

## Compliance with treatment: related-issues and insights for pharmacist intervention

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Low patient compliance with pharmacotherapy remains one of the greatest challenges for success of treatments, especially in chronic diseases, since it can negatively influence treatment effectiveness and patient quality of life, increase health expenses and decrease productivity of the patient. Compliance is an important but complex issue in clinical practice. Its complexity begins with the difficulty in adopting terminology that can express its exact meaning. Moreover, many methods to evaluate compliance have been established but no consensus exists on which method should be considered the gold standard. Additionally, socioeconomic, disease and therapy-related factors, healthcare team and system related-factors and patient-related factors can simultaneously influence compliance levels. In this highly complex scenario, pharmacist interventions have been identified as an effective strategy to enhance patient compliance with treatment. The objectives of this paper were: (1) to provide useful information for pharmacists about issues related to compliance such as terminology and definitions; methods for measuring compliance and persistence; influencing factors and the impact of low compliance; and (2) to offer insight into how these healthcare professionals can effectively contribute toward improved compliance levels.

**Uniterms:** Pharmacotherapy/compliance with treatment. Medicines/use. Chronic diseases/therapy. Pharmacists/interventions.

A baixa adesão dos pacientes ao tratamento medicamentoso de doenças crônicas continua sendo um dos maiores desafios da medicina, por comprometer a efetividade do tratamento, repercutindo na qualidade de vida, aumentando os gastos com saúde e diminuindo a produtividade do indivíduo doente. O tema adesão é tão relevante para a prática clínica quanto complexo, a começar pelas tentativas de adoção de uma terminologia que expresse com exatidão o seu significado. Além disso, vários métodos para sua determinação foram estabelecidos sem, contudo, se chegar a um consenso sobre qual seria o “ótimo”. Adicionalmente, as condições socioeconômicas, as características da doença, os tratamentos empregados, o sistema de saúde e seus profissionais ou o próprio paciente são alguns dos distintos fatores que influenciam, simultaneamente, o nível de adesão do paciente ao tratamento. Neste cenário de alta complexidade, intervenções realizadas pelo profissional farmacêutico têm sido apontadas como estratégias efetivas para o aumento dos níveis de adesão do paciente ao tratamento. Os objetivos deste artigo são: (1) fornecer aos farmacêuticos algumas informações úteis relacionadas ao assunto adesão tais como: terminologia e definições, métodos para medir adesão e persistência, fatores influenciadores e impacto da baixa adesão; (2) fornecer algumas idéias a respeito de como estes profissionais de saúde podem efetivamente contribuir para a melhora dos níveis de adesão.

**Unitermos:** Tratamento medicamentoso/adesão. Medicamentos/uso. Doenças crônicas/tratamento. Farmacêutico /intervenções.

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## INTRODUCTION

Cardiovascular diseases are the main cause of mortality in Brazil and account for about 30% of all causes of death (Brasil. Ministério da Saúde, 2008). In spite of the many available drugs for these conditions that provide efficacy in reducing morbidity and mortality, low patient compliance with treatment remains one of the greatest challenges in routine clinical practice (Wu *et al.*, 2006).

There is no consensus on the level of compliance considered to be adequate (Osterberg, Blaschke, 2005). Rates of compliance vary widely in the literature even in controlled clinical trials (Kenreigh, Wagner, 2005). The rate of compliance can also vary according to type of study, patient population, method of data collection and technique used to measure compliance (Muszbek *et al.*, 2008).

According to the World Health Organization, rates of compliance with antihypertensive agents range from 50% to 70%, while 16% to 50% of patients give up their treatments within the first year (World Health Organization, 2003).

Regarding antilipemic agents, it is estimated that only 50% of patients who are being treated with statins continue to use their medication after six months, and only 30% to 40% after one year (American Heart Association, 2002).

In studies assessing the cost-consequences of non-compliance, compliance rates were 45-80% in diabetes, 15-35% in hypertension, 31-59% in hypercholesterolemia and 60-96% in other diseases such as heart failure and coronary heart diseases (Muszbek *et al.*, 2008).

Reviews of compliance-enhancing interventions suggest that many educational and behavioral interventions are efficacious, especially those conducted by pharmacists. However, practitioners generally lack formal training on these techniques (Svarstad *et al.*, 2009).

The objectives of this paper were to provide useful information for pharmacists about issues related to compliance and to offer insight into how these healthcare professionals can effectively contribute toward improving compliance levels.

## TERMINOLOGY AND DEFINITIONS

Many terms have been found in the literature as synonyms for compliance such as adherence, concordance, fidelity, obedience and observance (Zanini, Paulo, 1997; Wahl *et al.*, 2005; Gusmão, Mion Jr., 2006).

At the end of the 1970's, "compliance" was defined as the level of extent to which a person's behavior (in terms of taking medications, following diet regimens or

executing life style changes) coincides with medical or health advice (Lutfey, Wishner, 1999).

This definition reflects how health professionals at the time, perceived the physician-patient relationship: patients had to obey physician's instructions, demonstrating a kind of paternalistic behavior (Strömberg, 2006). However, Zanini and Paulo (1997) had previously called attention to the fact that treatment effectiveness also depends on patient trust in the physician: patient feelings of respect and admiration for the physician could encourage him/her to better tolerate adverse effects of drugs whereas no trust, or lack of credibility in physician's recommendations could lead patients to worrying excessively about their health and adverse effects of drugs, resulting in noncompliance with drug treatment (Zanini, Paulo, 1997).

Advances in knowledge about the determinants of human behavior for health has highlighted the fact that the patient needs to be seen as a person who actively influences their treatment through their beliefs, willingness and attitudes (Tourette-Turgis, Rebillon, Pereira-Paulo, 2005).

In 1995, the Royal Pharmaceutical Society of Great Britain (RPSGB) performed a study to better understand patients' difficulties in following prescribed drug treatment (Royal Pharmaceutical Society, 1997). After this research, at the end of the 1990's, the term "concordance" started to be used in Great Britain to describe the new way that physicians handled patient consultations: empowering patients to achieve effective treatment (Hobden, 2006).

At the same time, in the Anglo-Saxon literature, the term "adherence" replaced the term "compliance" meaning approval, consent, or concordance. This term suggests that the patient assumes a more active role in issues regarding their health: defining and pursuing goals for the treatment of their disease (Osterberg, Blaschke, 2005; Tourette-Turgis, Rebillon, Pereira-Paulo, 2005).

Thus, interactions with patients should not be viewed simply as opportunities for reinforcing instructions centered on treatment, but rather, they should be seen as a space where the expertise of patients and health professionals can be pooled to arrive at mutually agreed goals (Bissel, May, Noyce, 2004).

