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Article

Clinical outcomes of medication therapy management services in primary health care

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This study evaluates whether the integration of pharmacists into health-care teams through the delivery of pharmaceutical care-based medication therapy management (MTM) services can improve the clinical outcomes of patients with chronic health conditions in the primary health-care setting. A retrospective descriptive study of 92 outpatients assisted by MTM pharmacists in primary health-care units was carried out over 28 months (median follow-up: 05 months). Patients were followed up by MTM pharmacists, with a total of 359 encounters and a ratio of 3.9 encounters per patient. The prevalence of hypertension, diabetes mellitus and dyslipidaemia was 29.5%, 22.0% and 19.4%, respectively. There was a high prevalence of drug-related problems with a ratio of 3.4 per patient. Pharmacists performed a total of 307 interventions to prevent or resolve drug-related problems. With regard to control of the most prevalent chronic medical conditions, a high percentage of patients reached their therapy goals by the last encounter with the pharmacist: 90.0% for hypertension, 72.3% for diabetes mellitus and 90.3% for dyslipidaemia. MTM services provided by pharmacists resolved drug therapy problems and improved patients' clinical outcomes. This study provides evidence for health-care managers of the need to expand the clinical role of pharmacists within the Brazilian public health-care system.

Uniterms: Pharmaceutical care/primary care. Medication therapy management. Chronic health/conditions. Pharmacists/professional practice/Brazil

INTRODUCTION

In pharmaceutical care practice the pharmacist takes responsibility for meeting patients' drug-related needs by detecting and resolving drug-related problems (DRPs). In this study, this professional practice is materialized into the clinical service known as medication therapy management (MTM). MTM services follow the philosophy and patient care process of pharmaceutical care practice as proposed by Cipolle, Strand and Morley (2012) and, for this reason, they are called "pharmaceutical care-based MTM" (Ramalho de Oliveira, 2009; Obreli Neto *et al*., 2011; de Souza *et al*., 2007; Lee, Grace, Taylor, 2006; Cipolle, Strand, Morley, 2012).

Various studies have demonstrated the positive impact of pharmaceutical care practice on patients' health outcomes. A recently published study showed that exposure to face-to-face MTM services resulted in improvement of medication adherence measured by proportion of days covered across multiple chronic disease medication classes (Brummel, Carlson, 2016). Fikri-Benbrahim *et al*. (2013) showed that adherence to antihypertensive therapy in a pharmacist intervention group was 4.07 times higher than in a control group. Tan *et al.* (2014) demonstrated that the integration of pharmacists into primary care clinics had positive effects on primary outcomes related to medication use or clinical outcomes. Strand *et al.* (2004) showed that 88.0% of patients' DRPs were resolved by pharmacists, while Borges *et al.* (2010) successfully resolved 62.7% of the identified DRPs.

Despite the potential impact of pharmaceutical care on medication use, and while professionals and researchers in developed countries are involved in understanding and improving the sustainability of MTM

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services (Sorensen *et al.*, 2016), these are still limited in developing countries such as Brazil. Pharmacists in developing countries work mainly in activities related to acquisition and inventory control of drugs, with little involvement in direct patient care (Obreli Neto *et al.*, 2011). There are a few published studies on the clinical outcomes of this practice in Brazil, mainly in the primary care setting (Mourão *et al.*, 2013; Obreli Neto *et al.*, 2011; Obreli Neto, Cuman, 2010; Lyra Júnior, Marcellini, Pelá, 2008; de Souza *et al.*, 2007; Lyra Júnior *et al.*, 2007).

Primary care is the main option for access to health care for approximately 70% of the Brazilian population (Obreli Neto *et al*., 2011). In primary care, the high prevalence of chronic conditions is associated with an increase in the use of medications Obreli Neto *et al*., 2011; Lee, Grace, Taylor, 2006). Also, the high use of medications is associated with the development of DRPs, which can negatively impact on patients' health and increase the total health-care costs (Obreli Neto *et al*., 2011; Lee, Grace, Taylor, 2006; Cipolle, Strand, Morley, 2012).

