

## Adherence to medication before and after the use of a Drug-Dispensing System with usage control

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The aim of the present work was to assess the adherence to medication from polymedicated patients before and after the use of a Drug-dispensing System with Usage Control (DDSUC) and compare the levels of the clinical parameters – blood pressure, postprandial glycemia, glycated hemoglobin, triglycerides and cholesterol. DDSUC consisted of a monthly drug-dispensing package, in the shape of a blister with a calendar. This quasi-experimental study was performed in a Basic Health Unit. Twenty four patients were selected to use DDSUC for 4 months. Medication adherence was assessed through Morisky-Green test. Among the participants of the study, 62.5% were women and the average age was 67 years old. Before the use of DDSUC, 83.3% of the patients were considered as “less adherent”. After the use of the system, 100% were considered as “more adherent” ( $p < 0.01$ ), the means of the systolic blood pressure decreased 23.7 mmHg ( $p=0.000$ ), the diastolic blood pressure decreased 12.1 mmHg ( $p=0.004$ ) and glycemia diminished 79.3 mg/dl ( $p=0.000$ ). The use of DDSUC improved the adherence to medication and decreased the values of the clinical parameters, making patients safer when it comes to respecting the correct use of their medication.

**Uniterms:** Medication/treatment adherence. Medicines/safety use. Medicines/dispensing. Drug-Dispensing System and Use Control. Polymedication.

O objetivo deste estudo foi avaliar a adesão ao tratamento medicamentoso de pacientes polimedicados antes e após o uso de um Sistema de Dispensação de Medicamentos e Controle de Uso (SDMCU) e comparar os níveis dos parâmetros clínicos - pressão arterial, glicemia pós-prandial, hemoglobina glicada, triglicérides e colesterol. O SDMCU foi constituído por uma embalagem mensal de dispensação de medicamentos, em forma de *blister* com calendário. Este estudo, do tipo quase-experimental, foi realizado em uma Unidade Básica de Saúde. Selecionaram-se 24 pacientes para utilizar o SDMCU por 4 meses. A adesão medicamentosa foi avaliada através do Teste de Morisky e Green. Entre os participantes do estudo, 62,5% eram mulheres e a idade média foi de 67 anos. Antes do uso do SDMCU, 83,3% dos pacientes foram considerados “menos aderentes”. Após o uso do sistema, 100% foram considerados “mais aderentes” ( $p<0,01$ ), a média da pressão arterial sistólica diminuiu 23,7 mmHg ( $p=0,000$ ), a diastólica diminuiu 12,1 mmHg ( $p=0,004$ ) e a glicemia diminuiu 79,3 mg/dL ( $p=0,000$ ). O uso do SDMCU melhorou a adesão medicamentosa e diminuiu os valores dos parâmetros clínicos, proporcionando aos pacientes uma segurança no que diz respeito à utilização correta de seus medicamentos.

**Unitermos:** Medicação/adesão ao tratamento. Medicamentos/uso seguro. Medicamentos/dispensação. Sistema de Dispensação de Medicamentos e Controle de Uso. Polimedição.

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## INTRODUCTION

The World Health Organization defines adherence as the extent to which the behavior of a person towards the proposed treatment responds to recommendations made by health professionals (WHO, 2003; Haynes *et al.*, 2008; Ahmed, Aslani, 2014). The lack of adherence to treatment is a widely recognized major problem both in the national and international scenarios. The average adherence rate of patients to treatment in developed countries is as low as 50%, whereas in developing countries this percentage is even lower (WHO, 2003; Ahmed, Aslani, 2014).

Non-adherence to pharmacological treatment consists of not using the drug in the correct dose, either by forgetting or by not respecting the dose frequency and/or discontinuing treatment before the recommended time. Non-adherence to the prescribed treatment has been responsible for the increase in hospitalization and health service costs (Sokol, 2005). Studies performed in the USA have showed that 33 to 69% of all hospitalizations were due to the low adherence to the pharmacological treatment prescribed, resulting in a cost of around US\$100 billion per year to the health system (Braithwaite *et al.*, 2013; Osterberg, Blaschke, 2005).