Although adherence is the word preferred by many healthcare providers, both terms, "adherence" and "compliance" are imperfect and uninformative descriptions of medication-taking behavior (Osterberg, Blaschke, 2005).

According to the World Health Organization, patient compliance with treatment is defined as the extent to which a person's behavior – taking medication, following a diet and/or executing lifestyles changes – corresponds with agreed recommendations from healthcare providers (World Health Organization, 2003).

Regarding the use of medicines, a person's behavior can be analyzed from two slightly different aspects: (1) taking medications at the prescribed frequency / interval and dose / dosing regimen and (2) continuing their use for the specified treatment time period (Halpern *et al.*, 2006). For each of these components of patient compliance with drug treatment, two specific terms are adopted, namely, compliance (or adherence) and persistence, respectively.

With the objective of enabling comparisons among compliance studies, the International Society of Pharmacoeconomics and Outcomes Research (ISPOR) suggested the standardization of compliance and persistence definitions as follows (Cramer *et al.*, 2008a):

1. Medication compliance (synonym: adherence) refers to the act of conforming to the recommendations made by the healthcare provider with respect to timing, dosage and frequency of medication taking. Adherence is measured over a period of time and reported as a percentage of doses taken as prescribed.

2. Medication persistence is defined as "the duration of time from initiation to discontinuation of therapy". Continuing to take any amount of the medication is consistent with the definition of persistence. By definition, persistence is reported as a continuous variable in terms of number of days for which therapy was available. It may also be reported as a dichotomous variable measured at the end of a predefined time period, considering patients as being 'persistent' or 'nonpersistent'.

## METHODS FOR MEASURING COMPLIANCE

The available methods for measuring compliance with drug treatment can be classified into direct and indirect methods. Each method has advantages and disadvantages but there is no consensus on which method can be considered the gold standard (Osterberg, Blaschke, 2005).

Direct methods seek to confirm whether there was ingestion of medicines by the patient, while in the indirect methods there is no confirmation as to whether the patient had taken the medicine (Oigman, 2006).

There are three direct methods: (1) directly observed therapy; (2) measurement of the level of medicines or metabolites in blood or urine; (3) measurement of biological markers in blood (World Health Organization, 2003; Osterberg, Blaschke, 2005; Oigman, 2006).

In the directly observed therapy, the medicine is offered to the patient by a healthcare professional that witnesses medicine ingestion by the patient. Although this is the most accurate method, patients can potentially hide pills in their mouth and discard them later. Additionally, the method is impractical for routine use (Osterberg, Blaschke, 2005).

Measurements of concentrations of a drug or its metabolite in blood or urine constitute another direct method. However, variations in metabolism can give a false impression of compliance with drug treatment (World Health Organization, 2003). Another important consideration is that a patient who exceptionally takes the prescribed medicine only immediately before collection of biological material for laboratorial analysis, could be classified as compliant while a patient who takes the medicine regularly but has interrupted the treatment in the last 24 or 48 hours before biological material collection could be classified as noncompliant. In spite of these drawbacks, it is considered a reliable method (Rocha Jr., 1997).

Finally, in the measurement of biological markers in blood, an innocuous substance is added to the drug formulation and measurements of concentrations of this marker in blood are subsequently performed. This method implies the handling of the medicines and this raises some ethical aspects (Rocha Jr., 1997; Oigman, 2006). Additionally, the method calls for expensive quantitative assays and collection of body fluids (Osterberg, Blaschke, 2005). Therefore, it is considered an expensive method, available for a limited number of medicines that is both inconvenient to patients and impractical for routine use (Oigman, 2006; Mori *et al.*, 2008).

Indirect evaluations of compliance can be performed by several methods: (1) assessing clinical response; (2) performing pill counts; (3) using electronic monitors; (4) ascertaining rates of refilling of prescription; (5) collecting information from healthcare professionals or from patients (World Health Organization, 2003; Osterberg, Blaschke, 2005; Oigman, 2006; Gusmão *et al.*, 2009).

Assessing clinical response has been considered the simplest method which is generally easy to execute. It assumes that clinical response is a variable that depends only on adherence, and does not consider the possibility that other factors influence this clinical response (Oigman, 2006). However, health problems can sometimes be solved or controlled by factors other than adherence (Delgado, Lima, 2001). Further, patients can show good adherence and yet may not necessarily present the desired clinical response. Clinical response can be used as measurement of drug adherence when the treatment is associated with a specific result, for example glycemic or blood pressure levels. However, some authors consider the occurrence of the "toothbrush effect", i.e., the patient is compliant only immediately before visiting the doctor (Delgado, Lima, 2001).

In the counting of pills method, the compliance rate is determined by the difference between the number of pills acquired by the patient and the number of pills remain-

ning in the box during a specified time period. Although simple, this approach has the disadvantage of being useful only for solid medicines and it is not possible to know whether the patient has ingested the correct amount of medicine per day or whether they have ingested the correct daily amount for fewer days (Rocha Jr., 1997).

Regarding electronic monitors such as Medications Events Monitoring System (MEMS), medication dosage units (pills, drops, etc) are separately placed in vials fitted with an electronic processor that can record the precise moment in which the vial is opened. This method assumes that each opening of the vial corresponds to an ingestion of medication (Osterberg, Blaschke, 2005; Oigman, 2006) and provides detailed information to calculate the number of doses taken daily at appropriate intervals, for instance approximately 12 hours for a twice-daily dosing regimen. Additional details can also be obtained such as number of days with extra doses or with no dose (Cramer, 2004). It is an expensive method and the majority of monitors are useful only for solid formulations. As in the counting of pills method, results can be overestimated (Rocha Jr., 1997).

Measuring compliance by ascertaining rates of refilling of prescriptions requires a closed pharmacy system which provides information for the Medication Possession Ratio (MPR) calculation. When a person has their prescription filled out by a pharmacy included in this integrated system, the prescription data and the amount of medication delivered to the patient are registered (Oigman, 2006; Halpern *et al.*, 2006).

The MPR is defined as the sum of the days' supply of medication divided by the number of days between the first fill and the last refill, plus the days' supply of the last refill (Sikka, Xia, Aubert, 2005). Figure 1 exemplifies the MPR calculation.

