Application of multiple criteria decision analysis (MCDA) for the selection of pharmacological treatments

Aplicação da análise de decisão baseada em múltiplos critérios para seleção de tratamentos farmacológicos

Juliana Pereira de Castro
Master in Administration and Management of Pharmaceutical Assistance, Master Professional
Program, Fluminense Federal University (UFF), Niterói, Rio de Janeiro, Brazil
Address: Avenida Sete de Setembro, 234. Jardim Icaraí, Niterói - RJ
E-mail: juliana.decastro@globomail.com

Gabriela Bittencourt Gonzalez Mosegui
PhD in Collective Health by Rio de Janeiro State University
Institution: Health and Society Department, Fluminense Federal University, Niterói, Rio de
Janeiro, Brazil
Address: Rua: Marques do Paraná, 303, 3º andar, prédio anexo. Centro, Niterói, RJ.
E-mail: gabriela.mosegui@gmail.com

Talita Martins Alves da Costa
Pharmacy Degree. Faculty of Pharmacy, Fluminense Federal University, Niterói, Rio de Janeiro,
Brazil
Institution: INI- Instituto Nacional de Infectologia Evandro Chagas
Address: Av. Brasil, 4365 - Manguinhos, Rio de Janeiro - RJ,
E-mail: talitamartins@id.uff.br

ABSTRACT
Introduction: Health Technology Assessment (HTA) is a tool that assists in the management of health systems, in which economic assessments are frequently applied. It is possible that the use of multicriteria analysis (MCDA) increases the quality of decisions. **Objective:** Identify the potentialities of the application of Multiple Criteria Decision Analysis (MCDA) in studies that used this type of method for the selection of treatments. Methods: An integrative review was executed based on articles where MCDA methods had been applied for the selection of treatments between February and April 2017 in the following databases: Pubmed (MEDLINE), Literatura Latino-Americana e do Caribe em Ciências da Saúde (LILACS), Embase, Science Direct, Scopus, Web of Science and Wiley Online Library. **Results**: Eighteen studies published between 1998 and 2017 in which different MCDA techniques were applied were selected. Growth in the number of published studies was observed, showing increasing interest in the use of this type of method in health decision making. **Conclusion**: MCDA may guide more adequate decisions compared to the traditional Health Technology Assessment (HTA) methods and has the potential to help in the selection of treatments and the construction of medicines' lists.

Key words: Biomedical technology, Technology assessment, biomedical, Therapeutics, Review.

RESUMO
Introdução: A Avaliação de Tecnologias em Saúde (ATS) é uma ferramenta que auxilia na gestão dos sistemas de saúde, na qual são aplicadas com frequência avaliações econômicas. É possível que o uso de análises multicriteriais (MCDA) aumente a qualidade das decisões. **Objetivo**: Identificar as potencialidades da aplicação da análise de decisão baseada em múltiplos critérios em pesquisas onde foi utilizado este tipo de método para seleção de tratamentos. **Método**: Uma revisão integrativa foi executada com base em artigos onde métodos de análise multicritério foram aplicados para seleção de tratamentos entre fevereiro e abril de 2017, nas seguintes bases de dados: Pubmed (MEDLINE), Literatura Latino-Americana e do Caribe em Ciências da Saúde (LILACS), Embase, Science Direct, Scopus, Web of Science and Wiley Online Library. **Resultados**: Foram selecionados 18 estudos publicados entre 1998 e 2017 em que diferentes técnicas multicriteriais foram aplicadas. Foi observado crescimento no número de estudos publicados, demonstrando aumento no interesse do uso deste tipo de método na tomada de decisão em saúde. **Conclusão**: Análises multicriteriais podem direcionar para decisões mais adequadas em comparação aos métodos tradicionais de avaliação de tecnologias em saúde (ATS) e têm potencial opara ajudar na seleção de tratamentos e construção de listas de medicamentos.

Palavras chave: Tecnologia biomédica, Avaliação da tecnologia biomédica, Terapêutica, Revisão.

1 INTRODUCTION

Health Technology Assessment (HTA) is frequently used during decision making, with emphasis on the incorporation of technologies into Health Systems. HTA acts to analyze the "clinical, social, ethical and economic implications of the development, diffusion, and use of health technology" and represents a tool in the management of health systems, capable of improving the State's regulatory capacity (VANNI et al., 2015).

In this evaluation, a research question is defined, and with the purpose of answering it, economic evaluations, that are widely used in HTA and required for the analysis of the incorporation of health technologies, can be used (NITA et al., 2009).