The aim of this study was to evaluate whether the integration of pharmacists into health-care teams through the delivery of pharmaceutical care-based medication therapy management services can improve the clinical outcomes of patients with chronic health conditions in the primary care setting.

PATIENTS AND METHODS

A retrospective descriptive study was conducted including all patients (n=92) assisted by MTM pharmacists in primary health-care units in Divinópolis (MG, Brazil) between October 2010 and February 2013.

Ethical approval

The study was conducted following the Declaration of Helsinki guidelines (WMO, 1996) and the provisions of the Brazilian National Health Committee. The Institutional Human Experimentation Committee of UFSJ (No. 007/2011) approved it.

Setting

MTM services were provided in three units of the Family Health Strategy (FHS) in the city of Divinópolis, Minas Gerais, Brazil. Two clinical faculties, three pharmacy students and one pharmacist from the local health system composed the team. The criteria for patient referral to the MTM service were: multiple medication use (two or more medications), old age (≥ 60 years), lack of response to treatment, presence of adverse drug reactions and non-adherence to the prescribed treatment. Patients were eligible if they met at least one criterion. The number and frequency of appointments were individualized according to the patient's needs (weekly, fortnightly or monthly) and the interventions were implemented either directly with the patient or with the physician.

Data collection and analysis

Data were collected from the patient's medical record. The first consultation was called "before initiating delivery of MTM services" and "abandonment of service" or "final data collection (February of 2013)" was identified as "after delivery of MTM services". A coded structured instrument was constructed, which included: clinical conditions according to the International Classification of Diseases-10 (WHO, 1992), pharmacotherapy utilized [according to the Anatomical Therapeutic Chemical Code (WHO, 2012), medicine dosage forms and duration of treatment], clinical status of the patient according to the established goals of therapy, DRPs, interventions implemented by the pharmacist and the therapy goals achieved. The data were stratified by polypharmacy (use of five or more medications) according to Flores and Mengue (2005).

To analyze the results, we used the theoretical framework proposed by Cipolle, Strand and Morley (2012) for the description of the pharmacotherapeutic needs, types of DRPs and the categorization of pharmacist interventions. The following parameters were utilized in assessing whether or not the therapy goals were met: hypertension, blood pressure ≤ 139/89 mmHg (Dipiro *et al*., 2011); type 2 diabetes mellitus, pre- and postprandial glucose levels of < 130 mg/dL and <180 mg/dL, respectively (Dipiro *et al*., 2011); hyperlipidaemia, LDL < 130 mg/dL (Semla, Beizer, Higbee, 2012); anxiety disorder, absence of insomnia, muscle tension, irritability or restlessness (Young *et al*., 2005); major depression, absence of changes in sleep, appetite, daily accomplishment of tasks, absence of distress and suicide ideation (Young *et al*., 2005); osteoporosis, the absence of fractures, reduction of pain, increase in functional capacity and maintenance of bone mass (Dipiro *et al*., 2011); pain, absence of pain (Dipiro *et al*., 2011); hypothyroidism, free T4 in the range of 5.0–12.0 mcg/dL and TSH in the range of 0.4–4.5 mU/L (Young *et al*., 2005); dyspepsia, lack of heartburn and stomach discomfort (Dipiro *et al*., 2011); and epilepsy and absence of seizure (Dipiro *et al*., 2011).

As proposed by Cipolle, Strand and Morley (2012), in this study the health status was used to measure patients' clinical outcomes. The clinical outcome status of each of the patients' medical conditions was assessed by the research team at the last MTM visit and compared with the baseline health status using data from the patient's medical record. The baseline health status was classified as positive when the health condition was controlled and negative when it was not controlled. According to Cipolle, Strand and Morley (2012), the clinical outcome status at the last MTM visit was considered positive when it was classified as "resolved", "stable", "improved" or "partially improved". The following categories were used when the clinical status was considered negative: "no improvement", "worsened", "therapeutic failure" and "death".