An MPR of 1.0 indicates full (100%) compliance.  $MPR < 1$  indicates lapses in prescription refilling.  $MPR$  equal to 1.0 can indicate that the patient has refilled the prescription before their medication has run out or has hoarded medication for later use. This value can be capped at 1.0 if it is unlikely that the patient has used a greater amount of medicine than that prescribed (Halpern *et al.*, 2006). For patients receiving concomitant medications, MPR should be calculated for each medication separately, and the overall MPR taken as the average of the individual MPR. However, care should be taken since compliance can vary according to the medication being evaluated. The main limitation of this method is the assumption that the proportion of days covered by a prescription corresponds to the proportion of days of medication used. Additionally, there is a chance a patient has refilled the prescription at the correct time intervals yet has not taken their medica-

Day count	Refilling process	Days' supply of medication
Day 1	1 <sup>st</sup> refill	30
From day 31 to day 45	No refill	0
Day 46	2 <sup>nd</sup> refill	30
From day 76 to day 90	No refill	0
Day 91	3 <sup>rd</sup> refill	30
From day 121 to day 130	No refill	0
Day 131	4 <sup>th</sup> refill	30
From day 161 to day 335	No refill	0
Day 336	5 <sup>th</sup> refill	30
Total number of days	-	150
MPR (Medication Possession Ratio) = $150/365 = 0.41$ or 41%		

**FIGURE 1** - MPR Calculation. Based on Sikka and colleagues (2005).

tion according to the physician's recommendations. Other limitations are related to the nature of databases, i.e. a patient may have acquired their medication from sources for which data are not captured, such as drug samples, from friends or family members or from pharmacies which are not included in the integrated system for capturing electronic data (Halpern *et al.*, 2006).

Indirect evaluation can also be carried out by collecting information from healthcare professionals or from patients (patient self-reported assessment). This method is commonly used (Osterberg, Blaschke, 2005) being considered easy to apply and inexpensive, especially compared with the use of electronic monitors, biologic analyses or determining rates of refill of prescriptions (Kripalani *et al.*, 2009). Nevertheless, indirect evaluation involves some degree of subjectivity (World Health Organization, 2003). Patient self-reported assessment presents varying levels of concordance with other methods due to the use of different instruments for collecting data and administration techniques (Kripalani *et al.*, 2009).

As a final point, patient information can be collected using different instruments such as patient diaries, structured questionnaires, questionnaires with scales, through interviews or simple reports (Oigman, 2006; Mori *et al.*, 2008; Kripalani *et al.*, 2009). Among these instruments, the questionnaire incorporating a scale developed by Morisky and colleagues (1986), the Morisky-Green Scale, has been in use for approximately 20 years (Kripalani *et al.*, 2009). It was originally developed for evaluating patient behavior patterns associated with the use of antihypertensive drugs and consists of four-items with yes/no answer format, on a scale from 0 to 4. Each "yes" scores 0 (zero)

points and each “no” is worth 1 (one) point. According to the sum of points, the patient can be classified into the following levels of compliance: high (4 points), medium (2-3 points) and low (0-1 point). With this method, compliance can also be analyzed as a dichotomous variable: perfect compliance [score = 4 points] and imperfect compliance [score  $\leq$  4 points] (Morisky, Green, Levine, 1986).

Regarding measurement of persistence, Sikka and colleagues (2005) identified three methods in their review of studies measuring refilling persistence: (1) persistence as a function of MPR; (2) as a function of medication possession at a fixed point in time; and (3) as a gap between refills (Sikka, Xia, Aubert, 2005).

In the first method, persistence is defined as a MPR  $\geq$  80%. MPR is used as a dichotomous variable, and patients with MPR  $\geq$  80% are considered to be persistent for drug treatment (Sikka, Xia, Aubert, 2005). Although there is no statistic rationale for this cut-off point (MPR  $\geq$  80%), it has been used in many studies (Cramer *et al.*, 2008b).

It is important to note that the MPR alone is not sufficient to provide information about the consistency of prescription refilling for a specific time period (Sikka, Xia, Aubert, 2005). For instance, during a one-year period Patient A has acquired their medication for 30 days' supply every other month. Patient B has acquired their medication for 30 days' supply, in the first month. After first acquisition, Patient B has not acquired their medication for the proceeding six months and then carried on acquiring their medications for 30 days' supply every month for the rest of the one-year period. At the end of one-year period, Patients A and B will have the same MPR value. However, Patient A has shown a more consistent behavior pattern regarding refill of prescription compared with Patient B.

According to Sikka and colleagues (2005), this fact could be reasonable grounds for justifying the setting of an MPR value to greater than or equal to 80% to classify the patient as persistent or nonpersistent. The 80% cut-off suggests that the patient has gone only a few days without medication on hand and consequently could use this medication regularly (Sikka, Xia, Aubert, 2005).

Evaluating persistence as a function of medication possession at a given point in time assumes that if the patient is in possession of medication on that specific date, then they are considered to have been persistent from the initial prescription up to this date. The timing and gaps between refills are not considered in this method. Let us take two patients (A and B) who have initiated their drug treatments in the first month of the year. Patient A acquired their medication 12 times per year, every consecutive month and each time acquired sufficient medication for 30 days' supply. The last acquisition by Patient A was made

at the beginning of month 12. Patient B acquired their medication 4 times per year, with intervals between each acquisition and each time acquired sufficient medication for 30 days' supply. The last acquisition by Patient B was made at the beginning of month 12. Considering month 12 was the date set for the evaluation, both patients will be considered to be persistent to drug treatment.

In the third method, persistence to drug treatment is evaluated as a function of gaps between refills. Each patient is given a certain grace period in which they can go without refilling prescription. Generally, this period is equal to half the number of days supplied with the filling of one prescription. The grace period can also be calculated as a function of the number of days supplied with previous prescription refill, and can be equal to half or three times the number of days supplied with the previous filling. If the patient refills the prescription by the end of the grace period, they are considered persistent to drug treatment at that point in time, where persistence is measured in days. If the patient refill gap exceeds the determined grace period, then the patient is considered nonpersistent at that point in time.

The main advantage of this method compared with the other two is that it enables a profile of survival analysis to be built and consequently allows the persistence of a specific population to drug treatment to be determined (Sikka, Xia, Aubert, 2005).

Figure 2 exemplifies how persistence can be measured by these three different methodologies.

Finally, medication compliance can be evaluated through prospective and retrospective studies, both of which can provide data on the “real world”. However, participants in prospective studies cannot be compared with large populations and can introduce biases, especially those related to patient behaviors. Although the use of retrospective data does not introduce this kind of bias, the lack of consistent methods hampers comparison of results among studies (Halpern *et al.*, 2006).

## FACTORS THAT INFLUENCE COMPLIANCE

Numerous factors can simultaneously influence levels of compliance with treatment including those related to socioeconomic condition, disease and treatment characteristics, healthcare team and system and those factors related to patient characteristics (World Health Organization, 2003).