It is possible that the use of multiple criteria analysis increases the quality of decision making using different multi-criteria decision-making techniques (MCDA). These methods are widely applied in several areas, but in health their implementation is recent. Through the consideration of several criteria, the relevance of each one may be observed. The use of MCDA can help increase the consistency, transparency, and legitimacy of decisions (THOKALA et al., 2016).

Economic analyzes may not be sufficient to evaluate the benefit of a technology for society. Some types of patients tend to value gained years of life more (for example, patients with dependents), while others value them less (such as those at the end of life). In addition to the quality of life and years of life, other aspects can be considered such as return to work, improvement of subjective characteristics and increased satisfaction with aspects of health care (DEVLIN et al., 2011).

To ensure better decision making at the time of inclusion or exclusion of medicines in the health systems, it is appropriate to use methods that meet different criteria, providing greater equity and fairness. In this way, the multicriteria analysis constitutes a tool capable of promoting an adequate evaluation, possibly useful in the elaboration of Clinical Protocols and Therapeutic Guidelines referring to rare diseases (VIDAL et al., 2015). The use of multicriteria analysis methods is considered positive, with the potential to improve the quality of decision making (MARSH et al., 2014). This paper aims to review the literature of multicriteria analysis methods used in pharmacological treatments and discuss how these methodologies have been used in the selection of drugs for the treatment of several clinical conditions.

2 METHODOLOGY

This integrative literature review involves the following steps: (a) definition of the research question; (b) determination of inclusion and exclusion criteria of studies; (c) search for studies in databases; (d) selection of the studies found; (e) preparation of an instrument for the extraction of study data with subsequent extraction; (f) critical analysis of the data obtained; (g) discussion of results; (h) conclusion of the study (WHITTEMORE et al., 2005; SOUZA et al., 2010).

In compliance with the first stage of the study, the following research question was defined: how has multi-criteria analysis been applied in the selection of pharmacological treatments?

The following inclusion criteria were applied: primary studies in Portuguese, English, and Spanish; pharmacological treatment selection studies that applied multicriteria methodologies; no restrictions on the year of publication; and a focus on users of public and private health systems. The exclusion criteria were as follows: studies not published in periodicals; event summaries; review articles; and studies that addressed the multicriteria analysis but did not apply it.

Although it is sometimes considered in integrative reviews, the present work did not consider gray literature. This decision is based on the impossibility of analyzing many publications given the limited time and workforce.

The following electronic databases were used: Pubmed (MEDLINE), LILACS, Embase, Science Direct, Scopus, Web of Science and Wiley Online Library. Two search strategies were implemented, using the following descriptors: "MCDA", "multiple criteria decision analysis", "multi-criteria decision analysis", "multicriteria decision analysis", "multicriteria decision", "multiple criteria decision", "pharmaceutical services", "pharmaceutical care", "pharmac", "medicine", "drug", "treatment", "therap". The studies were systematized in the Mendeley reference manager (MENDELEY, 2019).

After the bibliographic search, the duplicates were removed, and then the selection was made. The first stage of the selection involved the sorting of the studies found independently by two researchers (J.P.C. and T.M.A.C.). The first selection had the purpose of verifying if the studies fulfilled the defined inclusion and exclusion criteria through the reading of titles and summaries. For cases of doubt or disagreement regarding the fulfillment of the criteria, the second stage of selection was applied, with a reading of the works in full. In this stage, a third reviewer, G. B. G. M., was present for cases of discordance after reading the articles.

The selected studies were then organized into Microsoft® Excel spreadsheets. For the extraction of data from the selected studies, three worksheets were created based on the proposal

for the elaboration of integrative review studies and the Brazilian Network of Evaluation of Technologies in Health (REBRATS) for systematic reviews since a manual for elaboration of integrative reviews is not available (BRASIL, 2012a; SOUZA et al., 2010).

After data extraction from the studies and data systematization, the results were described, and discussions relevant to the presented topic were followed by the conclusion of the study.