For data analysis, the database was set up using the technique of double entry and processed using the Statistical Package for the Social Sciences (SPSS – version 22). Statistics consisted of measures of central tendency, variability and proportions. McNemar's test was used to verify the effect of pharmacist intervention. This test examines treatment effect and tests the hypothesis that the change in proportions between the different time points is due to chance. Thus, when we reject this hypothesis, we can say that there is evidence of a treatment effect (Pagano, Gauvreau, 2004).

RESULTS

The median age of patients was 63.0 years and 67.4% (n=62) were females. With regard to the follow-up of patients, there were 359 consultations with a median of 3.9 per patient. Three hundred and twenty health problems were found, with a median of 3.5 per patient.

Ten medical conditions represented 83.8% (n=268) of the total reported. The most prevalent medical conditions were: hypertension (29.5%), type 2 diabetes mellitus (22.0%) and dyslipidemia (19.4%). Dyspepsia, type 2 diabetes mellitus and dyslipidemia had the greatest proportion of patients who had uncontrolled disease: 80.0%, 66.0% and 54.1%, respectively (Table I).

Most medications were prescribed for the treatment and control of non-communicable diseases (NCDs) such as hypertension, diabetes and dyslipidemia. The 15 most commonly used drugs accounted for 65.3% of the total number of drugs (Table II). On average, each patient used 6.0 different medications.

During MTM visits, 316 DRPs were detected with an average of 3.4 DRPs per patient and 88.6% of DRPs were related to polypharmacy. The most prevalent DRP was adverse reaction (31.0%) (Table III).

The causes of DRPs were the following: 24.1% (n=71) undesirable effect, unsafe medication, presence of a contraindication and treatment of preventable adverse reactions; 22.4% (n=66) drug interactions; 7.8% (n=23) frequency, dosage and/or incorrect administration; 7.5% (n=22) lack of clinical indication; 6.1% (n=18) patient preference for drug cessation; 5.8% (n=17) patient failure to understand instructions; 4.8% (n=14) high dose; 4.4% (n=13) duplicate therapy; 4.1% (n=12) ineffective dose (low dose); 3.7% (n=11) more effective drug available or the drug is not indicated for the condition; and 9.5% (n=28) were related to other problems.

A total of 307 interventions were performed, and most of them contributed to the achievement of the patient's therapeutic goal. The most common intervention was medication change (Table IV).

At the beginning of the MTM service (at baseline), the clinical status of the patients' medical conditions was considered negative in almost half of the times, 47.5%. After the service was delivered, the final evaluation showed that 83.9% (n=156) of the clinical status was positive (Table I). In 21.2% (n=65) of interventions there was no record about its impact on the goal of therapy.

DISCUSSION

The high prevalence of polypharmacy in this study can be explained by the fact that it was one of the criteria for referral to MTM services. However, the high prevalence of chronic diseases also contributed to polypharmacy (Sousa *et al*., 2012; Flores, Mengue, 2005). The high incidence of DRPs in patients with polypharmacy has also been shown in other studies (Correr *et al*., 2007; Koh *et al*., 2005).

The therapeutic goal at the first MTM visit of most of the health conditions associated with polypharmacy, especially hypertension, diabetes and dyslipidaemia, was not being achieved. As shown in the present study and in previously published research, MTM services represent an effective strategy for the resolution of DRPs, which can significantly improve patients' clinical outcomes (Tan *et al*., 2014; Fikri-Benbrahim *et al*., 2013; Zaman Huri, Chai Ling, 2013; Mourão *et al*., 2013; Obreli Neto *et al*., 2011; Alencar *et al*., 2011; Correr *et al*., 2011; Borges *et al*., 2010; Obreli Neto, Cuman, 2010). In a study examining 10 years of pharmaceutical care services in Minnesota, Ramalho de Oliveira *et al*. (2010) also pointed out the importance of pharmacist-delivered medication management services for the control of hypertension, diabetes and dyslipidemia.