Factors such as gender, socioeconomic condition, race and marital status have not been consistently associated with levels of compliance (Ockene *et al.*, 2002; Osterberg, Blaschke, 2005). On the other hand, age has been reported as a factor that can influence compliance at

Day count	Refilling process	Days supply of medication	Days without medicine
Day 1	1 <sup>st</sup> refill	30	0
From day 31 to day 45	No refill	0	15
Day 46 <sup>t</sup>	2 <sup>nd</sup> refill	30	0
From day 76 to day 90	No refill	0	15
Day 91	3 <sup>rd</sup> refill	30	0
From day 121 to day 130	No refill	0	10
Day 131	4 <sup>th</sup> refill	30	0
From day 161 to day 335	No refill	0	175
Day 336	5 <sup>th</sup> refill	30	0

1. Persistence evaluated as a function of MPR

MPR (Medication Possession Ratio) =  $150/365 = 0.41$  or 41%  
 Patient is considered persistent to drug treatment if  $MPR \geq 80\%$ .  
 Result: not persistent

2. Persistence evaluated as a function of Medication Possession at a fixed point in time

Fixed point in time: Day 365.

Result: At the point in time fixed for evaluation, the patient has medication available so he/she is considered persistent to drug treatment from Day 1 to Day 365 or persistent at 1 year.

3. Persistence evaluated as a function of the gaps between refills  
 Grace period: 15 days.

Result: From Refill 4<sup>th</sup>, patient exceeds grace period. Thus, from this point in time he/she is considered to be nonpersistent to treatment. In other words, patient was persistent to drug treatment until Day 160.

**FIGURE 2** - Evaluation of persistence to drug treatment using three different methodologies. Based on Sikka and colleagues (2005).

different times in life (Pan American Health Organization, 2003). Poor compliance may be a way for young people to rebel against the treatment regimen's control over their lives. Senior patients may not be compliant with treatment for a variety of reasons such as: memory or cognitive dysfunction; lack of understanding on the importance of medication or the recommendations regarding their disease treatment; inability to manage or to take multiple medicines; attitudes (refusal to follow healthcare professionals' recommendations); beliefs (related to culture and spirituality); limited access to medications due to lack of transportation or money (Romano-Lieber *et al.*, 2002; Murray *et al.*, 2004).

There is evidence that patient knowledge about their disease and treatment is a critical factor for encouraging them to actively participate in the decision-making process related to their health (Golin *et al.*, 1996). However, knowledge alone cannot be considered a guarantee of compliance. Nevertheless, patients who have been educated by physicians or nurses and understand their disease process, the treatment goals, potential side effects associated with their medications, and the consequences of low compliance, tend to be more compliant (Neutel, Smith, 2003). On the other hand, a study involving diabetic patients which sought to verify the relationship between compliance and patients' knowledge about their disease revealed a disparity between what the patients were taught and what they were actually doing (Chan, Molassiotis, 1999).

Low compliance can be expected in the presence of chronic disease, in the absence or oscillation of symptoms, or even when the treatment is complex or includes life-style changes (Delamater, 2006). Levels of compliance are higher among patients with acute diseases compared to patients with chronic diseases, and persistence among patients with chronic conditions is low, dropping most dramatically after the first six months of therapy (Osterberg, Blaschke, 2005). Patient perception of disease severity is associated with more elevated levels of compliance even if treatment lasts a long period of time (Leite, Vasconcelos, 2003). Comorbidities, drug and alcohol abuse can also negatively impact compliance/persistence levels (Pan American Health Organization, 2003). Some studies suggest that depression and anxiety have a detrimental influence on compliance, whereas others have failed to find this influence (Ockene *et al.*, 2002).

Limited financial means may lead patients to total or partial interruption of their treatments (World Health Organization, 2003; Sokol *et al.*, 2005). However, low compliance is present even if medicines are freely distributed to patients but involve a complex therapeutic scheme and large number of prescribed medicines (Leite, Vasconcelos, 2003).

The effect of dosage frequency has been extensively studied and there is evidence that compliance with drug treatment decreases as the number of different medicines, number of pills and dosage frequency increases (Royal Pharmaceutical Society of Great Britain, 1997; Claxton, Cramer, Pierce, 2001). It has been demonstrated that people are less likely to continue their medication regimen over long periods, and are less likely to be compliant with treatment when daily doses increase from 1 pill to 4 pills (Gottlieb, 2000). Results of a meta-analysis showed that for antihypertensive medications, once daily dosing regimens

are associated with higher rates of compliance than either twice-daily or multiple-daily dosing regimens (Iskedjian *et al.*, 2002).

Many reasons have been cited to explain the inverse relationship between number of medicines that a patient has to take and their compliance with treatment, such as cost [greater cost associated with multiple drugs], convenience [easier to forget to take multiple drugs] and confusion [patients often become confused by multiple drugs and frequently dose them incorrectly] (Neutel, Smith, 2003). Additionally, the occurrence of side effects has been associated with low compliance, especially in the treatment of chronic diseases such as hypertension (Neutel, Smith, 2003; Burnier, 2006). All these factors, generally classified as therapy-related factors, are actually partially related to the patient's decision on changing their life style or accepting some medication side effects (Leite, Vasconcelos, 2003). Pathak and Thomas (2006) have shown that patients' medication beliefs can also explain a significant portion of variation in medication noncompliance (Phatak, Thomas, 2006). Gatti and colleagues (2009) also verified that patients who had negative beliefs about medications had low compliance.

Finally, a positive supporting and trusting relationship between healthcare professional and patient improve compliance with treatment (Krueger, Berger, Felkey, 2005). Certain attitudes of healthcare professionals such as communication, time spent for consultation, friendly service, respect for patient needs and doubts, and encouraging patient to follow the agreed therapy, are important factors cited in the literature (Leite, Vasconcelos, 2003).

## IMPACT OF LOW COMPLIANCE AND COMPLIANCE-ENHANCING STRATEGIES

Low compliance with treatment of chronic diseases has a negative impact on effectiveness of therapy and is a critical factor in the health and quality of life of populations, as well as being an important factor from an economic perspective (Pan American Health Organization, 2003).

In a study of survivors of acute myocardial infarction exploring the relationship between compliance with drug treatment and mortality, results showed that patients who had high levels of compliance with statins also had lower risk of mortality compared to those patients who had low compliance (Rasmussen, Chong, Alter, 2007).

Breekveldt-Postma and colleagues (2008) studied the effect of antihypertensive treatment discontinuation on risk of infarction and stroke in daily clinical practice. Of the 77,193 patients included, the percentage of nonper-

sistent patients was 55% at 2 years. Nonpersistence was associated with a 15% higher risk of acute myocardial infarction [RR 1.15; 95% CI 1.00-1.33] and a 28% higher risk of stroke [RR 1.28; 95% CI 1.15-1.45] (Breekveldt-Postma *et al.*, 2008).

