherence to therapy. However, a recent study demonstrated that generic substitution of antihypertensive drugs does not lead to lower adherence or more discontinuation and cardiovascular disease-related hospitalizations compared with brand-name therapy [42].

Pill organisers

Segmented pill containers (e.g., a container with four columns and 7 rows, into which are dispensed the appropriate number of pills for each morning, noon, dinner and night-time for the week) have improved adherence.

Patient self-monitoring

The patient can be asked to measure his or her own BP. Patient self-monitoring often has a beneficial effect on adherence, especially in hypertension. Home BP monitors typically reveal higher BP after patients have omitted their medications for a few doses. Several studies have shown that compliance has significantly increased with self-measurements and a large proportion of the patients who were not compliant at the beginning of the study became so [33].

Involving family members and significant others

Involving family members and significant others in BP measurements and pill taking generally improves adherence, although some patients do not appreciate the decrease in autonomy when others become partially responsible for their BP [28].

Recently, depression was added to the list of factors associated with non-compliance with antihypertensive medications, and family members are important in this aspect [19].

Pharmacists and nurses

Other health care professionals such as pharmacists or nurses have a role to play in compliance as they have special contact with the patient and often the patient confides in them [43, 44].

Electronic pill cap monitors, "alarm clocks"

Electronic pill cap monitors can be rented to check the adherence of patients. Adherence to therapy may be increased by follow-up reminders or telephone contacts. Several companies now make "alarm clocks" that ring when pill taking is scheduled, and do not stop ringing until the pill bottle is opened. For longer term drug therapies, several methods of improving adherence have been proven effective, but have not become popular because of their cost.

Computer based reminder systems, remote home monitoring systems

Computer based reminder systems are effective, but expensive if the person does not already have a computer. Hypertensive patient remote home monitoring systems (e.g. Docobo) can significantly increase treatment compliance [45].

References

1. Turnbull F; Blood Pressure Lowering Treatment Trialists' Collaboration. Effects of different blood pressure lowering regimens on major cardiovascular events: results of prospectively – designed overviews of randomised trial. Lancet 2003; 362: 1527-35.
2. Collins R, MacMahon S. Blood pressure, antihypertensive treatment and the risk of stroke and coronary heart disease. Br Med Bull 1994; 50: 272-98.
3. Erdine S, Aran SN. Current status of hypertension control around the world. Clin Exp Hypertens 2004; 26: 731-8.
4. Setaro JF, Black HR. Refractory hypertension. N Engl J Med 1992; 327: 543-7.

