



RESEARCH ARTICLE

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## NEGATIVE RESULTS ASSOCIATED WITH MEDICINES AND QUALITY OF LIFE IN MULTIPLE SCLEROSIS

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### ABSTRACT

Increased morbimortality related to non-transmissible diseases and pharmacotherapy required a new attitude of the pharmacist and greater involvement in the prevention of negative clinical outcomes associated with the use (or non-use) medicines. For patients with chronic diseases such as multiple sclerosis (MS), the influence of treatment on quality of life (QOL) is a crucial determinant during therapy. The aim of the study was to identify the impact of NRM on QL of MS patients. **Method:** Cross-sectional, descriptive and analytical study of MS patients. In this study was used data from the clinical interview, computerized system, medical records and patient health documents. The NRM were identified and evaluated by the investigator. QOL was determined by the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36). **Results:** Eighty-one patients with MS participated in the study. All patients presented at least 01 NRM, mean of 03 NRM per patient (ranging from 01 to 04). A total of 354 NRM was identified. Regarding QOL, results were observed with below-desirable averages in all domains, with the domain "physical limitations" being the lowest average while "social aspects" being the highest average. Regarding QOL, results were observed with below-desirable averages in all domains, with the domain "physical limitations" being the lowest average while "social aspects" being the highest average. Bivariate analysis of the NRM quantitative and its influence on patients' quality of life showed a significant correlation with all domains of the physical and mental component (Spearman's linear correlation test,  $p < 0.005$ ). **Conclusions:** The NRM impacted the QOL of the patients, evidencing the need to assure better conditions of care and follow-up of the NRM in MS patients.

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### INTRODUCTION

The growth of morbimortality inherent to non communicable diseases and pharmacotherapy has impacted the health systems and required a new new attitude from pharmacists. Thus, active collaboration of these professionals is necessary for the

redesign of the model of attention to chronic conditions (FEDERAL COUNCIL OF PHARMACY, 2016). The WHO highlights the role of pharmacist in health care system, evidencing the need for greater involvement of these professionals to improve the process of medication use and outcomes in patient health (WHO, 2004). There were several concepts about the problem related to pharmacotherapy that

permeate the discussions between the researchers. However, there is now a standardized and internationally accepted classification. Negative clinical outcomes or outcomes associated with NRM are undesirable (or suspected) changes in the patient's health status attributable to the use (or non-use) of medications (CIPOLLE; STRAND; MORLEY, 2012; CONSENSUS, 2007; CORRER; OTUKI, 2013). To detect negative clinical outcomes or outcomes associated with NRM, clinical variables (symptom, signal, clinical event, metabolic or physiological measurement, death) are used to demonstrate that the therapeutic objectives initially established for the patient were not reached (AMARILES; FERNÁNDEZ-LLIMÓS; FAUS, 2006; HEPLER; STRAND, 1999; SABATER-HERNÁNDEZ, 2016). In patients with chronic disorders, the impact of the treatment of the disease on their quality of life is considered a determinant factor to guarantee a good therapeutic evolution (NOURBAKHS; JULIAN; WAUBANT, 2017). Multiple sclerosis (MS) is a chronic, autoimmune disease that affects the central nervous system (CNS) and is considered one of the non-traumatic neurological conditions that most causes disability in young (VEAUTHIER, 2015), causing significant physical and psychosocial damage to its bearer (AMATYA, *et al.*, 2017). Natural evolution of this disease often has a negative impact on the routine activities of its patients, leading, in particular, to a significant decline in their quality of life (FERNÁNDEZ *et al.*, 2011; NOURBAKHS; JULIAN; WAUBANT, 2017; TORKILDSEN; MYHR; BØ, 2016).

The WHO defines health-related quality of life (HRQL) as: "The individual's perception of how well he or she performs his or her functions in daily life and assesses his or her well-being in the context of the culture and values of the society in which he lives, their goals, expectations, standards and interests" (WHO, 2000). In the field of health, the scientific literature tends to use the HR QoL concept and it refers to dimensions of quality of life that are compromised by health status and can be affected by health care (MEYERS; GAGE; HENDRICKS, 2000; MCCABE; MCKERN, 2002; LATIMER-CHEUNG, *et al.*, 2013). Estimates of the quality of life in MS patients allow us to identify the impact of the disease and the proposed treatments in the physical, psychic, emotional and social spheres throughout its progression, thus constituting important elements that aid in clinical decision making (BERRIGAN, *et al.*, 2016; MCCABE; MCKERN, 2002; MEYERS; GAGE; HENDRICKS, 2000; LATIMER-CHEUNG, *et al.*, 2013). Thus, the present study aimed to identify the impact of NRM on the quality of life of MS patients.