In a retrospective cohort study that included 49,479 chronic-medication treated patients, Bailey and colleagues (2010) verified that ambulatory visits and antihypertensive medication exposures were associated with reduced mortality. Increasing compliance by one pill per week for a once-a-day regimen reduced the hazard of stroke by 8-9% and death by 7% (Bailey *et al.*, 2010).

In fact, patients who presented high compliance with antihypertensive drugs were more likely to meet blood pressure goals (Bramley *et al.*, 2006), their risk of cardiovascular events and hospitalization were decreased (Halpern *et al.*, 2006) and they consumed less healthcare resources compared with patients who were not compliant with the prescribed treatment (Sokol *et al.*, 2005)

The impact of compliance with treatment for diabetes, hypertension, hypercholesterolemia and heart failure on healthcare usage and costs was investigated in a retrospective study which included patients on a pharmacy benefit plan. For diabetes and hypercholesterolemia, a high level of compliance with drug treatment was associated with lower disease-related medical costs. Under these conditions, higher medication costs were more than offset by medical cost reductions, producing a net reduction in overall healthcare costs. For all four studied conditions, hospitalization rates were significantly lower for patients who had high compliance with drug treatment (Sokol *et al.*, 2005).

Beyond direct costs, there are many other indirect costs related to noncompliance/nonpersistence such as absenteeism, loss of quality of life, loss of productivity, family problems, partial or total patient incapacity for self-care and premature retirement (Lessa, 2006).

Among many initiatives focused on improving compliance with treatment, the multidisciplinary approach has been recognized as one of the most effective strategies (Osterberg; Blaschke, 2005; V Diretrizes Brasileiras de Hipertensão Arterial, 2007). In a systematic review assessing the effectiveness of quality improvement strategies in lowering blood pressure, Wash and colleagues (2006) suggested that a team change involving pharmacists may be one of the most effective quality improvement strategies for improving blood pressure control (Wash *et al.*, 2006).

Glynn and colleagues (2010) reviewed all articles (any year) in the Cochrane Controlled Trial Register (CCTR) and on Medline and Embase from January 1980

onwards, to determine the effectiveness of interventions to improve control of blood pressure in patients with hypertension. The search yielded seventy-two randomized controlled trials (RCT's) that met the inclusion criteria. Among all analyzed strategies, nurse and pharmacist-led care may be a promising way of improving control in patients with hypertension, with the majority of RCT's being associated with improved blood pressure control, improved systolic blood pressure, and more modestly improved diastolic blood pressure (Glynn *et al.*, 2010).

Svarstad and colleagues (2009) indicated five core compliance barriers that can be successfully addressed by pharmacists: regimen knowledge barriers [poor understanding of drug regimen and its elements such as dosage schedule treatment duration, purpose], recall barriers [difficulty remembering multiple drugs and doses], motivational barriers [doubts regarding drug efficacy, benefits, or need therapy], side-effect barriers [bothersome side effects or concerns about long-term effects], and access barriers [difficulty affording or obtaining refills] (Svarstad *et al.*, 2009).

Over recent years, many studies have emphasized the role of pharmacists in improving patient compliance levels. Smith and colleagues (1997) demonstrated that when there is a patient counseling by pharmacists before hospital discharge, patients' level of compliance with treatment tends to be higher compared to levels of compliance of patients who have not received pharmacists counseling (Smith *et al.*, 1997).

Wu and colleagues (2006) investigated the effectiveness of periodic telephone counseling by a pharmacist in reducing mortality in patients receiving polypharmacy. In this single-centre, randomized and controlled study, telephone counseling was associated with a 41% reduction in risk of death.

Lee and colleagues (2006) showed that levels of compliance with treatment can be improved after interventions performed during a pharmacy care program that included individualized medication education; medications dispensed using a compliance aid (blister packs) and regular follow-up with clinical pharmacists every 2 months. After 8 months of interventions, the proportion of patients in whom all chronic medications were taken with a compliance rate of at least 80%, increased from 5.0% to 98.7% (Lee, Grace, Taylor, 2006).

In a retrospective analysis, Pindolia and colleagues (2009) evaluated the effectiveness of a medication therapy management program. In this program, clinical pharmacists, through telephone contact, ascertained patients' healthcare goals and needs. Subsequently, a patient-centered pharmacotherapy plan was created and implemented

collaboratively with the patient's physician. Among the types of interventions performed by pharmacists, 60% involved changing therapy to improve efficacy and 40% involved changing therapy to improve safety. Additionally, patients received counseling on medication and correlated diseases states. These interventions produced a trend toward improved compliance with drug therapy for heart failure, insulin use, to reduced pharmacy costs and sustained pharmacy cost savings for patients who enrolled in the program compared with those who declined enrollment.

Elliot and colleagues performed a study intervention assessing the cost effectiveness of pharmacists giving advice via telephone to patients receiving a new medicine for a chronic condition (Elliot *et al.*, 2008). At 4-week follow-up, noncompliance was significantly lower in the intervention group (9% *versus* 16%;  $p = 0.032$ ). The number of patients reporting medicine-related problems was significantly lower in the intervention group compared with the control group (23% *versus* 34%;  $p = 0.021$ ) and there was a significant reduction in mean total patient costs at 2-month follow-up in the intervention group compared with the control group.

Kaboli and colleagues (2009) evaluated the published literature on the effects of interventions by clinical pharmacists on processes and outcomes of care in hospitalized adults. The reviewed studies showed that the introduction of clinical pharmacist services in the care of inpatients generally resulted in improved care. Pharmacist interactions with the healthcare team involved in patient rounds, interviewing patients, reconciling medications, providing patient discharge counseling and follow-up, all resulted in improved outcomes.

Duru and colleagues (2010) performed one of the first studies examining the characteristics of patients using mail-order pharmacies. Findings confirmed that patients who received newly prescribed medications through the mail were more likely to have good compliance than patients who obtained them from traditional pharmacies. Mail-order users had better compliance with antiglycemic, antihypertensive and lipid-lowering medications.

In Brazil, some initiatives have demonstrated the importance of pharmacists in increasing patient compliance levels. One such initiative was the pharmacotherapy management program implemented by the Pharmacy Service of UNIMED, a Brazilian cooperative of physicians in Piracicaba, Sao Paulo State, between August 2006 and July 2007 (Martins *et al.*, 2007). In Porto Alegre, Rio Grande do Sul State, a double-blind randomized study, which enrolled 71 patients with uncontrolled blood pressure in a pharmaceutical care program, showed that pharmacists



can contribute toward improving patient compliance levels and outcomes (Castro *et al.*, 2006).