5. Heagerty A. Optimizing hypertension management in clinical practice. J Hum Hypertens 2006; 20: 841-9.
6. Chobanian AV, Bakris GL, Black HR, et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. J Am Med Assoc 2003; 289: 2560-72.
7. World Health Organization: Adherence to long-term therapies. Evidence for action. Geneva: World Health Organization, 2003. Available at: http://www.who.int/chronic_conditions/adherencereport/en/index.html.
8. Burnier M. Medication adherence and persistence as cornerstone of effective antihypertensive therapy. Am J Hypertens 2006; 19: 1190-6.
9. McDonald HP, Garg AX, Haynes RB. Interventions to enhance patient adherence to medication prescriptions: scientific review. JAMA 2002; 288: 2868-79.
10. Cramer JA, Scheyer RD, Mattson RH. Compliance declines between clinic visits. Arch Intern Med 1990; 150: 1509-10.
11. Rudd P. Compliance with antihypertensive therapy: a shifting paradigm. Cardiol Rev 1994; 2: 230-40.
12. Krousel-Wood M, Thomas S, Muntner P, Morisky D. Medication adherence: a key factor in achieving blood pressure control and good clinical outcomes in hypertensive patients. Curr Opin Cardiol 2004; 19: 357-62.
13. Haynes RB, McDonald HP, Garg AX. Helping patients follow prescribed treatment: clinical applications. JAMA 2002; 288: 2880-3.
14. DiMatteo MR. Variations in patients'adherence to medical recommendations: a quantitative review of 50 years research. Med Care 2004; 42: 200-9.
15. Banegas JR.Control of high blood pressure in primary health care. Am J Hypertens 2006; 19: 146.
16. Menard J, Chatellier G. Limiting factors in the control of blood pressure: why is there a gap between theory and practice? J Human Hypertens 1995; 9 (Suppl 2): 19-23.
17. Conlin PR, Gerth WC, Fox J, Roehm JB, Boccuzzi SJ. Four-Year persistence patterns among patients initiating therapy with the angiotensin II receptor antagonist losartan versus other artihypertensive drug classes. Clin Ther 2001; 23: 1999-2010.
18. Chapman RH, Benner JS, Petrilla AA, et al. Predictors of adherence with antihypertensive and lipid-lowering therapy. Arch Intern Med 2005; 165: 1147-52.
19. Morris AB, Li J, Kroenke K, Bruner-England TE, Young JM, Murray MD. Factors associated with drug adherence and blood pressure control in patients with hypertension. Pharmacotherapy 2006; 26: 483-92.
20. Degli Esposti L, Degli Esposti E, Valpiani G, et al. A retrospective, population-based analysis of persistence with antihypertensive drug therapy in primary care practice in Italy. Clin Ther 2002; 24: 1347-57.
21. Bloom BS. Continuation of initial antihypertensive medication after 1 year of therapy. Clin Ther 1998; 20: 671-81.
22. Osterberg L, Blaschke T. Adherence to medication. N Engl J Med 2005; 353: 487-97.
23. European Society of Hypertension-European Society of Cardiology Guidelines Committee. 2003 European Society of Hypertension – European Society of Cardiology guidelines for the management of arterial hypertension. J Hypertens 2003; 21: 1011-53.
24. Schroeder K, Fahey T, Ebrahim S. How can we improve adherence to blood pressure-lowering medication in ambulatory care? Systematic review of randomized controlled trials. Arch Intern Med 2004; 164: 722-32.
25. Cuspidi C, Macca G, Sampieri L, et al. High prevalence of cardiac and extracardiac organ damage in refractory hypertension. J Hypertens 2001; 19: 2063-70.
26. Rizzo JA, Abbott TA 3rd, Pashko S. Labour productivity effects of prescribed medicines for chronically ill workers. Health Econ 1996; 5: 249-65.
27. McCombs JS, Nichol MB, Newman CM, Sclar DA. The costs of interrupting antihypertensive drug therapy in a Medicaid population. Med Care 1994; 32: 214-26.
28. Elliott WJ. Optimizing medication adherence in older persons with hypertension. Int Urol Nephrol 2003; 35: 557-62.
29. Morisky DE, Green W, Levine DM. Concurrent and predictive validity of a self-reported measure of medication adherence. Med Care 1986; 24: 67-74.
30. Grégoire J, Moisan J, Guibert R, Ciampi A, Milot A. Predictors of self-reported noncompliance with antihypertensive drug treatment: A prospective cohort study. Can J Cardiol 2006; 22: 323-9.
31. Schroeder K, Fahey T, Hay AD, Montgomery A, Peters TJ. Adherence to antihypertensive medication assessed by self-report was associated with electronic monitoring compliance. J Clin Epidemiol 2006; 59: 650-1.
32. Malik P. Won't or don't: studying medication adherence. Can J Cardiol 2006; 22: 549.
33. Mallion JM, Schmitt D. Patient compliance in the treatment of arterial hypertension. J Hypertens 2001; 19: 2281-3.
34. Eisen SA, Woodward RS, Miller D, Spitznagel E, Windham CA. The effect of medication compliance on the control of hypertension. J Gen Intern Med 1987; 2: 298-305.
35. 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.
36. Hamilton GA. Measuring adherence in a hypertension clinical trial. Eur J Cardiovasc Nurs 2003; 2: 219-28.
37. White HD. Adherence and outcomes: it's more than taking the pills. Lancet 2005; 366: 1989-91.
38. Bailey BL, Carney SL, Gillies AH, McColm LM, Smith AJ, Taylor M. Hypertension treatment compliance: what do patients want to know about their medications? Prog Cardiovasc Nurs 1997; 12: 23-8.
39. Roumie CL, Elasy TA, Greevy R, et al. Improving blood pressure control through provider education, provider education, provider alerts, and patient education: a cluster randomized trial. Ann Intern Med 2006; 145: 165-75.
40. Szirmai LA, Arnold C, Farsang C. Improving control of hypertension by an integrated approach – results of the "Manage it well!" programme. J Hypertens 2004; 23: 203-11.
41. 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.
42. Van Wijk BL, Klungel OH, Heerdink ER, de Boer A. Generic substitution of antihypertensive drugs: does it affect adherence? Ann Pharmacother 2006; 40: 15-20.
43. Harmon G, Lefante J, Krousel-Wood M. Overcoming barriers: the role of providers in improving patient adherence to antihypertensive medications. Curr Opin Cardiol 2006; 21: 310-5.
44. Hill MN, Miller NH. Compliance enhancement. A call for multidisciplinary team approaches. Circulation 1996; 93: 4-6.
45. Port K, Palm K, Viigimaa M. Daily usage and efficiency of remote home monitoring in hypertensive patients over a one-year period. J Telemed Telecare 2005; 11 (Suppl 1): 34-6.