## MATERIALS AND METHODS

A cross-sectional, descriptive and analytical study, developed at the Pharmacy School of the Federal University of Mato Grosso do Sul (UFMS), Brazil, with MS patients. All patients were assisted by the Specialized Component of Pharmaceutical Assistance reference in the State for free dispensation of medicines for treatment of MS by the Unified Health System (SUS). Patient data were obtained from the computerized system, medical records from the neurology clinic referred to in the SUS, patient health documents and clinical pharmaceutical interviews. The study was carried out according to Resolution n°. 466 of December 12, 2012, of the National Council of Ethics in Research of the Ministry of Health. The project was approved by the Committee of Ethics

in Research in Human Beings of the UFMS on October 17, 2016, through opinion n°. 1.777.902. Clinical interviews, access to medical records and other patient health records were conducted from October 2016 to August 10, 2017. The study included patients with MS according to the International Classification of Diseases (ICD-10 G-35), assisted by the State of Mato Grosso do Sul and belonging to the dispensing nucleus of the Pharmacy School of UFMS. Patients with three consecutive months or more without records of drug dispensing at the Pharmacy School (considered inactive) were excluded from the study; patients who did not agree to participate in the study and/or did not sign the Informed Consent Form; patients of indigenous origin, quilombolas and belonging to border populations or institutionalized also were excluded in order to avoid bias in research due to cultural difference. The follow-up procedure applied by the pharmacist during the consultations consisted of the following phases: 1) patient recruitment 2) initial clinical interview, 3) pharmaceutical evaluation with detection of NRM 4) care plan and pharmaceutical interventions, and 5) quality assessment life of MS patients. Return visits followed a clinical protocol previously developed for the service, as well as an evaluation of the individualized needs of each patient. The NRMs were categorized according to the consensus and considerations of the area's authors (AMARILES; FERNÁNDEZ-LLIMÓS; FAUS, 2006; CIPOLLE; STRAND; MORLEY, 2012; CONSENSUS, 2007; CORRER; OTUKI, 2013; HEPLER; STRAND, 1999; SABATER-HERNÁNDEZ, 2016).

The NRMs were identified by means of the individual case study, evaluating the pharmacotherapy in a standard form and classified according to the variables: need, therapeutic adherence, effectiveness and safety of medication use, signs and symptoms presented by the patient, physiological, biochemical and metabolic outcomes related to the control of the disease, and its relation with the drug use or non-use process. Doubts in the classification of RNM were healed through consultation and discussion with a second researcher with clinical experience. Quality of life was determined by the application of the *Medical Outcomes Study 36-Item Short-Form Health Survey* (SF-36) (WARE; KOSINSKI; GANDEK, 1993; CICONELLI, 1997). Based on a multidimensional health model, the SF-36 scale is divided into two components, physical and mental. The physical component consists of the following domains: functional capacity (with ten items), general health (with five items), pain (with two items) and physical aspects (with four items). The mental component consists of the domains: mental health (with five items), vitality (with four items), social aspects (with two items) and emotional aspects (with three items). The evaluation of each item was performed by means of the summed points method (*Likert* method), with values ranging from 0 to 100 points, being the highest scores indicative of a better quality of life (FERNÁNDEZ *et al.*, 2011; CICONELLI, 1997; WARE; KOSINSKI; GANDEK, 1993). The statistical analysis comprised a descriptive presentation of the variables considered in the study. All the information collected was double-digested in a database and tested for normal distribution by the *Kolmogorov-Smirnov* test, prior to the selection of the statistical tests. Numerical and ordinal descriptive analysis was expressed as mean and standard deviation (SD). For bivariate analysis of correlation between data, Pearson's or Spearman's coefficient was used. The organization of the database and statistical analysis was performed using the programs Microsoft Excel® 2016 and

SPSS® 17.0 for Windows. A probability of error of type I of 5% was considered acceptable, being considered significant value of  $p < 0.05$ .