3 RESULTS

The selection stage resulted in 18 articles in English (HOSHIKAWA et al, 2017; MARSH et al., 2017; SCHEY et al., 2017; AL-BRADRIYEH et al., 2016; GREEF-VAN DER SANDT et al., 2016; GOETGHEBEUR et al., 2016; KOLASA et al., 2016; NWOKORO et al., 2016; BROEKHUIZEN et al., 2015; HSU et al., 2015a; HSU et al., 2015b; RAMLI et al., 2013; ERJAEE et al., 2012; GOETGHEBEUR et al., 2012; CHEN et al., 2011; TERVONEN et al., 2011; FANG et al., 2010; PEREZ ENCINAS et al., 1998). The studies referred to several diseases according to specific evaluation criteria, as shown in the table below.

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Table 1 – Characteristics of the selected studies

Author and year	Method	Disease	Alternatives
Perez Encinas *et al*., 1998	Not specified	Intermittent claudication	Pentoxifylline Buflomedil Neftidrofuryl Ticlopidine
Fang, Yao, Tseng, 2010	Data envelopment analysis. AHP used for weight assignment.	Diseases treated by proton pump inhibitor drugs	Proton pump inhibitor drugs (1, 2, three e 4)
Tervonen *et al*., 2011	Stochastic multicriteria acceptability analysis	Depression	Venlafaxine Fluoxetine Placebo
Chen, Chiu, Bau, 2011	Not specified	Not specified	Meglitinide DPP4 inhibitor Sulfonylurea Glinide Thiazolidinedione α-glucosidase
Erjaee *et al*., 2012	Analytical Hierarchy Process (AHP)	*H. pylori* infection	Three schemes: a) omeprazole + amoxicillin + metronidazole + bismuth b) omeprazole + amoxicillin + clarithromycin c)omeprazole + amoxicillin + clavulanate + metronidazole
Goetghebeur *et al*., 2012	Evidence and Value Impact on Decision Making (EVIDEM)	Not specified	Drugs defined only as A, B, C, D, E, F, G, H, I, J
Ramli *et al*., 2013	Not specified	Hypercholesterolemia	Pravastatin Simvastatin Lovastatin Atorvastatin Rosuvastatin Fluvastatin
Hsu, Tang, Lu, 2015	Not specified, AHP used for weight assignment.	Erectile dysfunction	Sildenafil Tadalafil Vardenafil
Hsu *et al*., 2015	Not specified, AHP used for weight assignment.	Non-valvular	Warfarin Dabigatran

Author and year	Method	Disease	Alternatives
		atrial fibrillation	Rivaroxaban Apixaban
Broekhuizen et al., 2015	Not specified.	Depression	Antidepressive drugs (A, B, C) and placebo. A and B were drugs already in use, C was a new drug.
Nwokoro et al., 2016	Not specified.	Diseases treated with antibiotics	Antibiotic biomaterials, Antimicrobial nanoparticles, Antimicrobial peptides, Anti-virulent materials, bacteriophages, Fecal microbiota transplant, probiotics, Fast diagnosis at the point of care, vaccines, therapeutic antibodies
Al-Bradriyeh et al., 2016	Weighted sum aggregation method	Diseases treated by proton pump inhibitor drugs	Esomeprazole Lansoprazole Pantoprazole Rabeprazole
Goetghebeur et al., 2016	EVIDEM (Evidence and Value: Impact on Decision Making), about the needs of real life, identified on WP5 (PROTECT - Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium – Workforce 5)	Plaque psoriasis	Efalizumab Placebo Etanercept 25 mg Etanercept 50 mg Infliximab Adalimumab 40 mg on alternate weeks Adalimumab 40 mg weekly
Greef-van der Sandt et al., 2016	Not specified	Overactive bladder	Mirabegron, Solifenacin, and Placebo (the two first isolated or combined)
Kolasa et al., 2016	Value Measurement Model	Rare diseases	Orphan drugs used for the treatment of rare diseases (that were subject to evaluation

Author and year	Method	Disease	Alternatives
			by the local agency of HTA – AHTAPol)
Marsh *et al*., 2017	Not specified	Chronic obstructive pulmonary disease (COPD)	Aclidinium Tiotropium
Schey *et al*., 2017	Study based on a model developed in previous research, by Hughes-Wilson et al. (2012)	Rare diseases	Six drugs, not specified
Hoshikawa, Ono, 2017	Not specified	Diseases treated with drugs from the class of statins	Three hypothetical drugs, from the class of statins (A, B, C) and placebo

Source: Own Elaboration

4 DISCUSSION

In 1998, a multicriteria published study aimed to select medications for the treatment of intermittent claudication (PEREZ ENCINAS et al, 1998), a clinical condition involving leg pain caused by exercise and relieved with rest (PINTO et al., 2005). Another selected study was published in 2010 (FANG et al., 2010$^)$, and from then until 2017, there was at least one publication per year, except for 2014. The studies referred to different diseases, with each using specific criteria. There was more than one publication for the following conditions: depression (BROEKHUIZEN et al., 2015; TERVONEN et al., 2011), diseases treated by proton pump inhibitors (FANG et al, 2010; AL-BRADRIYEH et al., 2016) and rare diseases (SCHEY et al., 2017; KOLASA et al., 2016).

