ABSTRACT
The use of multi-criteria decision analysis (MCDA) in the economic evaluation of drugs has been widely discussed. Thus, this study aims to propose a way to enhance the cost-effectiveness analysis (CEA) of health interventions using the PROMÉTHÉE II multi-criteria method. In order to accomplish this, PROMÉTHÉE II was applied to the same data used in the CEA of lipegfilgrastim in the Brazilian healthcare system for the reduction of chemotherapy-induced neutropenia. In this application, lipegfilgrastim and its comparators formed a set of alternatives. The cost parameters used to compute the total costs of the treatments along with the effectiveness outcomes formed a set of criteria, showing that a conventional CEA is in an MCDA setting. The CEA demonstrated lipegfilgrastim as a cost-saving strategy over its comparators. PROMÉTHÉE II generated the following outcomes to contribute to the CEA: (1) a ranking of studied interventions; (2) a classification level for each intervention from A (best level) to E (worst level); (3) a positioning scenario showing the dominance relation and distance among the interventions; and (4) a criteria panel classifying each criterion as strong or weak point for each intervention when compared to the others. The MCDA approach presented in this study does not exclude the use of CEA but complements it to support the decision-making process.

Keywords: Cost-effectiveness analysis, multi-criteria decision analysis, PROMÉTHÉE II method.

RESUMO
O uso da análise de decisão multicritério na avaliação econômica de medicamentos tem sido amplamente discutido. Assim, este estudo tem como objetivo propor uma forma de aprimorar a análise de custo-efetividade de medicamentos usando o método multicritério PROMÉTHÉE II. Para tanto, o PROMÉTHÉE II foi aplicado aos mesmos dados utilizados na análise de custo-efetividade do lipegfilgrastim no sistema de saúde brasileiro para redução da neutropenia induzida por quimioterapia. Nesta aplicação, lipegfilgrastim e seus comparadores formaram um conjunto de alternativas. Os parâmetros de custo usados para calcular os custos totais dos tratamentos junto com os desfechos de eficácia formaram um conjunto de critérios, mostrando que uma análise de custo-efetividade convencional está em um ambiente multicritério. A análise de custo-efetividade demonstrou o lipegfilgrastim como uma estratégia dominante em relação aos seus comparadores. O PROMÉTHÉE II gerou os seguintes resultados para contribuir com a análise de custo-
1 INTRODUCTION

1 Background

Cost-effectiveness analysis (CEA) has been widely used to support health technology assessment decision-making process [1-3]. The main result of CEA is called the incremental cost-effectiveness ratio (ICER) which means the cost-effectiveness of a health intervention when compared to another [4, 5]. In this ratio, the difference between total costs of two interventions represents the ratio numerator and the difference between total effectiveness of these treatments represents the ratio denominator.

On the other hand, multi-criteria decision analysis (MCDA) has supported structuring of complex problems when a set of alternatives should be analysed in the presence of a set of criteria, mainly when the studied criteria are conflicting. MCDA methods have been applied in several fields of study to select, order, classify, or describe alternatives according to their performances from multiple criteria [6, 7].

Applying MCDA to contribute to the economic evaluation of drugs has been vastly discussed by many researchers [8-18]. A proximity between a CEA and an MCDA setting can be easily noted if the analysed treatments of a CEA be considered as a set of alternatives, and all costs used to compute a total cost and the effectiveness outcomes used in CEA generate together a set of criteria [19]. Thus, this study proposes a way to enhance a conventional CEA using the PROMÉTHÉE (Preference Ranking Organization Method for Enrichment of Evaluations) II MCDA method. To accomplish this, PROMÉTHÉE II was applied to the same data used to perform the lipogfilgrastim CEA in Brazil by Szende et al. (2018) [20] to complement its outcomes and facilitate the decision-making process.

2 MCDA METHODS

There are two major schools that aggregate some MCDA methods to aid multi-criteria decision making: the French School, also called European School and the North American School.
The French school methods involve the concept of an outranking relation and emerged from the influence from French workers. The two families of the main methods that belong to the French school are: the ELECTRE (an acronym in French for Elimination and Choice Expressing the Reality) family of methods that holds six methods, ELECTRE I, IS, II, III, IV, TRI; and the PROMÉTHÉE family of methods, that also holds six methods, PROMÉTHÉE I, II, III, IV, V, VI [6, 7, 21, 22].