Adherence is a multi-dimensional phenomenon influenced by several factors (Santos *et al.*, 2013; WHO, 2003). Among the reasons identified in literature to non-adherence to medication are: side effects of the drugs, forgetfulness to take them, economic cost, fear for interaction with alcohol and other drugs, no awareness of the necessity of the treatment continuity; use of alternative treatments and fear for intoxication (Cavalari *et al.*, 2012; Nair *et al.*, 2011). Nevertheless, some researchers consider that the capacity of understanding and the knowledge in health of the patients may interfere positively in the treatment adherence (Zhang, Terry, Mchorney, 2014).

Furthermore, the presence of chronic diseases and the use of multiple medications are some of the various factors affecting adherence (WHO, 2003). The use of five or more medications, also known as polypharmacy, is associated with an increased risk and severity of adverse drug reactions, precipitation of pharmacological interactions, medication errors and especially the reduction of treatment adherence as well as the increase of morbidity and mortality (Secoli, 2010).

However, polypharmacy is a common practice within the health system, especially among elderly patients diagnosed with chronic diseases. Likewise, several factors may contribute to polypharmacy, such as a high prevalence of health problems, elevated number of doctors' appointments and self-medication (Baldoni *et al.*,

2013). That shows the need to adopt clinical intervention and educational and managerial measures to analyze and promote rationality in the use of drugs among the users of the Brazilian Public Health System (Baldoni *et al.*, 2013).

Among the proposed strategies and devices to improve medication adherence are: educational instruction for the patient (on diseases, treatments and lifestyle); educational assistance for health professionals; the supply of dispensing systems (electronic monitoring, blister packs, drug organizers); self-monitoring and recording of blood pressure; medication reminders (guidelines, phone calls and visits from a clinical pharmacist) (Zedler *et al.*, 2011; Haynes *et al.*, 2008). Most of these interventions show an improvement in adherence to medication, but few have significant results (Morgado *et al.*, 2011; Zedler *et al.*, 2011; Haynes *et al.*, 2008; Connor, Rafter, Rodgers, 2004).

Among the strategies mentioned previously, one can point out that the blister with calendar is a pack in which each pill is labeled with weekdays or month dates, providing a visual record of when the patient took the last pill (Zedler *et al.*, 2011). Each blister may contain single or multiple drugs (Ruppar, Conn, Russell, 2008; Zedler *et al.*, 2011). Drugs organized in blister packs, especially combined with orientation, may help patients to use their medication correctly, decrease medication errors and increase adherence to drug treatment (Zedler *et al.*, 2011).

Thus, the present work was based on the following hypothesis: the patients increased the adherence to medication after the use of a Drug-dispensing System with Usage Control (DDSUC). Considering the great quantity of drugs used in the treatment of chronic diseases, the difficulties from patients to keep adherence to the treatment and also the complications of the disease due to this lack of adherence, the present study aimed at evaluating adherence to drug treatment of polymedicated patients, before and after the use of a Drug-Dispensing System with Usage Control (DDSUC); also, we aimed at comparing the blood pressure levels, postprandial glycemia, glycosylated hemoglobin, triglycerides and cholesterol, between pre- and post-intervention.

## MATERIAL AND METHODS

### Location and study design

This is a quasi-experimental study conducted in a Pharmacy of the Brazilian Public Health System of Luiz Antônio, a town with 11,286 inhabitants in the inner area of the São Paulo state, Brazil (IBGE, 2013). The study was approved by the Research Ethics Committee of the Faculty

of Pharmaceutical Sciences of Ribeirão Preto, University of São Paulo (protocol CEP/FCFRP No. 121).

## Patients

From the database of the city's information system, a spreadsheet was generated using the Excel® program, containing the list of registered patients and drugs dispensed to them from August to December 2007. That survey showed that 6,573 patients attended the outpatient pharmacy during this period, adding up to 58.2% of the city population.