Souza and Bertoincin (2008) followed and provided weekly counseling to 10 hypertensive adult volunteers for 2 months in Pouso Alegre, Minas Gerais State, to evaluate blood pressure levels, motivate patients on correctly use of medicines, and to improve levels of compliance with treatment. This study suggested that pharmaceutical home care is important for monitoring hypertensive patients and motivating patients to improve compliance with therapy.

Sixty-four diabetic patients who were being treated at a Public Healthcare Center in Ribeirão Preto, São Paulo State, Southeast of Brazil, were followed by pharmacists. At the end of a 9-month follow-up period reductions were seen in the values of glycated hemoglobin (2.15%), fasting glycemia level (8.91%), systolic blood pressure level (3.55%), and diastolic blood pressure level (1.85%) compared to initial values on biochemical tests (Ferreira *et al.*, 2006).

Despite the encouraging evidence, implementing compliance-enhancing strategies through pharmacist interventions on a large scale is quite challenging due to the total costs involved, lack of user-friendly tools, need for training of healthcare professionals, and difficulties in program implementation (Svarstad *et al.*, 2009).

## CONCLUSION

Compliance with treatment is a complex and challenging issue for healthcare professionals and patients. It is well known that the effectiveness of pharmacotherapy depends on an agreement between patients and healthcare providers. In the event that this agreement proves impossible for whatever reason, society faces an important problem which frequently results in increased healthcare costs and rising demand for human resources.

Over recent years, many studies have shown the impact of pharmacist intervention on improving compliance levels and patient outcomes, especially for treatment of chronic diseases. The greatest challenge today is the successful implementation of compliance-enhancing strategies for large populations.

## DISCLOSURE

N.L.Silva and J.L. Navarro are formal employees of Novartis Biociencias S.A., Brazil. The opinions expressed in this article are solely the authors' and do not reflect those of their employers, nor are they endorsed by Novartis.

## REFERENCES

- AMERICAN HEART ASSOCIATION. Third report of the National Cholesterol Education Program (NCEP) expert panel on the detection, evaluation, and treatment on high blood cholesterol in adults (Adult Treatment Panel III). Final report. *Circulation*, v.106, n.25, p.3143-421, 2002.
- BAILEY, J.E.; WAN, J.Y.; TANG, J.; GHANI, M.A.; CUSHMAN, W.C. Antihypertensive medication adherence, ambulatory visits, and risk of stroke and death. *J. Gen. Intern. Med.*, v.25, n.6, p.495-503, 2010.
- BISSEL, P.; MAY, C.R.; NOYCE, P.R. From compliance to concordance: barriers to accomplishing a re-framed model of health care interactions. *Soc. Sci. Med.*, v.58, n.4, p.851-862, 2004.
- BRAMLEY, T.J.; GERBINO, P.P.; NIGHTENGALE, B.S.; FRECH-TAMAS, F. Relationship of blood pressure control to adherence with antihypertensive monotherapy in 13 managed care organizations. *J. Manag. Care Pharm.*, v.12, n.3, p.239-245, 2006.
- BRASIL. MINISTÉRIO DA SAÚDE. Indicadores e dados básicos – Brasil – 2008. IDB – 2008. Available at: <<http://tabnet.datasus.gov.br/cgi/deftohtm.exe?idb2008/c04.def>>. Accessed on: 27 jun. 2010.
- BREELVELDT-POSTMA, N.S.; PENNING-VAN BEEST, F.J.A.; SIISKONEN, S.J.; FALVEY, H.; VINCZE, G.; KLUNGEL, O.H.; HERINGS, R.M.C. The effect of discontinuation of antihypertensives on the risk of acute myocardial infarction and stroke. *Curr. Med. Res. Opin.*, v.24, n.1, p.121-127, 2008.
- BURNIER, M. Medication adherence and persistence as the cornerstone of effective antihypertensive therapy. *Am. J. Hypertens.*, v.19, n.11, p.1190-196, 2006.
- CASTRO, M.S.; FUCHS, F.D.; SANTOS, M.C.; MAXIMILIANO, P.; GUS, M.; MOREIRA, L.B.; FERREIRA, M.B.C. Pharmaceutical Care Program for Patients With Uncontrolled Hypertension. Report of a Double-Blind Clinical Trial with Ambulatory Blood Pressure Monitoring. *Am. J. Hypertens.*, v.19, n.5, p.528-533, 2006.

