



REVIEW

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Disease modifying therapies in multiple sclerosis: cost-effectiveness systematic review

Terapias modificadoras de la enfermedad en esclerosis múltiple: revisión sistemática de costo-efectividad

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Abstract

Objective: To identify and describe cost-effectiveness studies that evaluate disease modifying therapies in the context of relapsing-remitting multiple sclerosis.

Method: A systematic review of the literature was carried out by searching MEDLINE, Embase, the Cochrane Library, LILACS, the Tufts Medical Center Cost-Effectiveness Analysis Registry, the National Health Service Economic Evaluation Database and Open Grey. The search was performed in January 2018 and covered articles published between January 2010 and December 2017. The studies reviewed were payer-perspective cost-effectiveness analyses for interferon beta-1a, interferon beta-1b, glatiramer acetate, teriflunomide, fingolimod, dimethyl fumarate, natalizumab, alemtuzumab and rituximab. The Quality of Health Economic Studies instrument was used to determine the quality of the studies reviewed. Risk of bias was assessed without a standardized tool. An analysis was made of direct costs, quality-adjusted life-years and the incremental cost-effectiveness ratio. Data extraction and evaluation of information were conducted separately by each author.

KEYWORDS

Cost-effectiveness analysis; Quality-adjusted life-years; Multiple sclerosis; Incremental cost-effectiveness ratio; Systematic review; Disease-modifying therapy.

PALABRAS CLAVE

Análisis de costo-efectividad; Años de vida ajustados por calidad; Esclerosis múltiple; Razón de costo-efectividad incremental; Revisión sistemática; Terapia modificadora de la enfermedad.

Resumen

Objetivo: Identificar y describir los estudios de costo-efectividad que evalúan las terapias modificadoras de la enfermedad en esclerosis múltiple recurrente-remitente.

Método: Revisión sistemática de la literatura en MEDLINE, Embase, Cochrane Library, LILACS, Tufts Medical Center cost-effectiveness analysis registry, National Health Service economic evaluation database y Open Grey; búsqueda limitada entre enero de 2010 y diciembre de 2017, se ejecutó en enero de 2018. Se incluyeron modelos de costo-efectividad con perspectiva de pagador para interferón beta-1a, interferón beta-1b, acetato de glatiramer, teriflunomida, fingolimod, dimetilfumarato, natalizumab, alemtuzumab y rituximab. La herramienta Quality of Health Economic Studies fue usada para determinar la calidad de los estudios, el sesgo se evaluó sin una herramienta estandarizada, dada su no existencia. Se analizaron costos directos, años de vida ajustados por calidad y la razón de costo-efectividad incremental. La extracción de los datos y la evaluación de la información se realizaron por cada autor de forma independiente.



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Results: Four hundred one references were found; nine studies were included. A great degree of variability was identified for several methodological aspects. Two studies that applied the incremental cost-effectiveness ratio (cost) showed no first-line therapy to be cost-effective. A third study demonstrated dominance of interferon beta-1b over placebo (USD -315,109.45) and a fourth paper showed dominance of teriflunomide over interferons and glatiramer acetate (USD -121,840.37). As regards second-line therapies, dimethyl fumarate was cost-effective in a study that compared it to glatiramer acetate and interferon beta-1a and it was dominant in another study that compared it with glatiramer acetate (USD -158,897.93) and fingolimod (USD -92,988.97). In the third line of treatment, one study showed natalizumab to be cost-effective as compared with fingolimod, and another study showed alemtuzumab to be dominant over fingolimod (USD -49,221). A third trial demonstrated alemtuzumab to be dominant over natalizumab (USD -1,656,266.07). Many of the trials have sponsorship bias. Eight of the trials received a high QHES score.

Conclusions: The present paper shows that cost-effectiveness studies have high levels of methodological variability, some of them reaching contradictory results. As a result, it is not possible to determine which disease-modifying therapy is really cost-effective in the context of relapsing-remitting multiple sclerosis.

Introduction

Multiple sclerosis is a chronic inflammatory demyelinating disease of the central nervous system that results in neuroaxonal degeneration in the long term¹. Clinical presentation is variable as the disease may affect the pyramidal, extrapyramidal, cerebellar and/or sensitive systems, and result in a neurocognitive disorder in the long term². It has a 3:1 predilection for women and a latitude-dependent prevalence: Colombia (1.48-4.89 per 100,000 inhabitants)³, United Kingdom (112 per 100,000 inhabitants), Canada (55-248 per 100,000 inhabitants), USA (65-160 per 100,000 inhabitants) and Spain (50 per 100,000 inhabitants)⁴.