The North American school MCDA methods believe in an aggregation of all the information regarding the problem through a synthesis. The main methods of this school are the MAUT (Multi-attribute Utility Theory) and the AHP (Analytic Hierarchy Process) methods [6, 7, 23-25]. There are also hybrid methods, which are methods that neither belong to the French school nor to the North American school of multi-criteria. Some hybrid methods are the TOPSIS (Technique for Order of Preference by Similarity to Ideal Solution) [26, 27] and the TODIM (an acronym in Portuguese for Interactive and Multi-criteria Decision Making) [28, 29], among others. Different MCDA methods are used to aid the decision-making process in many branches of knowledge, each one with its particularity [30, 31]. To perform an ICER, the difference of total cost and total effectiveness between two treatments must be computed to reach an incremental cost and an incremental effectiveness [32]. Thus, the use of an MCDA method that performs a pairwise comparison between treatments’ performances difference, criterion per criterion, can be a way to complement CEA due to the similarity of these methodologies.

There are some MCDA methods that perform a pairwise comparison between the studied alternatives’ performances [6, 7, 21-26]. As the main methods that rely on those comparisons, one can cite the AHP, the ANP (Analytic Network process), the MACBETH (Measuring Attractiveness by a Categorical Based Evaluation Technique), the PROMÉTHÉE II, the ELECTRE I, and the TODIM methods, among others.

PROMÉTHÉE II performs a pairwise difference of alternatives’ performances on each criterion, aiming to establish a ranking of alternatives [33]. In the TODIM pairwise comparisons the positive and negative differences, i.e., results from subtracting performance measures, are expressed in a distinct way [28, 29, 34]. In ELECTRE methods, when subtracting the performances of two alternatives to obtain the concordance and discordance indexes, not all values of subtractions are used [35]. Furthermore, the notions of weak preference and pseudo-criteria must be used.

The AHP, ANP and MACBETH methods also rely on pairwise comparisons, but in a global way [23, 24, 26, 36-38]. In the PROMÉTHÉE II and in the ELECTRE I methods, the same
does not occur, just as in CEA. Thus, it is possible to note that there is a similarity between CEA and PROMÉTHÉE II when they compare alternatives. This similarity can be highlighted by the fact that both methodologies perform the difference between performances of studied alternatives and use the outcomes of these differences to compare alternatives. It is important to emphasize that PROMÉTHÉE II does not perform a ratio but generates a ranking that can complement the results of a CEA.

3 METHODS

This study applied the PROMÉTHÉE II method to demonstrate a way to enhance a conventional CEA. This method does not exclude the use of CEA, it only seeks to complement it using an MCDA approach. To accomplish this, PROMÉTHÉE II was applied to the same data used in the CEA of lipegfilgrastim in the Brazilian healthcare system for the reduction of chemotherapy-induced neutropenia [20]. Table 1 presents the lipegfilgrastim CEA.

Table 1: Cost-effectiveness results of lipegfilgrastim in the Brazilian healthcare system

| Cost parameter                  | Treatment   | ICER                      |
|---------------------------------|-------------|---------------------------|
| G-CSF drug cost (R$)            | Lipegfilgrastim | Pegfilgrastim | Filgrastim | Lipegfilgrastim vs. pegfilgrastim | Lipegfilgrastim vs. filgrastim |
| Injection administration cost   | 12,501       | 12,501                   | 13,031     | -3503                              | -23,738                      |
| Severe neutropenia management   | 294          | 602                      | 797        |                                    |                            |
| Injection administration cost   | 200          | 120                      | 1,320      |                                    |                            |
| Severe neutropenia risk         | 0.356        | 0.445                    | 0.451      | -3503                              | -23,738                      |
| Febrile neutropenia risk        | 0.027        | 0.081                    | 0.124      | -5859                              | -23,250                      |
| Mortality risk                  | 0.003        | 0.008                    | 0.012      | -61,782                            | -244,880                     |
| Neutropenia duration (days)     | 6.35         | 8.10                     | 8.23       | -178*                              | -1196*                       |
| Chemotherapy delay risk         | 0.111        | 0.139                    | 0.141      | -11,223                            | -76,203                      |

G-CSF: granulocyte colony-stimulating factor. AEs: adverse events. ICER: incremental cost-effectiveness ratio. *Cost (R$) per day. Source: Szende et al. (2018) [20]

Observing Table 1, two comparators for lipegfilgrastim were used: pegfilgrastim and filgrastim. Four cost parameters were used to compute the total cost for each intervention and five effectiveness measures were used. Five ICERs between lipegfilgrastim and pegfilgrastim and five
ICERs between lipegfilgrastim and filgrastim were performed, each considering one of the five effectiveness measures.