- CHAN, Y.M.; MOLASSIOTIS, A. The relationship between knowledge and compliance among Chinese with non-insulin dependent diabetes mellitus in Hong Kong. *J. Adv. Nurs.*, v.30, n.2, p.431-438, 1999.
- CLAXTON, A.J.; CRAMER, J.; PIERCE, C. A systematic review of the associations between dose regimens and medication compliance. *Clin. Ther.*, v.23, n.8, p.1296-1310, 2001.
- CRAMER, J. A systematic review of adherence with medications for diabetes. *Diabetes Care*, v.27, n.9, p.1218-1224, 2004.
- CRAMER, J.A.; ROY, A.; BURRELL, A.; FAIRCHILD, C.J.; FULDEORE, M.J.; OLLENDORF, D.A.; WONG, P.K. Medication compliance and persistence: terminology and definitions. *Value Health*, v.11, n.1, p.44-47, 2008a.
- CRAMER, J.A.; BENEDICT, A.; MUSZBECK, N.; KESKINASLAN, A.; KHAN, Z.M. The significance of compliance and persistence in the treatment of diabetes, hypertension and dyslipidaemia: a review. *Int. J. Clin. Pract.*, v.62, n.1, p.76-87, 2008b.
- DELAMATER, A.M. Improving patient adherence. *Clin. Diabet.*, v.24, n.2, p.71-77, 2006.
- DELGADO, A.B.; LIMA, M.L. Contributo para a validação concorrente de uma medida de adesão aos tratamentos. *Psicol. Saúde Doenças*, v.2, n.2, p.81-100, 2001.
- DURU, O.K.; SCHMITTDIEL, J.A.; DYER, W.T.; PARKER, M.M.; URATSU, C.S.; CHAN, J.; KARTER, A.J. Mail-order pharmacy use and adherence to diabetes-related medications. *Am. J. Manag. Care*, v.16, n.1, p.33-40, 2010.
- ELLIOTT, R.A.; BARBER, N.; CLIFFORD, S.; HORNE, R.; HARTLEY, E. The cost effectiveness of a telephone-based pharmacy advisory service to improve adherence to newly prescribed medicines. *Pharm. World Sci.*, v.30, n.1, p.17-23, 2008.
- FERREIRA, L.D.; QUEIROZ, M.U.; BORGES, A.P.S.; PEREIRA, L.R.L. Avaliação da importância da atenção farmacêutica no controle glicêmico dos usuários portadores de diabetes mellitus tipo 2 (dm2) atendidos por uma Unidade Básica de Saúde em Ribeirão Preto-SP.2006 Available at: <<http://www.usp.br/siicusp/Resumos/14Siicusp/1647.pdf>>. Accessed on: 2 nov. 2009.
- GATTI, M.E.; JACOBSON, K.L.; GAZMARARIAN, J.A.; SCHMOTZER, B.; KRIPALANI, S. Relationships between beliefs about medications and adherence. *Am. J. Health. Syst. Pharm.*, v.66, n.7, p.657-664, 2009.
- GLYNN, L.G.; MURPHY, A.W.; SMITH, S.M.; SCHROEDER, K.; FAHEY, T. Interventions used to improve control of blood pressure in patients with hypertension. *Cochrane Database of Systematic Review*, v.3, 2010. Available at: <<http://www2.cochrane.org/reviews/en/ab005182.html>>. Accessed on: 02 sep. 2010.
- GOLIN, C.E.; DIMATTEO, M.R.; GELBER, G.L. The role of patient participation in the doctor visit: implications for adherence to diabetes care. *Diabetes Care*, v.9, n.10, p.1153-1164, 1996.
- GOTTLIEB, H. Medication nonadherence: finding solutions to a costly medical problem. *Drug Benefit Trends*, v.12, n.6, p.57-62, 2000.
- GUSMÃO, J.L.; MION Jr., D. Adesão ao tratamento: conceitos. *Rev. Bras. Hipertens.*, v.13, n.1, p.23-25, 2006.
- GUSMÃO, J.L.; GINANI, G.F.; SILVA, G.V.; ORTEGA, K.C. MION, Jr, D. Adesão ao tratamento em hipertensão arterial sistólica isolada. *Rev. Bras. Hipertens.*, v.16, n.1, p.38-43, 2009.
- HALPERN, M.T.; KHAN, Z.M.; SCHMIER, J.K.; BURNIER, M.; CARO, J.J.; CRAMER, J.; DALEY, W.L.; GURWITZ, J.; HOLLENBERG, N.K. Recommendations for evaluating compliance and persistence with hypertension therapy using retrospective data. *Hypertension*, v.47, n.6, p.1039-1048, 2006.
- HOBDEN, A. Concordance: a widely used term, but what does it mean? *Br. J. Community Nurs.*, v.11, n.6, p.257-260, 2006.
- ISKEDJIAN, M.; EINARSON, T.R.; MACKEIGAN, L.D.; SHEAR, N.; ADDIS, A.; MITTMANN, N.; ILERSICH, A.L. Relationship between daily dose frequency and adherence to antihypertensive pharmacotherapy: evidence from a meta-analysis. *Clin. Ther.*, v.24, n.2, p.302-316, 2002.
- KABOLI, P.J.; HOTH, A.B.; McCLIMON, B.J.; SCHNIPPER, J.L. Clinical pharmacists and inpatient medical care: a systematic review. *Arch. Intern. Med.*, v.166, p.955-964, 2006.

- KENREIGH, C.A.; WAGNER, L.T. Medication adherence: a literature review. *Medscape Pharmacists*, v.6, n.2, 2005. Available at: <<http://www.medscape.com/viewarticle/514164>>. Accessed on: 7 sep. 2007.
- KRIPALANI, S.; RISSER, J.; GATTI, M.E.; JACOBSON, T.A. Development and evaluation of the adherence to refills and medications scale (ARMS) among low-literacy patients with chronic disease. *Value Health*, v.12, n.1, p.118-123, 2009.
- KRUEGER, K.P.; BERGER, B.A.; FELKEY, B. Medication adherence and persistence: a comprehensive review. *Adv. Ther.*, v.22, n.4, p.313-356, 2005.
- LEE, J.K.; GRACE, K.A.; TAYLOR, A.J. Effect of a pharmacy care program on medication adherence and persistence, blood pressure, and low-density lipoprotein cholesterol: a randomized controlled trial. *J. Am. Med. Assoc.*, v.296, n.21, p.2563-2571, 2006.
- LEITE, S.N.; VASCONCELOS, M.P.C. Adesão à terapêutica medicamentosa: elementos para a discussão de conceitos e pressupostos adotados na literatura. *Ciênc. Saúde Coletiva*, v.8, n.33, p.775-782, 2003.
- LESSA, I. Impacto social da não-adesão ao tratamento da hipertensão arterial. *Rev. Bras. Hipertens.*, v.13, n.1, p.39-46, 2006.
- LUTFEY, K.E.; WISHNER, W.J. Beyond “compliance” is “adherence”: improving the prospect of diabete care. *Diabetes Care*, v.22, n.4, p.635-639, 1999.
- MARTINS, C.B.; PAROLINA, R.D.; CARAVANTE Jr, F.P.G.; FARHAT, F.C.L.G; CARMO, T.A. Melhoria da adesão ao tratamento medicamentoso de portadores de diabetes mellitus e hipertensão arterial por meio da atenção farmacêutica. In: AMOSTRA ACADÊMICA UNIMEP, 5., Piracicaba, 2007. *Posters*. Available at: <<http://www.unimep.br/phpg/mostraacademica/anais/5mostra/2/371.pdf>>. Accessed on: 2 nov. 2009.
- MORI, A.L.P.M.; YOCHIY, A.; STORPIRTIS, S. Educação sanitária. In: STORPIRTIS, S.; MORI, A.L.P.M.; YOCHIY, A.; RIBEIRO, E.; PORTA, V. *Farmácia clínica e atenção farmacêutica*. Rio de Janeiro: Guanabara Koogan, 2008. cap.31, p.298-306.
- MORISKY, D.E.; GREEN, L.W.; LEVINE, D.M. Concurrent and predictive validity of self-reported measure of medication adherence. *Med. Care*, v.24, p.67-74, 1986.
- MURRAY, M.D.; MORROW, D.G.; WEINER, M.; CLARK, D.O.; TU, W.; DEER, M.M.; BRATER, C.; WEINBERG, M. A conceptual framework to study medication adherence in older adults. *Am. J. Geriatr. Pharmacother.*, v.2, n.1, p.36-43, 2004.
- MUSZBEK, N.; BRIXNER, A.; BENEDICT, A.; KESKINASLAN, A.; KHAN, Z.M. The economic consequences of noncompliance in cardiovascular disease and related conditions: a literature review. *Int. J. Clin. Pract.*, v.62, n.2., p.338-351, 2008.
- NEUTEL, J.M.; SMITH, D.H.G. Improving patient compliance: a major goal in the management of hypertension. *J. Clin. Hypertens.*, v.5, n.2, p.127-132, 2003.
- OCKENE, I.S.; HAYMAN, L.L.; PASTERNAK, R.C.; SCHRON, E.; DUNBAR-JACOB, J. Adherence issues and behavior changes: achieving a long-term solution. *J. Am. Coll. Cardiol.*, v.40, n.4, p.630-640, 2002.
- OIGMAN, W. Métodos de avaliação da adesão ao tratamento anti-hipertensivo. *Rev. Bras. Hipertens.*, v.13, n.1, p.30-34, 2006.
- OSTERBERG, L.; BLASCHKE, T. Adherence to medication. *N. Engl. J. Med.*, v.353, p.487-497, 2005.
- PAN AMERICAN HEALTH ORGANIZATION. Poor adherence to long-term treatment of chronic diseases is a worldwide problem. *Rev. Panam. Salud Publica*, v.14, n.3, p.218-221, 2003.
- PHATAK, H.M.; THOMAS, J. Relationships between beliefs about medications and nonadherence to prescribed chronic medications. *Ann. Pharmacother.*, v.40, n.10, p.1737-1742, 2006.
- PINDOLIA, V.K.; STEBELSKY, L.; ROMAIN, T.M.; LUOMA, L.; NOWAK, S.N.; GILLANDERS, F. Mitigation of medication mishaps via medication therapy management. *Ann. Pharmacother.*, v.43, n.4, p.611-620, 2009.
- RASMUSSEN, J.N.; CHONG, A.; ALTER, D.A. Relationship between adherence to evidence-based pharmacotherapy and long-term mortality after acute myocardial infarction. *J. Am. Med. Assoc.*, v.297, n.2, p.177-186, 2007.