The accumulating burden of disease results in physical and mental disability, which eventually makes patients dependent on caregivers and reduces their productive lifespan⁵. Although little is known about what causes the disease, a plethora of different medications are currently available, each with its own mechanism of action and routes of administration^{6,9}. Multiple sclerosis is considered a high-cost disease. The actual cost varies depending on the type of drug used, the complications associated with the given therapy, the relapse rate, and the accumulated disability. A study carried out between 2003 and 2008 in Colombia¹⁰, reported that 91.5% of the expenditure during the relapsing-remitting phase corresponded to the direct cost of disease-modifying therapies (DMTs). Such direct costs, however, tend to go down when patients have moved to the secondary progressive phase. Nevertheless, it is during this phase that indirect costs (associated to disability and disability support) usually experience a significant increase, accounting for 39.1% of the overall expense. In 2008, the cost per patient in Colombia was up to USD 25,714 during the relapsing-remitting phase and up to USD 1,237 for each relapse. In 2014, Colombia spent approximately USD 42,952,209 on treatments for their multiple sclerosis population⁵.

There is a global trend toward evaluating the economic impact of different treatments in order to determine which should be reimbursed¹¹. The purpose is to generate high-quality healthcare services within a context of limited economic resources^{12,14}. The purpose in this paper is to carry out a systematic review of the literature in order to analyze the information published through cost-effectiveness models. The ambition is that the conclusions drawn from this study might contribute to clinical decision-making, thus having a beneficial effect on the rational and appropriate use of public resources.

The main goal of this study was to identify and describe cost-effectiveness studies that evaluated DMTs in the context of relapsing-remitting multiple sclerosis.

The secondary goal was to review the studies that evaluated first, second and third-line therapies.

Methods

A combination of controlled vocabulary (MeSH, Emtree, DeCS, including exploded terms) and free-text terms (considering spelling variants,

Resultados: Se encontraron 401 referencias, se incluyeron nueve estudios; hubo variabilidad en múltiples aspectos metodológicos. Según la razón de costo-efectividad incremental (costo), dos trabajos mostraron que ninguna terapia de primera línea fue costo-efectiva, un tercer estudio reportó al interferón beta-1b como dominante sobre placebo (-315.109,45 dólar estadounidense [US\$]) y un cuarto artículo expone a teriflunomida como dominante sobre interferones y acetato de glatiramer (121.840,37 US\$). Respecto a las terapias de segunda línea, dimetil fumarato fue costo-efectivo en un estudio comparado con acetato de glatiramer e interferón beta-1a y fue dominante en otro trabajo frente a acetato de glatiramer (-158.897,93 US\$) y fingolimod (-92.988,97 US\$). En la tercera línea de tratamiento, natalizumab fue costo-efectivo sobre fingolimod en un artículo, y alemtuzumab fue dominante contra fingolimod (-49.221 US\$) en un segundo estudio. En un tercer ensayo el alemtuzumab fue dominante sobre natalizumab (-1.656.266,07 US\$). Muchos estudios tuvieron sesgo de patrocinador. Ocho artículos obtuvieron alta puntuación de calidad con la herramienta Quality of Health Economic Studies.

Conclusiones: Este trabajo demuestra que existe una gran variabilidad metodológica entre los estudios de costo-efectividad, y algunos de ellos tienen resultados contradictorios. No es posible determinar qué terapia modificadora de la enfermedad en esclerosis múltiple recurrente-remitente es costo-efectiva.

synonyms, acronyms and truncation) with field labels (title and abstract), proximity operators (adj) and boolean operators (OR, AND) were used. The sensitivity of the search strategy was enhanced including keywords that were relevant to the types of studies to be considered. Searches were performed in: MEDLINE (through Ovid), Embase (through de Ovid), the Cochrane Library, LILACS, the Tufts Medical Center Cost-Effectiveness Analysis Registry and the National Health Service Economic Evaluation Database. Open Grey was used for "grey literature" searches.