## RESULTS

The study included 81 MS patients with a mean age of  $41 \pm 11.6$  years, 74% female, 74% white, 42% with higher education, 53% with co morbidities and 52% with physical limitations. Patients were diagnosed on average at  $33 \pm 10.6$  years, 51% had up to five years of treatment. The most frequent comorbidities found were depression, anxiety disorder, hypothyroidism, dyslipidemia, and systemic arterial hypertension. The most used drugs were betainterferone 44 mcg (30%) and glatiramer acetate 20 mg / dL (25%), and 64% of the patients were using drugs considered of the first line for the treatment of MS. The general profile of drug use showed that 65% were polymedicated. Among the patients, 54% reported an adverse reaction to the drug in use for conventional treatment of MS. As adjunctive therapy, 88% of the patients used vitamin D<sub>3</sub> and 57% used doses higher than those considered safe (10.000 IU/day) by the Consensus of the Scientific Department of Neuroimmunology of the Brazilian Academy of Neurology (BRUM, *et al.*, 2014). In 100% of the evaluated patients, NRM was observed, with an average of three RNMs per patient (ranging from 01 to 04). A total of 354 RNMs were identified, considering the established categories. The stratification of the NRM into categories is presented in table 01. Considering the total number of patients evaluated, it was observed that the mean scores obtained with the SF-36 scale in each domain presented variations among themselves, with the "physical limitations" domain presenting the lowest mean and the "social aspects" domain presenting the higher, as shown in table 02.

**Table 1. Distribution of MS patients according to MRI stratification into sub categories according to the amount affected by patient**

Stratification of the RNM	%	n
Necessity	21	76
Untreated health problem	09	32
Changes in pharmacotherapy	12	44
Effectiveness	14	50
Ineffective	07	25
Low dose	07	25
Safety	36	127
Druginteraction	05	17
RAM	14	48
No monitoring of risk situations	18	62
Adherence	29	101
Forgetfulness	14	48
Has difficulty following the indicated time	10	35
Stop taking medications when you feel bad	04	14
Stops use of medication when you feel well	01	04
Grand total	100	354

In relation to the domain "physical limitations", 33.3% of the patients presented score equal to 0 (zero), representing a high degree of impairment, and 59.3% scored 50 points or less in that area. Regarding the "functional capacity" domain, it was verified that 32.3% of the patients presented results less than or equal to 50 points and 25.8% scored between 90 and 100 points. In the "pain" domain, 32% of the patients scored less than 50 points. Regarding the "general health" domain, 48.1% achieved less than 60 points in the test. The domain "social aspects" was highlighted because, although 37% did not reach 50 points, 33.4% totaled 100 points in the score. The domains

"vitality", "emotional aspects" and "mental health" were marked by a markedly heterogeneous distribution in patient scores.

**Table 2. QVRS score by domain of the SF-36 Scale applied to patients with (n=81)**

SCALE DOMAINS F-36		Total population		
		Average	DP	Overall Average
MENTAL COMPONENT	Functional capacity	63,2	31,2	58,1
	Physical Limitations	46,4	41,2	
	Pain	64,8	28,2	
	General state	57,9	21,0	
	Vitality	56,9	20,7	59,7
	Social aspects	69,3	29,3	
	Emotional Aspects	52,1	46,4	
	Mental health	60,5	23,0	

Bivariate analysis of the quantitative of NRM and its influence on patients' quality of life showed that there was a significant correlation with all domains of the physical and mental component of the SF-36 scale, according to the data presented in table 03. Thus, result showed that the increase in NRM was associated with a decrease in the quality of life of MS patients in the physical component (functional capacity, physical limitations, pain and general condition) and the same phenomenon was observed for the mental component (vitality, emotional aspects, social aspects and mental health).

**Table 3. Correlations between scale domains SF-36 and NRM (n = 81)**

SF-36	Negative clinical outcomes associated with drug use	
	r	p
Functional capacity	-0,379 <sup>1</sup>	0,000
Physical Limitations	-0,355 <sup>1</sup>	0,001
Pain	-0,278 <sup>2</sup>	0,012
General state	-0,264 <sup>2</sup>	0,017
Vitality	-0,409 <sup>1</sup>	0,000
Social aspects	-0,228 <sup>2</sup>	0,041
Emotional Aspects	-0,400 <sup>1</sup>	0,000
Mental health	-0,469 <sup>1</sup>	0,000

<sup>1</sup>Significant correlation (linear correlation test of Spearman's  $p < 0,05$ ), negative and moderate ( $r \geq -0,30$ ). <sup>2</sup>Significant correlation (linear correlation test of Spearman's  $p < 0,05$ ) negative and weak ( $r \leq -0,30$ ).