### 3.1 STRUCTURING

In Table 1 it is possible to observe that the CEA of lipegfilgrastim is in an MCDA setting where three health interventions are analysed: lipegfilgrastim; pegfilgrastim; filgrastim. Thus, these interventions formed a set of alternatives. The four cost parameters used to compute the total cost of each intervention along with the five effectiveness measures formed a set of criteria. Table 2 presents this multi-criteria performance matrix.

| Criteria                                      | Alternatives       |
|-----------------------------------------------|--------------------|
| G-CSF drug cost (R$)                          | Lipefilgrastim     |
|                                               | Pegfilgrastim      |
|                                               | Filgrastim         |
| Injection administration cost (R$)            | 120                |
|                                               | 120                |
|                                               | 1,320              |
| Severe neutropenia management cost (R$)       | 294                |
|                                               | 602                |
|                                               | 797                |
| AEs management cost (R$)                      | 5.05               |
|                                               | 8.23               |
|                                               | 20.06              |
| Severe neutropenia risk                       | 0.356              |
|                                               | 0.445              |
|                                               | 0.451              |
| Febrile neutropenia risk                      | 0.027              |
|                                               | 0.081              |
|                                               | 0.124              |
| Mortality risk                                | 0.003              |
|                                               | 0.008              |
|                                               | 0.012              |
| Neutropenia duration (days)                   | 6.35               |
|                                               | 8.10               |
|                                               | 8.23               |
| Chemotherapy delay risk                       | 0.111              |
|                                               | 0.139              |
|                                               | 0.141              |

G-CSF: granulocyte colony-stimulating factor. AEs: adverse events.
Source: Szende et al. (2018) [20]

In PROMÉTHÉE II, each criterion must have the sense of maximization or minimization [6, 7, 22, 26]. Thus, each cost parameter has the sense of minimization since the lower the cost, the better. The effectiveness criteria represent a consequence that should be avoided; thus, those criteria also have the sense of minimization.

### 3.2 CRITERIA WEIGHTING

How to designate weights for each studied criterion in an MCDA approach has been a question widely discussed [9, 11, 15, 17, 39-42]. In PROMÉTHÉE II the sum of all criteria weights must be equal 1.0. To designate the weight for each criterion the method used in CEA for criteria weighting was considered. That is, due to CEA being a ratio, all criteria that represent cost parameters had together a weighting sum equal to 0.5 and the same for all criteria that represent the effectiveness outcomes. In this way, each cost parameter (a criterion) had a weight equal to 0.5 divided by the number of parameters of costs used in the CEA, and the same method was used to designate the weight of each effectiveness measure (a criterion).
Four cost parameters to calculate the total cost of each treatment were used. A weight equal to 0.125 (0.5/4.0) for each cost parameter should then be designated. In the same way, five effectiveness measures were used; each should have a weight equal to 0.1 (0.5/5.0). Thus, each cost holds the same weight as the others and each effectiveness parameter holds the same weight as the others. This occurs because the CEA does not establish a weight for each cost or each effectiveness. All costs and all effectiveness are summed to calculate an incremental cost and an incremental effectiveness to reach an ICER.

Beyond establishing a weight for each criterion, a preference function for each should be defined. The preference function is the way to measure the difference between the performances of two alternatives of a criterion [43, 44]. As in the CEA, the absolute value of the incremental cost and incremental effectiveness is used to perform an ICER, the V-shape preference function is used for all criteria. To use the V-shape preference function a preference threshold (p) should be defined. To keep the PROMÉTHÉE II methodology close to CEA, the threshold p can be achieved according to the zero-max approach [45].

Thus, the higher difference between two alternatives of each criterion will be measured as 1.0 and any other value below this difference will be measured proportionally to zero [45, 46]. This is a mode to keep PROMÉTHÉE II close to CEA due to CEA using the absolute value of a difference, and PROMÉTHÉE II measures this value from 0.0 to 1.0. After this, PROMÉTHÉE II may be applied.