The MeSH (Medical Subject Headings) terms used were: Relapsing-Remitting Multiple Sclerosis, Cost Effectiveness Analysis, Interferon beta-1a, Interferon beta-1b, Glatiramer acetate, Teriflunomide, Fingolimod Hydrochloride, Dimethyl Fumarate, Natalizumab, Alemtuzumab and Rituximab. DeCS (*Descriptores en Ciencias de la Salud*) terms included were: *Esclerosis Múltiple Recurrente-Remitente, Análisis de Costo-Efectividad, Interferón beta-1a, Interferón beta-1b, Acetato de glatiramer, Teriflunomida, Clorhidrato de fingolimod, Dimetilfumarato, Natalizumab, Alemtuzumab, Rituximab*. The search was performed on 1 January 2018 and the strategy followed is described in the appendixes A to G.

Original economic evaluation studies were selected if included cost-effectiveness and cost-utility models. An analysis was conducted of those where the endpoint measured was the incremental cost-effectiveness ratio (ICER), i.e. cost/quality-adjusted life-years (QALY). Regardless of whether the model was purely theoretical or was based on clinical trials, the publications had to include information about patient outcomes and the direct costs of the treatments administered. Considering that costs typically vary over time, the search was limited to the period January 2010-December 2017. Publications could be written in English or in Spanish. The analyses had to be performed from the payer's perspective¹³. All kinds of DMTs approved by both the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for 2017 were taken into consideration (these drugs are also authorized for use in Colombia by the Instituto Nacional de Vigilancia de Medicamentos y Alimentos [INVIMA]). Although Rituximab has not been officially licensed, its use is authorized in specific cases taking into account the available scientific evidence^{15,19}. Following Hauser *et al.*²⁰, drugs were divided into three lines of treatment for analysis and comparison purposes. Studies where the information on outcomes and/or costs was not made clear (such as congress abstracts) were not evaluated. Nor did we evaluate studies that focused only on the adverse effects of DMTs but not on their cost, or those that analyzed drugs approved by only one of the two regulatory agencies mentioned.

Data processing

Two of the authors conducted the literature search independently, screening papers by title and abstract. Separately, an analysis was conducted of the methodology, design, quality and bias risk of each of the manuscripts. In

the event of discrepancy between the two authors, the assistance of a third evaluator (methodological advisor) was enlisted. Data extraction was also carried out independently, including direct costs (disease-associated costs, relapse costs, medication costs), QALYs, ICER values and methodological data (authors, year of publication, type of study, study sponsor, country/context, model used, model cycles, origin of data, evaluated interventions, currency and year, method used for effect evaluation, target population, time horizon, discount rate, sensitivity analysis, outcome as evaluated by the model, conclusion of the study). Given the risk that there may be some degree of heterogeneity across studies and that the results might prove impossible to group together, it was decided not to perform a meta-analysis^{21,22}. The CCE-MG-EPPI-Centre Cost Converter virtual tool (v 1.5, updated 29 April 2016, <http://epi.ioe.ac.uk/costconversion/default.aspx>) was used to convert the different amounts reported in different currencies to a common currency (the US dollar). All ICER values were recalculated in the light of the primary data provided by the model. The Microsoft Office 365 Excel software® (Microsoft Corporation) was used to store all the information obtained in templates structured at the time of designing the protocol.

The QHES instrument (Quality of Health Economic Studies) was selected to evaluate the quality of the studies²³. The tool was developed specifically for cost-effectiveness analyses and provides a quantitative result that allows for more objective comparisons. It is a validated instrument made up of 16 items that provides a score between 0 and 100, where 100 represents the highest quality. Each author independently applied the instrument to each one of the articles included in the analysis. A decision was made not to use the CHEERS (Consolidated Health Economic Evaluation Reporting Standards) tool²⁴ as it is a qualitative instrument that does not prove useful in helping authors decide whether an article is high quality or not. The risk of bias of each study was evaluated by each author