In the evaluation of the category stratified NRM with the domains of the SF-36 scale, it was found that the "effectiveness" NRM showed a significant correlation with all domains of this scale (Spearman's linear correlation test,  $p < 0.005$ ). The "necessity" category NRM in the physical component of the SF-36 scale significantly influenced the "functional capacity" and "physical limitations" domains. In the mental component, they interfered in the domains "vitality", "emotional aspects" and "mental health" (Spearman's linear correlation test,  $p < 0.005$ ). NRM of the "adherence" category showed a significant correlation only with the "mental health" domain. Therefore, "safety" NRM showed no significant correlation with any domain of the SF-36 scale (Spearman's linear correlation test,  $p > 0.005$ ). These data are shown in Table 4. Observation among the NRM categories for "effectiveness" was highlighted for impacting the patient's quality of life, both on the physical and mental

Table 4. Correlations between scale domains SF-36 e os RNM (n = 81)

SF-36	Negative clinical outcomes associated with drug use							
	Requirement		Adherence		Effectiveness		Safety	
	R	p	r	p	r	p	r	P
Functional capacity	-0,298 <sup>2*</sup>	0,007	0,042 <sup>3</sup>	0,710	-0,401 <sup>1</sup>	0,000	-0,093 <sup>2</sup>	0,406
Physical Limitations	-0,284 <sup>2</sup>	0,010	0,067 <sup>3</sup>	0,552	-0,442 <sup>1</sup>	0,000	-0,014 <sup>2</sup>	0,904
Pain	-0,204 <sup>2</sup>	0,068	-0,110 <sup>2</sup>	0,328	-0,295 <sup>2</sup>	0,007	0,110 <sup>3</sup>	0,329
General state	-0,149 <sup>2</sup>	0,184	-0,118 <sup>2</sup>	0,293	-0,234 <sup>2</sup>	0,035	-0,201 <sup>2</sup>	0,072
Vitality	-0,303 <sup>1</sup>	0,06	-0,125 <sup>2</sup>	0,266	-0,409 <sup>1</sup>	0,000	-0,089 <sup>2</sup>	0,429
Social aspects	-0,081 <sup>2</sup>	0,475	-0,168 <sup>2</sup>	0,134	-0,213 <sup>2</sup>	0,057	0,070 <sup>3</sup>	0,537
Emotional Aspects	-0,239 <sup>2</sup>	0,031	-0,136 <sup>2</sup>	0,226	-0,401 <sup>1</sup>	0,000	-0,095 <sup>2</sup>	0,400
Mental health	-0,251 <sup>2</sup>	0,024	-0,300 <sup>1</sup>	0,006	-0,444 <sup>1</sup>	0,000	0,003 <sup>3</sup>	0,977

<sup>1</sup>Significant correlation (linear correlation test of Spearman's  $p < 0,05$ ), negative and moderate ( $r \geq -0,30$ ). <sup>2</sup>Significant correlation (linear correlation test of Spearman's  $p < 0,05$ ) negative and weak ( $r \leq -0,30$ ).

<sup>3</sup>Significant correlation (linear correlation test of Spearman's  $p < 0,05$ ), positive and weak ( $r \leq 0,30$ ).

components of the SF-36 scale. In the physical component the domains "functional capacity" and "physical limitations" were more susceptible to the influence of these NRM. In the mental component, the domains behaved in a similar way, being only less vulnerable to the NRM of the "effectiveness" category of the domain "social aspects".