3.3 PROMÉTHÉE II CONTRIBUTION

This study used four outcomes from PROMÉTHÉE II to contribute to the lipegfilgrastim CEA: (1) a ranking of studied interventions; (2) a classification level for each intervention; (3) a positioning scenario among them; and (4) a criteria panel classifying each criterion as a strong or weak point for each intervention [47, 48].

The ranking of interventions must be established according to the value of net flow for each treatment. This value is in the -1.0 to 1.0 interval and represents the difference between positive flow and negative flow. The positive flow expresses how much an intervention is dominating (power) the others, while the negative flow expresses how much it is dominated (weakness) by the others [43, 44]. Both positive and negative flows are in the 0.0 to 1.0 interval. The classification level should be designated from A (best level) to E (worst level) for each studied intervention, according to the net flow values. This classification seeks to bring clarity to the
ranking already established, due to an intervention being able to obtain the best position in the ranking, but not obtain the best classification level or vice versa.

The positioning scenario of PROMÉTHÉE II presents the dominance relation among the studied interventions. This relation is demonstrated every time an arrow leaves an intervention towards another in the scenario. Thus, the intervention that is the origin of the arrow dominates the intervention that is the destination of the arrow. Furthermore, it is possible to note the distances among the studied treatments.

In addition, the criteria panel classifies each criterion as a strong or weak point for each intervention. In this way, it is possible to note which cost and effectiveness parameters are advantages and disadvantages for each intervention when compared to the others. In this panel, the criteria above each intervention are its strong points and the criteria below are its weak points.

4 RESULTS

PROMÉTHÉE II established the ranking of studied treatments according to their performances from the set of criteria (Table 3). This ranking was established as the following order: lipegfilgrastim, pegfilgrastim, filgrastim.

| Ranking | Treatment   | Net flow | Positive flow | Negative flow |
|---------|-------------|----------|---------------|---------------|
| 1st     | Lipegfilgrastim | 0.7472   | 0.7472        | 0.0000        |
| 2nd     | Pegfilgrastim  | 0.0056   | 0.2528        | 0.2472        |
| 3rd     | Filgrastim    | -0.7528  | 0.0000        | 0.7528        |

Source: The author

Lipegfilgrastim achieved a strong positive flow and a negative flow equal to 0.0. This occurs because lipegfilgrastim holds the best performance for all criteria (Table 2). However, it is important to note that lipegfilgrastim and pegfilgrastim hold the same performance for two criteria. Thus, lipegfilgrastim achieves a negative flow equal to 0.0 but does not achieve a positive flow equal to 1.0.

The classification level was attributed for each intervention from A to E according to the value of their net flows (Figure 1).
According to Figure 1, lipegfilgrastim holds level A, pegfilgrastim level B, and filgrastim level D. Thus, lipegfilgrastim achieved the first position in the ranking and holds the best classification level when compared to the others. On the other hand, despite filgrastim achieving the worst position in the ranking, it does not hold the worst classification level.

The positioning scenario among studied treatments is presented in Figure 2.
Lipegfilgrastim is dominant over pegfilgrastim and filgrastim. This occurs because the positive and negative flows of lipegfilgrastim are better than pegfilgrastim and filgrastim positive and negative flows. By the same way, pegfilgrastim is dominant over filgrastim.

The criteria panel generated by PROMÉTHÉE II is presented in Figure 3.

Figure 3: Criteria panel of treatments

![Criteria panel of treatments](image)

G-CSF: granulocyte colony-stimulating factor. AEs: adverse events.

Source: The author

Lipegfilgrastim had no criteria classified as weak points. Three cost parameters were classified as strong points for pegfilgrastim: G-CSF drug cost, injection administration cost, and AEs management cost. Filgrastim had all criteria classified as weak points. This occurs because this treatment holds the worst performance for all criteria when compared to the other treatments (Table 2).
5 DISCUSSION

Table 1 presents five ICERs between ligepegfilgrastim and pegfilgrastim; and five ICERs between ligepegfilgrastim and filgrastim, each using an effectiveness measure. To perform those ICERs, the total cost per patient during a course of four chemotherapy cycles was estimated at R$ 12,920 for ligepegfilgrastim, R$ 13,232 for pegfilgrastim and R$ 15,168 for filgrastim. Ligepegfilgrastim had the better outcomes in the five effectiveness measures studied and was demonstrated as dominant over its comparators by each ICER.