Interestingly, in the case of psychiatric disorders,

TABLE I – Analysis of patients regarding the clinical outcome status of their medical conditions before and after initiating the delivery of MTM services, stratified by polypharmacy

Medical condition[1]/ Clinical status[2,3]	Total % (n) n=268		With Polypharmacy % (n) n=229		P VALUE	Without Polypharmacy % (n) n=39		P VALUE
	Before	After	Before	After		Before	After	
Arterial Hypertension (n=79)								
Positive	51.9 (40)	90.0 (54)	50.8 (31)	88.0 (44)	0.0003	56.2 (9)	100.0 (10)	0.0455
Negative	48.1 (37)	10.0 (6)	49.1 (30)	12.0 (6)		43.8 (7)	-	
Diabetes mellitus 2 (n=59)								
Positive	34.0 (18)	72.3 (34)	38.6 (17)	74.4 (29)	0.0013	11.1 (1)	62.5 (5)	0.0833
Negative	66.0 (35)	27.7 (13)	61.4 (27)	25.6 (10)		88.2 (8)	47.5 (3)	
Dyslipidemia (n=52)								
Positive	45.9 (17)	90.3 (28)	51.5 (17)	92.9 (26)	0.0114	-	66.7 (2)	0.0833
Negative	54.1 (20)	9.7 (3)	48.5 (16)	7.1 (2)		100.0 (4)	33.3 (1)	
Anxiety (n=25)								
Positive	85.0 (17)	87.5 (14)	85.0 (17)	87.5 (14)	-	-	-	-
Negative	15.0 (3)	12.5 (2)	15.0 (3)	12.5 (2)		-	-	
Depression (n=13)								
Positive	75.0 (9)	70.0 (7)	75.0 (9)	70.0 (7)	0.5637	-	-	-
Negative	25.0 (3)	30.0 (3)	25.0 (3)	30.0 (3)		-	-	
Osteoporosis (n=13)								
Positive	100.0 (4)	100.0 (5)	100.0 (3)	100.0 (4)	-	100.0 (1)	100.0 (1)	-
Negative	-	-	-	-		-	-	
Pain (n=9)								
Positive	60.0 (3)	80.0 (4)	60.0 (3)	80.0 (4)	-	-	-	-
Negative	40.0 (2)	20.0 (1)	40.0 (2)	20.0 (1)		-	-	
Hypothyroidism (n=7)								
Positive	80.0 (4)	100.0 (3)	80.0 (4)	100.0 (3)	-	-	-	-
Negative	20.0 (1)	-	20.0 (1)	-		-	-	
Dyspepsia (n=6)								
Positive	20.0 (1)	60.0 (3)	20.0 (1)	60.0 (3)	-	-	-	-
Negative	80.0 (4)	40.0 (2)	80.0 (4)	40.0 (2)		-	-	
Epilepsy (n=5)								
Positive	100.0 (3)	100.0 (4)	100.0 (3)	100.0 (4)	-	-	-	-
Negative	-	-	-	-		-	-	
Total								

[1] Number of patients with medical conditions stratified by clinical status and polypharmacy (in the column). [2] The classifications of clinical status named controlled (first appointment) or resolved, stable, improvement and partial improvement (last appointment) were aggregated as POSITIVE, and the classifications not controlled (first appointment) or no improvement, worsening, therapeutic failure and death (last appointment) were aggregated as NEGATIVE. [3] There are patients whose therapeutic goal records, or clinical status, in the first and last MTM visit were not described.

there was not much difference in the attainment of therapeutic goals before and after service delivery. This may reflect the difficulty in objectively measuring clinical results or a deficiency in the skills of pharmacists in evaluating the subjective parameters utilized in mental health. In the case of osteoporosis, all patients were taking alendronate sodium and were achieving their therapeutic goals at the beginning of the study. The

TABLE II - Most used medications by patients referred to medication therapy management services, stratified by polypharmacy