## DISCUSSION

Results found in this study demonstrated that people with MS have low levels of quality of life in most areas of the SF-36 scale. Both the physical symptoms, evaluated through the domains general health, functional capacity, pain and physical and mental limitations (vitality, social aspects, emotional aspects and mental health) presented average results below the expectation of HRQL for the general population (BERRIGAN *et al.*, 2016; FERNÁNDEZ *et al.*, 2011; MCCABE; MCKERN, 2002; KLEVAN *et al.*, 2014). Since MS is a disease with very heterogeneous characteristics, HRQL evaluations can help in obtaining the general clinical aspect of the disease (BERRIGAN *et al.*, 2016; BRUM *et al.*, 2014; LATIMER-CHEUNG *et al.*, 2013). The overall mean of the physical and mental component in our study showed worrying values, with a mean score below 60, with emphasis on the domain "physical limitations" and "emotional aspects", which were around 50. Similarly, in 2014, a study conducted in Norway with 93 MS patients showed that the overall mean of the physical component was also lower than the general population. In addition, this study also calculated the overall mean of the mental component, and showed lower values than the individuals without MS (KLEVAN *et al.*, 2014). Other researchers also evaluated HRQoL in MS patients using the SF-36 (FERNÁNDEZ *et al.*, 2014; MCCABE; MCKERN, 2002) scale and obtained results similar to those found in our study. Low scores found in the physical component in our study, especially in the "physical limitation" domain, were consistent with data found in the literature (FERNÁNDEZ *et al.*, 2014; MCCABE; MCKERN, 2002; KLEVAN *et al.*, 2014) and can be explained by the high incapacitating potential of MS (AMATYA *et al.*, 2017; FERNÁNDEZ *et al.*, 2014). Patients accumulate deficiencies as a result of incomplete recovery from acute exacerbations and / or disease progression (COCCO *et al.*, 2015; FERNÁNDEZ *et al.*, 2014; TULLMAN, 2013). They may present various combinations of functional deficits such as physical deficiencies (asthenia, spasticity, sensory dysfunction, visual loss, ataxia), fatigue, pain, incontinence, cognitive deficits (memory, attention, executive dysfunctions), psychiatric disorders and behavioral problems.

This may explain the low levels found also in the mental component, especially in the "emotional aspects" (AMATYA *et al.*, 2017; BERRIGAN *et al.*, 2016; FERNÁNDEZ *et al.*, 2014; NOURBAKSH; JULIAN; WAUBANT, 2017). The present study verified that NRM influenced the physical and mental quality of life of MS patients, indicating that the increase in NRM led to a decrease in SF-36 scores. To date, studies comparing NRM with quality of life in this population were not found. It is worth mentioning that factors such as the presence of comorbidities and physical limitations may necessitate the use of a greater number of medications and, consequently, more NRM (CIPOLLE; STRAND; MORLEY, 2013; SABATER-HERNÁNDEZ, 2016). The presence of comorbidities has been pointed out as an important factor of analysis and intervention in MS patients, aiming to improve the patient's HRQL (BERRIGAN *et al.*, 2016; MARRIE *et al.*, 2015; MITCHELL *et al.*, 2005). This research proposes the need to evaluate, in addition to the presence of comorbidities, the process of using the drugs for these diseases. In addition, this study showed the relationship between the lack of effectiveness of general pharmacological treatment with lower quality of life scores, suggesting that the control of comorbidities in MS patients requires the same attention of health professionals as care for MS. The results obtained in this study lead to the need to incorporate comprehensive care strategies for MS patients.

Pharmaceutical care emerges as a real possibility to contribute to this process by including the systematic analysis of drug use in the clinical evaluation, since NRM can be prevented, promoting improvement in the patient's clinical and humanistic viewpoint. The pharmacist can trace, identify and evaluate RNM to effectively implement strategies and interventions that ensure that each patient, within their needs, receives the necessary care to ensure a better quality of life, especially those related to medications (CHARROIS *et al.*, 2012; NIGRO *et al.*, 2014; ROTTA *et al.*, 2015). This study is a preliminary investigation, which is justified by the limitation of studies in Brazil and in the world on the direct relationship of NRM with quality of life in MS patients. The results emphasize that when planning their interventions, the health professionals who make up the multidisciplinary team should consider the uniqueness of each patient and the effects of the process of using the medicines on HRQL. Knowledge of the most preserved and compromised HRQL domains, as well as their relationships with medication, may contribute to the systematization of care. Psychological support strategies that can be applied by multidisciplinary health professionals can contribute to attenuate the impact of the situations of threat and suffering experienced by MS patients, enhancing and

enhancing the emotional resources of patients to favor a more effective coping process.

## Conclusions

Based on the results analyzed, it can be concluded that NRM negatively impacted the patients HRQL domains, especially in the mental aspects, suggesting that they are factors modifying the quality of life of MS patients. It is necessary to carry out new studies, with an expanded casuistry and more sophisticated research designs, to subsidize the knowledge produced in this area and ensure better conditions of care and follow-up of patients with MS.

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