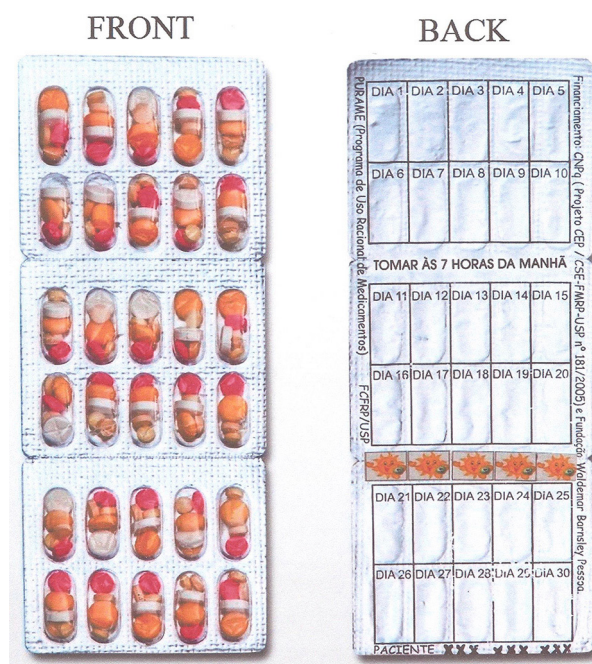
The inclusion criteria were: patients using polypharmacy, taking at least five different medications continuously to treat chronic diseases such as hypertension, diabetes mellitus, hypercholesterolemia and cardiovascular disease; patients that used monthly the services of the pharmacy from the Brazilian Public Health System, and that were under medical follow-up. The exclusion criteria were: individuals younger than 18 years old and those unable to manage their own medications, being dependent on others to do so.

## Intervention

In order to contribute to the medication treatment adherence and also to the safety of the polypharmacy patients, we developed the Drug-Dispensing System with Usage Control (DDSUC). The system is formed by a blister pack customized with written information containing the patient's name, the names of the medications and method of use. Each blister contains 30 compartments, which comprise the medication for a particular time of the day for a month of treatment. The blisters contain labels with icons that represent the timetable, such as the sun to show the day, the moon to show the night and food dishes to direct for the use of drugs together with meals.

For example, if the patient needs to take 5 pills at 7 am, they are together in the same compartment of the blister pack with the icon of the sun, ready for a month of use. The packs can be prepared for various times of the day, according to prescription and patient needs. For the protection of the photo-sensitive medication, amber-colored blisters are used. The blisters are marked from the 1<sup>st</sup> to the 30<sup>th</sup> day of the month (Figure 1).

For the follow-up of the participants of this study, the DDSUC was prepared by the pharmaceutical researcher according to the routine of each patient. The medications were organized in blister packages during the monthly meeting with the patient, which took place in a reserved room at the pharmacy and that lasted around 1 hour for



**FIGURE 1** - Drug-dispensing system with usage control for a month of use, at 7 in the morning.

each participant per month. In this very meeting, the patients were instructed by the pharmacist on how to correctly use the DDSUC.

Before the preparations of the blisters, studies on medicament interactions were performed with Micromedex (2007), in order to avoid potentially serious interactions, ensuring the pharmacotherapy safety. Whenever the researcher found evidence for interaction or incompatibility of the drugs, those were placed in different blisters so that they could be used at different times. Neither were there interventions with the doctors nor the gathering of information concerning the pharmacotherapeutic problems, in an attempt to keep the study focused on the assessment of the DDSUC use.

## Data collection

The period of data collection for the selected patients was four months with a total of six meetings which were conducted by the same researcher in a private room in the clinic, with a 60-minute average duration, to avoid any possible bias in the orientations and in the application of the data collection instrument among the patients.

In the first meeting, the guest participant in the study was asked to sign the consent form. At the same meeting, after acceptance to participate in the survey, socio-economic questionnaires were conducted, patients received information about medications they usually use (all



prescriptions were transcribed into an instrument containing the prescription date, the patient's identification number, drug names, dosage, frequency, time and duration of use). Hence, they performed the Morisky-Green test (MGT).

The MGT is an instrument used to measure individual compliance of pharmacological treatment. The scoring of MGT responses is as follows: Yes = 0 and No = 1. If all the answers are "no", the score will be 4 and if they are all "yes", the score will be 0, indicating adherence to the medication (Morisky, Green, Levine, 1986). This test was validated in the US in hypertensive patients, using blood flow control as the gold standard; it is also the most widely used questionnaire in Brazil (Bem, Neumann, Mengue, 2012).

In the second meeting after the first 30 days, the DDSUC was delivered for a month of treatment, and clinical parameters were measured (blood pressure, postprandial glycemia, triglycerides and cholesterol). Calibrated and accurate apparatus was used. The measure of the blood pressure was according to the technique described by the Brazilian Hypertension Guidelines (Sociedade Brasileira de Hipertensão, 2010).

In the other meetings, the DDSUC for monthly usage was delivered, clinical parameters were measured and the used packs were collected for usage control. The usage control was made through the pill count.

In the sixth and final meeting, the clinical parameters were measured; both the MGT and an instrument to assess the degree of patient satisfaction were applied to the DDSUC users.