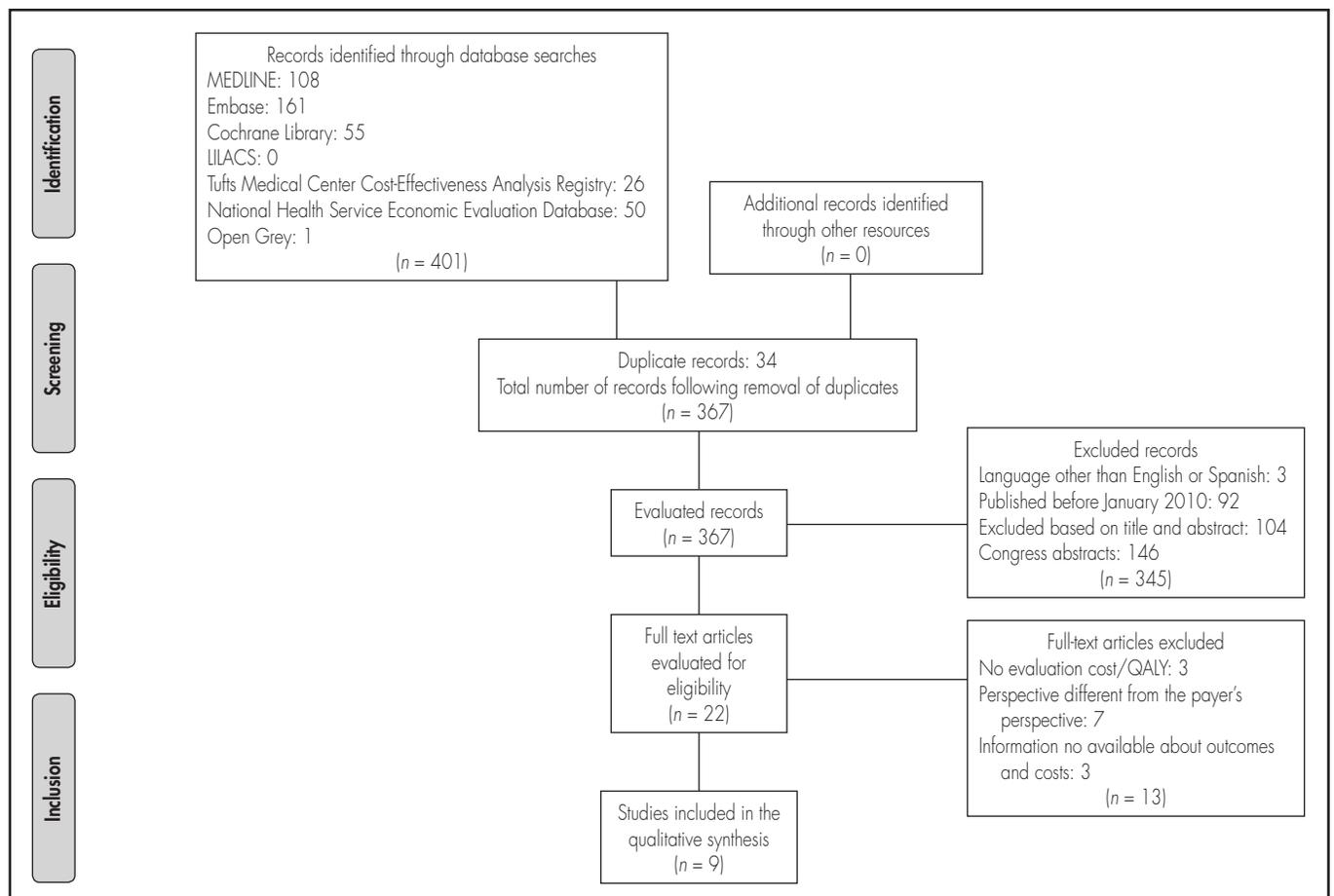
without any tool as there are no standardized instruments available for this purpose. The authors took into consideration the proposal by Evers *et al.*²⁵ (specified in the appendix I). Discrepancies were analyzed in conjunction with a methodological advisor. Biases typical of a systematic review such as the study selection bias, the information bias and the publication bias were carefully considered. Mitigation of intrinsic biases was performed as follows:

- Selection bias: each of two authors followed an independent search strategy; the results were compared and discrepancies were resolved with the help of the methodological advisor.
- Information bias: each author independently evaluated the quality of each manuscript and carried out a bias search. Discordant results were discussed with the methodological advisor.
- Publication bias: the "grey literature" search was performed with the aid of the Open Grey database.

Results

A total of 401 manuscripts were reviewed: 108 from MEDLINE, 161 from Embase, 55 from the Cochrane library, 0 from LILACS, 26 from the Tufts Medical Center Cost-Effectiveness Analysis Registry, 50 from the National Health Service Economic Evaluation Database and 1 from Open Grey. After removing duplicate records, manuscripts published before January 2010, those written in languages different from English and Spanish, those where the title and/or abstract had no bearing with the interventions to be analyzed, those who did not correspond to cost-effectiveness studies; and those that were congress abstracts, a total of 22 articles were left to be evaluated in their full form. After reviewing those full texts, 9 references were found to meet the inclusion criteria²⁶⁻³⁴ (figure 1)³⁵. A total of 13 studies were excluded as they were approached from a social perspective³⁶⁻⁴²; they did

Figure 1. PRISMA flowchart (Preferred Reporting Items for Systematic Reviews and Meta-Analyses).



not calculate the ICER (cost/QALY) when evaluating costs^{43,46}, or failing to clearly specify the total cost of each drug^{47,48}. Included and excluded studies are presented in the appendix I to J.