In PROMÉTHÉE II the three studied interventions formed together a set of alternatives, and the four cost parameters used to compute the total costs along with the five effectiveness measures formed a set of criteria (Table 2). By doing so, PROMÉTHÉE II aggregated the three studied interventions along with all cost and effectiveness parameters used in CEA in the same analysis. This corroborates that CEA is in an MCDA setting. On the other hand, each ICER presented in Table 1 represents an outcome between only two interventions, using an effectiveness measure and all parameters of costs.

PROMÉTHÉE II performed comparisons between pegfilgrastim and filgrastim and the results of those comparisons were also reflected in its outcomes. The CEAs previously established did not perform ICERs between pegfilgrastim and filgrastim. Thus, the decision maker must be aware that there are differences between the methodologies that can contribute to the CEA with a novel point of view.

The decision maker could opt to form a set of alternatives with just two interventions and form a set of criteria with total cost and effectiveness used to compute an ICER. This would certainly also be in an MCDA setting and the set of alternatives along with the set of criteria would be the same as used in an ICER, but the MCDA approach could complement only this single ICER. Even so, there would still be differences between the methodologies.

In the cases in which there are two or more comparators for a health intervention, as is the case of ligepegfilgrastim, a major potentiality of MCDA is to form a set of alternatives with more than two interventions and form a set of criteria using each parameter of cost and effectiveness, mainly due to the fact that it is not possible to compute this by a single ICER.

PROMÉTHÉE II generated a ranking as the following order: ligepegfilgrastim, pegfilgrastim, filgrastim (Table 3). This is similar for the same outcomes presented by the ICERs (Table 1) mainly due to ligepegfilgrastim being dominant over its comparators. The ranking of studied treatments can show if the best treatment in terms of ICER, according to a decision maker, is in the first position in PROMÉTHÉE II ranking.
The classification level designated for each intervention showed that lipegfilgrastim alone holds the best level when compared to the others (Figure 1). This complements the ranking previously established just like the ICERs, showing that although lipegfilgrastim dominates its comparators, it also holds the best classification level. Filgrastim did not obtain the worst level, even holding the last position in the ranking.

The positioning scenario presented in Figure 2 demonstrated the distance among studied interventions and their dominance relations. In PROMÉTHÉE II, lipegfilgrastim is dominant over its comparators just like the ICERs (Table 1). In other cases this may not occur, that is, an intervention can be dominated by another in CEA and not dominated by the same in PROMÉTHÉE II, mainly when MCDA uses each parameter of cost and effectiveness as a criterion, and CEA uses total costs and effectiveness, for example. It is also possible to note that pegfilgrastim is dominant over filgrastim. Filgrastim is dominated by lipegfilgrastim and pegfilgrastim. This information was not presented in Table 1 because it would be necessary to compute an ICER between pegfilgrastim and filgrastim. Thus, the positioning scenario can complement CEA through a visual form.

The criteria panel generated by PROMÉTHÉE II classified each criterion as a strong or weak point for each studied intervention (Figure 3). This clearly shows the advantages and disadvantages of each intervention when compared to the others. Pegfilgrastim, despite not presenting the best outcomes in terms of ICER or the best position in the ranking, presented three criteria classified as strong points. In this way, all PROMÉTHÉE II outcomes here discussed can be used to enhance CEA, contributing with visual additional information that CEA does not perform.

6 LIMITATIONS

The MCDA approach described in this study was applied to the same data used to perform the lipegfilgrastim CEA in Brazil, where pegfilgrastim and filgrastim were its comparators. Lipegfilgrastim was demonstrated to be dominant over pegfilgrastim and filgrastim. Furthermore, pegfilgrastim presented all parameters of costs and effectiveness more satisfactory than filgrastim. Thus, it would be interesting to apply PROMÉTHÉE II in other CEAs where this fact between the studied interventions does not occur, to test with more accuracy the MCDA support in CEA.
7 CONCLUSION

This study presented a proposal to enhance the CEA of health interventions using the PROMÉTHÉE II MCDA method. Hence, it was demonstrated that CEA is in an MCDA setting. To accomplish this, PROMÉTHÉE II was applied to the data of a lipegfilgrastim CEA in Brazil. PROMÉTHÉE II generated a ranking of studied interventions, designed a classification level for each one, engendered a positioning scenario among studied treatments, and produced a criteria panel classifying each as a strong or weak point for each intervention when compared to the others. The MCDA approach here presented does not exclude the use of CEA but complements it, generating additional outcomes through a visual form.
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