The instrument to assess the degree of patient satisfaction consisted of four questions and aimed at assessing satisfaction towards the system for drug dispensation in custom blisters. Before asked, the questions for the study participants were analyzed by two experienced professionals in the area of knowledge related to this study and were then adapted to meet suggestions. This instrument was applied by a research assistant properly trained.

Participants with diabetes mellitus were asked to take a clinical examination of glycated hemoglobin (GH) in the first and last meeting, i.e. before and after using the DDSUC. That exam was performed at the clinical laboratory. The drugs used in this study were obtained monthly and provided to the patients free of charge in the local pharmacy of the Brazilian Public Health System.

### Statistical analysis

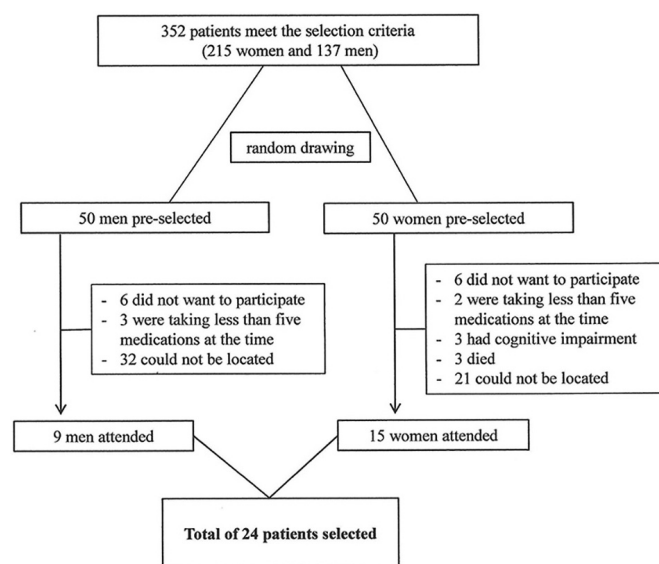
The database was constructed in an Excel spreadsheet (version 2007) and double data entry and data validation

were performed to identify possible errors. Descriptive statistics was used to analyze most variables and the results presented in terms of the absolute and relative frequency, mean  $\pm$  standard deviation (SD) with 95% confidence intervals. Statistical analysis was performed using the SPSS software, version 16.0.

In order to determine the sample normality, Kolmogorov-Smirnov's test was employed. For variables with normal distribution the "t Test" was applied, and for those which did not have normal distribution the "Wilcoxon Test" was performed (both for paired samples). P values  $\leq 0.05$  were considered significant.

### RESULTS

Following the selection criteria, 352 patients were pre-selected and, among those, 50 men and 50 women were randomly selected. Next, a phone call was made to all those selected. The ones that answered the phone call and that had time availability were invited to a meeting at the pharmacy in order to be invited to take part in the research, after the signature of a Term of Free Consent and Understanding. Some could not participate and others were not found. Convenience sampling was used because due to the available search period, it was not possible to include all patients. This way, we selected 24 patients. Figure 2 shows the flow diagram of patient selection.



**FIGURE 2** - Flow diagram of patient selection to use the Drug-Dispensing System with Usage Control.

Among the 24 study participants, there was a predominance of 62.5% females, mean age 67 years (SD 10.3), 54.2% were married, 79.2% retired, 54.2% received

1 to 3 minimum wages and 91.7% lived with their spouses or children. In relation to education, 25% were illiterate and 41.7% had 1 to 4 years of schooling.

Patients took an average of 8.4 (SD 2.9) different medicines per day for chronic use. In relation to the period of use, 29.1% of patients reported using for 1 to 7 years, 37.5% for 7 to 19 years and 33.4% were using their medications for more than 20 years, thus portraying the characteristics of chronic disease.

Regarding comorbidities, 50% of patients had two diagnoses and 37.5% had three. The average diagnosis was 2.3 per patient. Among the 24 patients, 20.8% had hypertension and diabetes, 20.8% hypertension and high triglycerides, and 25% hypertension, diabetes and high triglycerides concurrently.

Before the use of the DDSUC, 83.3% of the patients were considered as "less adherent" by MGT; after the use, 100% were considered as "more adherent". After the use of the system, the means of the systolic blood pressure decreased 23.7 mmHg ( $p=0.000$ ), the diastolic blood pressure decreased 12.1 mmHg ( $p=0.004$ ), glycemia decreased 79.3 mg/dl ( $p=0.000$ ) and glycated hemoglobin decreased 0.93% ( $p=0.011$ ). That result shows that the DDSUC significantly improved adherence to therapy (Table I).