Regarding the alternatives evaluated, 11 studies reported the drugs analyzed, while four cited only their therapeutic classes (HOSHIKAWA et al., 2017; BROEKHUIZEN et al., 2015; FANG et al, 2010). In three studies, the therapeutic class was not reported [two referring to orphan drugs (SCHEY et al., 2017; KOLASA et al., 2016) and a third with the objective of presenting a method (GOETGHEBEUR et al., 2016)].

The diversity of objectives justified the absence of a description of the technologies evaluated in the above-mentioned studies. Goetghebeur and collaborators (2016) presented and applied the multicriterial methodology in the testing of a new technique of analysis based on several previously developed criteria (GOETGHEBEUR et al, 2008).

Different techniques of multicriteria analysis were applied. Ten papers did not define the methodologies used, described as multicriteria analysis – MCDA (HOSHIKAWA et al, 2017; GREEF-VAN DER SANDT et al., 2016; NWOKORO et al., 2016; BROEKHUIZEN et al., 2015; HSU et al., 2015a; HSU et al., 2015b; RAMLI et al., 2013; PEREZ ENCINAS et al, 1998); multicriteria decision model – MCDM (CHEN et al., 2011); or multi-attribute value model (MARSH et al., 2017). Three studies used techniques developed by the respective authors or in previous studies (SCHEY et al., 2017; GOETGHEBEUR et al., 2016; GOETGHEBEUR et al., 2012).

Perez-Encinas *et al*. (1998) and Chen, Chiu, and Bau (2011) used standard MCDA methodology with criteria, weights, and scores. The former reported that multi-criteria analyses corresponded to precise and flexible decision-making methods, while the other study suggested that the recommendations obtained would assist physicians in the development of prescriptions.

Ramli and colleagues believed that MCDA would provide a structured approach to complex decisions (RAMLI et al., 2013). This study aimed to review the drugs of the statin class available in the Malaysian National Therapeutic Form. This type of technique would allow the presentation of the evidence in an organized way, facilitating the task of the decision makers. Before the study, six drugs of the same therapeutic class were available (atorvastatin, pravastatin, simvastatin, fluvastatin, lovastatin, and rosuvastatin). After its completion, the authors found that two were sufficient for the desired therapeutic goal (simvastatin and atorvastatin) (RAMLI et al., 2013), suggesting that MCDA may be able to maximize the efficiency of health systems. In 2011, a cost-effectiveness study evaluated the effect of simvastatin and atorvastatin compared to placebo in the perspective of the Brazilian Public Health System for the secondary prevention of cardiovascular events in dyslipidemic patients. The authors concluded that simvastatin alone was cost-effective (ARAUJO et al., 2011).

In 2011, Araújo *et al*. evaluated only simvastatin and atorvastatin, unlike Ramli *et al*. (2013) and Chong, Seeger, and Franklin (2001). These last two studies compared six drugs of the class, with the only difference being one drug in each analysis (cerivastatin and rosuvastatin). Ramli *et al*. (2013) used a multicriteria analysis to conclude that atorvastatin and simvastatin were sufficient for the Malaysian Therapeutic Formulary, while Chong, Seeger, and Franklin (2001) performed a cost-effectiveness assessment and found that the most cost-effective were fluvastatin, cerivastatin, and atorvastatin. Although the same drugs were evaluated, the different techniques of analysis reached different conclusions: only atorvastatin was present in both decisions. The

variation in scenarios and outcomes influenced the evaluation. At the moment of decision making, it is necessary to consider several factors for the choice of method of analysis, depending on the availability of information and trained human resources and the purpose of the analysis. In addition to the different scenarios, the 12-year temporal gap between studies by Ramli *et al*. (2013) and Chong, Seeger, and Franklin (2001) may have potentiated the difference between the observed results. Characteristics such as price and available knowledge about drug safety varied over time, which affected the selection process.