Study characterization

Of the nine studies included in the analysis, seven were conducted under the sponsorship of a pharmaceutical company^{27,33}. Seven studies were based on Markov's model^{26,29,32,34}, and two on a simulation of discrete events^{30,31}. Three studies analyzed first-line drugs^{26,28}, two looked into second-line medications^{32,33}, one study compared second-line with first-line medications²⁹, two compared third-line medications with one second-line drug^{30,31}, and another compared sequential interventions from the first to the third line³⁴. There was significant variability in the currencies used: some studies used US dollars (USD), others euros (EUR) and others used pound sterling (GBP). As regards the effects measured, quality of life was determined using the EuroQol-5D instrument in over half the studies^{27,31,33}, the others leaving the tool used to calculate QALYs unspecified. The time horizon was variable; in some cases it was between 10-15 years^{27,28} while in others it was 100 years^{30,31}. Discount rates were very similar, mostly between 3% and 5%. The specific details of each study are shown in table 1 and the appendix K.

Bias

Pre-study phase: All nine studies reviewed present a narrow perspective bias as they were all conceived from the payer's point of view, as specified in the Methods section¹³. Four studies were found to contain an inappropriate comparison bias: three compared drugs with placebo^{26,28} and one study compared two drugs in the context of highly-active multiple sclerosis but no studies were cited that demonstrated the effectiveness of the control drug in that setting³¹. A cost omission bias was detected in three studies^{26,27,34} and an intermittent data collection bias was observed in two studies^{26,27}.

Study phase: There were no cases with an invalid valuation bias. Nor were there ordinal ICER biases or double counting of costs. Inappropriate discount and limited sensitivity analysis biases were identified^{26,27}.

Post-study phase: No biases were identified with respect to the dissemination and reporting of the analyses. Six studies contained a potential bias with respect to the study's sponsor and the cost-effectiveness results presented^{28,33}. Three studies were sponsored by Novartis Pharmaceuticals, manufacturer of fingolimod^{30,32}, two studies were sponsored by Biogen Idec, manufacturer of dimethyl fumarate and natalizumab^{29,33}, and one study was sponsored by Sanofi Genzyme, manufacturer of teriflunomide²⁸. A study sponsored by Biogen Idec showed no results in favor of interferon beta-1a²⁷. The specific biases associated with each study are shown in the appendix M.

Quality of the studies included

Overall, studies obtained satisfactory quality scores (Table 2). None of them was in the low quality category and only one was rated as "class 2"²⁶. The remaining eight publications were considered to be "class 4", the highest quality rating^{27,34} (Table 2). All the studies expounded their purpose clearly, calculated costs appropriately and made a straightforward description of the methodology used. They also provided details of the economic model used and of the numerator and denominator components of the ICER. All of them justified their conclusions based on the results obtained and disclosed their funding sources. Most publications^{26,28,31,33,34} failed to discuss potential biases and their relationship with the results obtained.

Incremental cost-effectiveness ratio of the studies

As the protocols and the outcomes of each study were too heterogeneous to allow a statistical analysis of grouped data, the results are presented using a descriptive analysis approach (Table 3). The line of therapy evaluated in each study was clearly designated as a function of the drug