In relation to GH, 5 (38.46%) of the 13 (100%) patients with diabetes had a reduction of more than 1% in the GH value after use of the DDSUC. The average GH was 8.7% before and 7.4% after using the system. The United Kingdom Prospective Diabetes Study demonstrated that reducing GH by 1%, chronic complications decrease significantly, decreasing the risk of microvascular

complications by 35% and reducing deaths from diabetes by 25% (Sociedade Brasileira de Diabetes, 2009).

The analysis of the frequency and percentage of instrument variables to assess the degree of patient satisfaction using the DDSUC showed that only 8.3% of patients felt confused when using the DDSUC; 95.8% would not like to return to the previous method of dispensing medications; 95.8% thought that the new method brought benefits to their lives and 100% would recommend the DDSUC to friends in a similar situation. Concerning the frequency and percentage score of the satisfaction degree of DDSUC users, among the 24 patients interviewed, 87.5% ( $n=21$ ) obtained the maximum score, i.e. they were very satisfied with the new method of medication dispensation.

## DISCUSSION

It was observed that most of the patients in the study were elderly, i.e. were 60 years or older. Due to cognitive and physical changes associated with aging, the elderly population has an increased risk for problems with adherence to medication (Ruppar, Conn, Russell, 2008). Among adults aged 65 or older, the prevalence of patients with two or more chronic health problems is high (65%) and that leads to the frequent use of multiple medications (Wolff, Starfield, Anderson, 2002). Predictably, the complexity of these frequent-use regimes promotes non-adherence to medication (Lee, Grace, Taylor, 2006).

Furthermore, the presence of three or more diagnoses, the clinical complexity of the patient with multiple diseases, metabolic changes and, consequently,

**TABLE I** - Description and comparison of variables between the pre- and post-intervention, Luiz Antônio, SP, 2009

	Time	n	Maximum	Minimum	SD*	Median	Average	p-value
<b>Systolic blood pressure</b>	Pre	24	180	110	19.39	150	147.50	0.000 <sup>a</sup>
	Post	24	140	110	8.75	120	123.75	
<b>Diastolic blood pressure</b>	Pre	24	130	50	17.44	95	92.08	0.004 <sup>b</sup>
	Post	24	100	70	6.59	80	80.00	
<b>Glycemia</b>	Pre	24	409	72	94.67	146.0	185.75	0.000 <sup>a</sup>
	Post	24	196	63	28.71	98.5	106.42	
<b>Glycated hemoglobin</b>	Pre	13	9.9	5.9	1.33	8.7	8.26	0.011 <sup>a</sup>
	Post	13	9.5	6.0	1.04	7.4	7.33	
<b>Cholesterol</b>	Pre	24	316	128	42.63	163.5	177.96	0.017 <sup>b</sup>
	Post	24	229	150	18.59	150.0	159.83	
<b>Triglycerides</b>	Pre	24	350	70	83.00	224.5	202.54	0.000 <sup>b</sup>
	Post	24	276	70	65.26	70.0	119.33	

\*Standard Deviation; <sup>a</sup>Parametric tests (t Test); <sup>b</sup>Non-parametric tests (Wilcoxon Test)

the use of polypharmacy are factors that increase the chance of the occurrence of potential drug interactions, which can cause adverse drug reactions and contribute to the treatment failure and ineffective therapy (Spriet *et al.*, 2009).

Non-adherence to medication is particularly problematic for asymptomatic conditions such as hypertension and hyperlipidemia. The lack of quick and easy access to the control parameters such as blood pressure, glycemia, cholesterol and triglycerides can lead to serious complications. The inadequacy of therapy, besides the increasing demand for health services, foments hospitalization and contributes to extend its duration (Nóbrega, Karnikowski, 2005), increasing healthcare costs (Sokol, 2005). Such conditions pose great challenges to the healthcare, opening up new horizons for research to enable patient monitoring in an effort to ensure adherence to drug therapy, and in particular, their safety and well-being.