Regarding the use of MCDA in the selection of anticoagulants for the treatment of atrial fibrillation in different settings comparing dabigatran, rivaroxaban, apixaban and warfarin (HSU et al., 2015b), a study published in 2013 compared the same drugs using the cost-effectiveness methodology (CANESTARO et al., 2013). In the multicriteria evaluation (HSU et al., 2015b), evidence was obtained indicating dabigatran as the first-choice drug. In the economic analysis, the drug apixaban was the optimal choice in the same scenario (CANESTARO et al., 2013).

The application of standard MCDA methodology was also verified, plus the calculation of the mean incremental impact for each alternative (MARSH et al., 2017). An important limitation observed in this study was the definition of values in the attribution of weights to the criteria to be performed by physicians while reflecting patients' preferences and perspectives. The justifications for such a choice were that physicians are familiar with the information needed for the analysis, and if questioned, prior guidance would be required for patients. Because doctors treat many people, they could judge the perspectives of different types of patients without the need for large samples (MARSH et al., 2017). However, when requesting that a professional behave as a patient, the possibility of significant bias is introduced in the study, and these two actors would probably assign different values to the criteria.

In 2012, a study used the analytical hierarchy (AHP) process, a method established in the multicriteria analysis. The authors concluded that this type of approach increases the quality of decision making performed by physicians in addition to being useful in incorporating the contributions of patients and decision makers (ERJAEE et al., 2012; SAATY et al., 1990).

Two studies evaluating orphan drugs were selected in this integrative review. Kolasa and colleagues (KOLASA et al., 2016) analyzed the potential impact of the use of MCDA on price allocation and the process of reimbursement of orphan drugs to verify if the implementation of this type of analysis would lead to different incorporation decisions. Based on the combination of punctuation values and weights, a tool was developed using the established method of the MCDA

value measurement model, where the aggregate final values allowed the hierarchy of alternatives. It is a frequently used method; almost all authors who proposed the use of MCDA in health referred to this type of technique (Thokala et al., 2012). For Kolasa *et al*. (2016), economic factors played a less important role than in the techniques traditionally applied in ATS. Two drugs negatively analyzed by the Polish ATS Agency received the highest scores using MCDA. The authors concluded that the multi-criteria approach allowed for more transparent decision making and would support efforts for a more equitable distribution of health resources[25].

The second study involving orphan drugs is more recent, published in 2017 by Schey *et al*. (2017). The mentioned authors explored a multi-criteria methodology developed by Hughes-Wilson *et al*. (2012), with the definition of criteria and weights in three scenarios. They concluded that orphan drugs are generally not cost-effective because of their high cost, making it difficult for patients to access. For the authors, the MCDA did not capture the essential criteria for the analysis because the approach was developed from the perspective of the pharmaceutical industry (SCHEY et al., 2017).

Due to the high cost of medications, unavailability of comparators, and difficulty in demonstrating treatment efficacy, Schey *et al*. (2017) reported concerns that economic evaluations may lead to unfavorable decisions regarding orphan drugs. Considering that multicriteria methods of analysis allow the observation of several relevant criteria for the treatment of patients with rare diseases, providing transparency to the decision-making process, the use of MCDA is suggested for the evaluation of this class of drugs by decision makers (HUGHES-WILSON *et al*., 2012).

5 CONCLUSIONS

This integrative review allowed the verification of which MCDA techniques were used to select treatments in addition to the relationships of this type of method with other previously used methods.

The application of techniques that allow the approach of several criteria and weights allowed the incorporation of crucial factors for health decision making, whose consideration is not possible with the use of economic analysis. In several situations, MCDA-type analyses directed to decisions that were different from those obtained using economic analyses when the same health technologies were evaluated. In this way, the use of multicriteria methodologies has the potential to lead to more adequate decisions.

Given the diversity of characteristics in the studies found, the standardization of MCDA techniques and the ways to assign weights and criteria have the potential to facilitate the application of these methodologies in health systems. Specifications regarding the use of criteria in the same disease study would be ideal. The initial consideration of criteria referring to clinical conditions that have the greatest impact on society is proposed or even the consideration of those that, despite not presenting high prevalence, are relevant to diseases that currently do not have treatment provided by the public health systems and for which the evaluation is urgent.

The use of multicriteria analyses for decision making on the incorporation of medicines into health systems is likely to lead to fairer decisions regarding economic evaluations, particularly orphan drugs used in the treatment of rare diseases. These treatments are generally not cost-effective, and for a more appropriate assessment, other criteria may be considered.

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