Medication	Total %[1] (n) n=402	With Polypharmacy %[2] (n) n=344	Without Polypharmacy %[2] (n) n=58
Simvastatin	12.7 (51)	86.3 (44)	13.7 (7)
Metformin	11.9 (48)	79.2 (38)	20.8 (10)
Hydrochlorothiazide	11.4 (46)	73.9 (34)	26.1 (12)
Captopril	10.0 (40)	80.0 (32)	20.0 (8)
AAS	8.0 (32)	87.5 (28)	12.5 (4)
Insulin NPH	7.0 (28)	96.4 (27)	3.6 (1)
Losartan	8.0 (27)	88.9 (24)	11.1 (3)
Glyburide	6.5 (26)	73.1 (19)	26.9 (7)
Nifedipine extended-release	5.0 (21)	85.7 (18)	14.3 (3)
Furosemide	4.2 (17)	100.0 (17)	-
Propranolol	3.7 (15)	93.3 (14)	6.7 (1)
Omeprazole	3.7 (15)	86.7 (13)	13.3 (2)
Clonidine	3.0 (12)	100.0 (12)	-
Alendronate Sodium	3.0 (12)	100.0 (12)	-
Spironolactone	3.0 (12)	100.0 (12)	-

[1]Calculated estimates considering the column totals. [2]Calculated estimates considering the row totals in order to compare "with" and "without" polypharmacy.

TABLE III – Profile of DRPs stratified by polypharmacy

Pharmaceutical needs[1]	Types of DRP	Total % (n) n=316	With Polypharmacy % (n) n=280	Without Polypharmacy % (n) n=36
Indication	Unnecessary medication	15.5 (49)	91.8 (45)	8.2 (4)
	Need for additional medication	5.1 (16)	81.3 (13)	18.7 (3)
Effectiveness	Medicine ineffective	5.1 (16)	87.5 (14)	12.5 (2)
	Low Dose	18.0 (57)	86.0 (49)	14.0 (8)
Safety	Adverse reaction	31.0 (98)	89.9 (88)	10.1 (10)
	High Dose	12.0 (38)	97.4 (37)	2.6 (1)
Adherence	Non-adherence	13.3 (42)	81.0 (34)	19.0 (8)

[1]Pharmacotherapies

parameters used to assess the effectiveness of treatment were the absence of pain, fractures and an increase in functional capacity. One limitation of the study was that bone densitometry was not performed at the beginning or at the end of the service. However, patients receiving MTM did not have access to this examination, and the goal of this study was to evaluate the impact of MTM services in real life. This limitation is conservative for the purposes of the study, since it points to an underestimate of the effectiveness of MTM services.

Adverse drug reactions were the most prevalent DRP in the present study. The patient's attitudes toward medications, which reflect a personal evaluation of the drug as good or bad and harmful or beneficial, are thought to influence behaviour and adherence (Lyra Júnior *et al*., 2007; Mardby, Akerlind, Jorgensen, 2007; Phatak, Thomas, 2006; Osterberg, Blaschke, 2005; WHO, 2003; Ajzen, 2001; Petty, Wegener, Fabrigar, 1997). A study by Correr *et al*. (2007) found that the safety of the treatment was the most significant risk factor for DRPs.

TABLE IV - Interventions carried out during delivery of medication therapy management services and therapeutic goals achieved

Intervention performed	Total % (n) n=307	Therapeutic goal achieved % (n) n=202	Therapeutic goal not achieved % (n) n=40
Change medicine	22.1 (68)	84.2 (48)	15.8 (9)
Interrupt pharmacotherapy	16.3 (50)	75.0 (27)	25.0 (9)
Patient instructions *	16.0 (49)	79.4 (27)	20.6 (7)
Change dose	11.1 (34)	75.0 (18)	25.0 (6)
Remove barriers to treatment adherence	9.8 (30)	96.2 (26)	3.7 (1)
Start monitoring of adverse reaction	8.1 (25)	76.0 (19)	24.0 (6)
Start laboratory monitoring	6.8 (21)	94.1 (16)	5.9 (1)
Start new pharmacotherapy	4.9 (15)	90.9 (10)	9.1 (1)
Provide reminders with timetables for medicines	4.9 (15)	100.0 (11)	0.0 (0)

* Appropriate medication use, nutrition education and information about physical activity.