- ROCHA Jr., M.A. Compliance – você acha que a receita vai ser seguida? In: ZANINI, A.C.; PAULO, L.G. *Compliance: sobre o encontro paciente-médico*. São Roque: IPEX, 1997. cap.4, p.51-66.
- ROMANO-LIEBER, N.S.; TEIXEIRA, J.J.V.; FARHAT, F.C.L.G.; RIBEIRO, E.; CROZATTI, M.T.L.; OLIVEIRA, G.S.A. Revisão dos estudos de intervenção do farmacêutico no uso de medicamentos por pacientes idosos. *Cad. Saúde Pública*, v.18, n.6, p.1499-1507, 2002.
- ROYAL PHARMACEUTICAL SOCIETY OF GREAT BRITAIN. *From compliance to concordance: achieving shared goals in medicine taking*. London: Royal Pharmaceutical Society of Great Britain, 1997. 55 p.
- SIKKA, R.; XIA, F.; AUBERT, R.E. Estimating medication persistency using administrative claims data. *Am. J. Manag. Care*, v.11, n.7, p.449-457, 2005.
- SMITH, L.; MCGOWAN, L.; MOSS-BARCCLAY, C.; WEATHER, J.; KNASS, D.; CHRYSTYN, H. An investigation of hospital generated pharmaceutical care when patients are discharged home from hospital. *Br. J. Clin. Pharmacol.*, v.44, n.2, p.163-165, 1997.
- SOKOL, M.C.; MCGUIGAN, K.A.; VERBRUGGE, R.R.; EPSTEIN, R.S. Impact of medication adherence on hospitalization risk and healthcare cost. *Med. Care*, v.43, n.6, p.521-530, 2005.
- SOUZA, V.V; BERTONCIN, A.L. Atenção farmacêutica para pacientes hipertensos – nova metodologia e a importância dessa prática no acompanhamento domiciliar. *Rev. Bras. Promoç. Saúde*, v.21, n.3, p.224-230, 2008.
- STRÖMBERG, A. Patient-related factors of compliance in heart failure: some new insights into old problem. *Eur. Heart J.*, v.27, n.4, p.379-381, 2006.
- SVARSTAD, B.L.; KOTCHEN, J.M.; SHIREMAN, T.I.; CRAWFORD, S.Y., PALMER, P.A.; VIVIAN, E.M.; BROWN, R.L. The Team Education and Adherence Monitoring (TEAM) Trial: Pharmacy Interventions to Improve Hypertension Control in Blacks. *Circ. Cardiovasc. Qual. Outcomes*, v.2, n.3, p.264-271, 2009.
- TOURETTE-TURGIS, C.; REBILLON, M.; PEREIRA-PAULO, L. De l'adhésion à l'observance thérapeutique: réunir les conditions d'une primo-observance et développer une multiplicité d'interventions dans la durée. *Counseling, Santé et Développement Dossier*, n.1/2, p.1-8, 2005. Available at: <[http://www.counselingvih.org/fr/dossiers/dossier\\_pdf\\_doc/dossier\\_observance\\_mars04\\_complet.pdf](http://www.counselingvih.org/fr/dossiers/dossier_pdf_doc/dossier_observance_mars04_complet.pdf)>. Accessed on: 7 sep. 2007.
- V DIRETRIZES Brasileiras de Hipertensão Arterial. *Arq. Bras. Cardiol.*, v.89, n.3, p.E24-E79, 2007.
- WAHL, C.; GREGORIE, J.P.; TEO, K.; BEAULIEU, M.; LABELLE, S.; LEDUC, B.; COGHRANE, B.; LAPOINTE, L.; MONTAGUE, T. Concordance, compliance and adherence in healthcare: closing gaps and improving outcomes. *Healthcare Quarterly*, v.8, n.1, p.65-70, 2005.
- WASH, J.; McDONALD, K.M.; SHOJANIA, K.; SUNDARAM, V.; NAYAK, S.; LEWIS, R.; OWENS, D.K.; GOLDSTEIN, M.K. Quality improvement strategies for hypertension management: a systematic review. *Med. Care*, v.44, n.7, p.646-657, 2006.
- WORLD HEALTH ORGANIZATION. *Adherence to long-term therapies: evidence for action*. Geneva: World Health Organization, 2003. 198 p.
- WU, J.Y.F.; LEUNG, W.Y.S.; CHANG, S.; LEE, B.; ZEE, B.; TONG, P.C.Y; CHAN, J.C.N. Effectiveness of telephone counseling by a pharmacist in reducing mortality in patients receiving polypharmacy: randomized controlled trial. *BMJ*, v.333, n.7567, p.522-525, 2006.
- ZANINI, A.C.; PAULO, L.G. Expectativas, dúvidas e fantasias da consulta médica. In: PAULO, L.G.; ZANINI, A.C. *Compliance: sobre o encontro paciente-médico*. São Roque: IPEX, 1997. cap.1, p.1-8.