Concerning the medication adherence, the number of participants with low adherence (83.3%), before the use of DDSUC, is similar to the results of a research performed with 90 hypertensive elders, aging 66 years old, in a Health Center in the town of Novo Horizonte – SP. The aim of that study was to assess the level of adherence to the medication treatment by TMG and, in that opportunity, the researchers found that 72.2% of the elders did not use their medication correctly (Eid *et al.*, 2013).

However, similar studies of intervention using blister packs for the organization of drugs also showed positive results in improving adherence after the use of the intervention (Simmons, Upjohn, Gamble, 2000; Lee, Grace, Taylor, 2006). Simmons, Upjohn and Gamble (2000) performed a study to evaluate the impact of using a calendar blister pack for glycemia and blood pressure control. The randomized controlled study followed 68 patients with low control of glucose for 8 months. The values of GH and blood pressure decreased in the group that used the blister pack, compared to the control group. In this study, the calendar blister pack showed that it is possible to improve metabolic and blood pressure control in patients taking multiple medications. In another study, Lee, Grace and Taylor (2006) also tested the efficacy of the use of a blister pack to organize medications associated with a clinical follow-up. After 6 months of intervention, adherence to medication increased and was associated with significant improvements in systolic blood pressure and cholesterol.

Ruppar, Conn and Russell (2008) conducted a literature review to identify randomized controlled trials of adherence to medication from literature published between 1977 and 2005. The literature review explored the

variety and nature of 63 studies that tested interventions on medication adherence for adults over 60 years. Eleven of the 63 studies used interventions for drug packaging and of those, four had significantly better adherence in the intervention group over the control group.

Medications organized into packaging or blister packs with calendars, especially if combined with education and other reminding strategies, can help patients use their medications correctly, reducing medication errors (Zedler *et al.*, 2011). Thus, care for the individual needs of the patient from the beginning of the therapy, combined with a differentiated system of dispensing drugs, with guidance, can motivate and increase the satisfaction of the patient, thereby promoting adherence.

The results obtained in the study allowed to state that the participants considered the use of DDSUC relevant to the improvement of adherence to the prescribed medication; participants also presented a high degree of satisfaction with the DDSUC. A similar result was achieved by Atozqui and Noguera (2004), who assessed the satisfaction degree of 112 elderly patients after the use of the “*Sistema Personalizado de Dosificación (SPD)*”. This system is available in Spain’s pharmacies and organizes the patients’ medications in a weekly package. The authors concluded that the use of the SPD reached a high degree of satisfaction among the users, what notably improved adherence to the prescribed treatment (Atozqui, Noguera, 2004).

The present study had limitations due to the small number of participants and short follow-up period. The DDSUC provides evidence on the overall impact on adherence, blood pressure, glycemia, GH, cholesterol and triglycerides, but cannot distinguish the impact of its individual components (blister packs versus guidance). Another limiting factor of the study was the lack of randomization and the control group.

However, most studies of intervention in adherence share methodology limitations, such as: lack of patient-centered results, limited statistical power, sample size, short follow-up period and reliable adherence measures (Haynes *et al.*, 2008; Pladevall *et al.*, 2010).

Future research may enlarge the sample size and inclusion criteria. The study is significant because it may contribute to future researches that seek for new models of drug-dispensing systems, once we have not found in Brazil similar studies.

## CONCLUSIONS

The DDSUC was designed to meet the needs of the population that has difficulty using their medications and,

likewise, to adhere to treatment. The study showed through the MGT and comparison of clinical parameters that the DDSUC improved adherence to therapy, promising to be a new model for optimizing complex treatments and ensuring patient safety.

Therefore, it is considered that the DDSUC had its relevance remarked in the study, and can be seen as an important tool for the current moment, when Brazil's Health Ministry, especially its Department of Pharmaceutical Assistance, points out the importance to modify the practices for drug dispensation, ensuring not only the access, but also the information for the patients that receive their medication in the Health Units' Pharmacies.

Promoting quality attention to polymedicated patients and implementing interventions that ensure adherence to drug treatment are actions that may provide the rational use of medication.

It is hoped that Brazil's Unified Health System and the National Program for Pharmaceutical Assistance can rapidly implement educational and drug-dispensing interventions to ensure the adherence and rational use of drugs, decreasing hospital commitment caused by wrong therapeutics, as well as the expenses from such commitments.

The use of DDSUC improved adherence to drug treatment and decreased the values of blood pressure, providing the patient with more safety and satisfaction when it comes to organizing and correctly using their medication.

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## CONFLICTS OF INTEREST

None declared.

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