Adverse drug reactions can be associated with negative clinical outcomes in patients with chronic diseases, so interventions to solve this problem are very important (Gastelurrutia *et al*., 2011). A high occurrence of adverse drug reactions can lead to higher rates of treatment interruption (Vasconcelos *et al*., 2005; Firmo, Lima-Costa, Uchôa, 2004). Other authors pointed out the relationship between polypharmacy, adverse drug reactions and non-adherence (Secoli, 2010; Rocha *et al*., 2008; Rozenfeld, 2003).

Changes or recommendations for a change of a patient's medication were the most common intervention to resolve the DRPs of adverse drug reactions. For instance, many patients were on captopril (n=40) and had presented with a dry cough. Also, a significant number of patients were using clonidine (n=12) – mainly men, who complained about adverse reactions such as dry mouth, bradycardia and impotence, and abandoned the treatment due to these effects. Clonidine is mentioned in the Beers criteria as a drug that has a high risk of adverse effects, including those that affect the central nervous system, orthostatic hypotension and bradycardia. It is interesting to note that the mean age of our patients was 63 years, which is considered elderly in Brazil, and clonidine should not be routinely used for the treatment of hypertension in this population (Gastelurrutia *et al*., 2011). Therefore, the pharmacist recommended that the physician change the antihypertensive drug to a safer medication.

It was found that many diabetic patients were using non-selective beta blockers such as propranolol (n=10), which is contraindicated in these patients because of the difficulty in identifying symptoms of, and recovering from, hypoglycemia (Dipiro *et al*., 2011). In this case, a change to a selective beta blocker such as atenolol was recommended. Also, in some cases, a switch from metformin 850 mg once daily to metformin 500 mg slow release twice daily was suggested, depending on the occurrence of gastrointestinal intolerance (Dipiro *et al*., 2011; Young *et al*., 2005).

The DRP of low dose was also common, with the most frequent cause being an interaction between captopril and food. This result is in agreement with other studies, which also found that a low dose was the most prevalent DRP in clinical pharmacy services (Correr *et al*., 2007; Strand *et al*., 2004). The collaboration between pharmacists and physicians was essential in resolving and/or preventing DRPs in this study. The physicians were receptive to MTM pharmacists' interventions. Collaborative working relationships were developed over time as MTM pharmacists started taking more responsibility for patient care and demonstrated competency.

The significant clinical impact of pharmaceutical care-based MTM, as shown by the improvement in the clinical status of the most prevalent health conditions from the first to the last MTM visit, should be highlighted. As previously underscored (Strand *et al.*, 2004; Ramalho de Oliveira, Brummel, Miller, 2010), these positive results can be partly explained by the inclusion of a professional, an MTM pharmacist, whose main responsibility is to

improve drug therapy outcomes through collaboration with the patient and the health-care team. Moreover, this professional follows a standardized practice and a logical decision-making process that is based on science and reproducible in the real world.

The use of patient records as a source of information is another limitation of this study, as reported by other authors (Kahn, Ranade, 2010). This emphasizes the need for an improvement in the documentation process, as demonstrated by other authors (Sousa *et al*., 2012; Kahn, Ranade, 2010; Becker, Bjornson, Kuhle, 2004).

CONCLUSIONS

The study showed that a large proportion of patients using medications in the primary care setting were not reaching their therapy goals when cared for by the traditional health-care team. The management of patients' drug therapy by MTM pharmacists improves the control of medical conditions, particularly chronic conditions. There was a positive association between polypharmacy and occurrence of DRPs, demonstrating that polypharmacy should be a criterion for the referral of patients to MTM services. Considering that in this study most drugs were used to treat chronic conditions such as hypertension, diabetes and hyperlipidemia, the effective training of pharmacists in these conditions and their treatments might positively affect the health outcomes in primary care. The Brazilian public health system needs to adopt measures to improve control and prevent aggravation of chronic health conditions, and the provision of MTM services might be one of these measures.

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