Table 1. Characteristics of the studies included

Study	Country Year	Model	Cycles	Currency Year	Time horizon	Tool used to estimate QALY	Discount	Sponsor
26	Iran 2012	Markov's model	Monthly	USD 2011	Unspecified lifespan	Unspecified	Cost: 7.2% Effects: 7.2%	None
27	USA 2011	Markov's model	Yearly	USD 2005	10 years	SF-36	Cost: 3% Effects: Unspecified	Biogen Idec National Institutes of Health
28	Finland 2017	Markov's model	Yearly	EURO 2013-2014	15 years	EQ-5D	Cost: 3% Effects: 3%	Sanofi Genzyme
29	Canada 2016	Markov's model	Yearly	CAD 2013	20 years	EQ-5D	Cost: 3% Effects: 5%	Biogen Idec
30	UK 2016	Discrete event simulation model	Not applicable	GBP 2015	100 years	EQ-5D	Cost: 3.5% Effects: 3.5%	Novartis Pharmaceuticals
31	UK 2017	Discrete event simulation model	Not applicable	GBP 2015	100 years	EQ-5D	Cost: 3.5% Effects: 3.5%	Novartis Pharmaceuticals
32	UK 2014	Markov's model	Yearly	GBP 2013-2014	50 years	Unspecified	Cost: 3.5% Effects: 75% at 2 yrs, 50% at 5 yrs	Novartis Pharmaceuticals
33	USA 2015	Markov's model	Yearly	USD 2015	20 years	EQ-5D	Cost: 3% Effects: 3%	Biogen Idec
34	USA 2017	Markov's model	Yearly	USD 2014	20 years	Unspecified	Costs: 3% Effects: 3%	None

CAD: Canadian dollar; EQ-5D: EuroQol-5D quality of life questionnaire; EURO: euros; GBP: pound sterling; QALY: quality-adjusted life-years; SF-36: SF-36 quality of life questionnaire; USD: US dollar.

Table 2. Quality rating of the articles included in the study using the QHES (Quality of Health Economic Studies) tool

QHES Criterion (NO = 0 points)	Study (reference)								
	26	27	28	29	30	31	32	33	34
P1 (7)	7	7	7	7	7	7	7	7	7
P2 (4)	0	4	4	4	4	4	4	4	4
P3 (8)	0	0	8	8	8	8	8	8	8
P4 (1)	0	0	1	1	1	0	0	1	1
P5 (9)	0	9	9	9	9	9	9	9	9
P6 (6)	6	6	6	6	6	0	6	6	6
P7 (5)	0	5	5	5	5	5	5	5	5
P8 (7)	0	0	7	7	7	7	7	7	7
P9 (8)	8	8	8	8	8	8	8	8	8
P10 (6)	6	6	6	6	6	6	6	6	6
P11 (7)	0	7	7	7	0	7	0	7	0
P12 (8)	8	8	8	8	8	8	8	8	8
P13 (7)	0	7	7	7	7	7	7	7	7
P14 (6)	0	6	0	0	0	0	6	0	0
P15 (8)	8	8	8	8	8	8	8	8	8
P16 (3)	3	3	3	3	3	3	3	3	3
Total	46	84	94	94	87	87	92	94	87
Quality of the study	Low	Higher							

used as a control for the pharmacoeconomic analysis; when the control drug was a placebo, the study was considered to be concerned with the line of therapy which the drugs evaluated belonged to. Three studies analyzed the first line of treatment^{26,28}, five studies looked at the second line^{29,33}, and one study focused on the third line³⁴.

• First-line medications:

Three studies compared subcutaneous (SC) and intramuscular (IM) interferon beta-1a and interferon beta-1b^{26,28} with placebo. Two of those studies also evaluated glatiramer acetate^{27,28} while one study analyzed teriflunomide and dimethyl fumarate²⁸. Imani *et al.*²⁶, who chose their cost-effectiveness threshold in a random manner, reported that none of the DMTs analyzed stood below the willingness to pay (WTP) per QALY threshold. Noyes *et al.*²⁷ and Soini *et al.*²⁸ did not define a cost-effectiveness threshold. In the first study, none of the therapies was cost-effective; while in the second interferon beta-1b was shown to be dominant over placebo, and teriflunomide proved to be dominant over glatiramer acetate and interferons. Cost, QALY, threshold and ICER values are presented in table 3.

• Second-line medications:

Dimethyl fumarate was evaluated in three studies^{29,32,33}; fingolimod in four studies^{30,33}; glatiramer acetate in two studies^{29,33}; and SC interferon beta-1a, natalizumab and alemtuzumab in one study each^{29,30,32}. The selected cost-effectiveness threshold stood between USD 20,000 and 50,000 in four articles^{29,32}; one of the studies failed to establish a cost-effectiveness threshold³³. According to Su *et al.*²⁹ dimethyl fumarate was a cost-effective option as compared with glatiramer acetate and SC interferon beta-1a; Mauskopf *et al.*³³ showed this drug to be dominant over glatiramer acetate and fingolimod. According to Maruszczak *et al.*³²,

fingolimod was cost-effective in 73% of cases when compared with dimethyl fumarate. Montgomery *et al.*³⁰ showed natalizumab to be more cost-effective than fingolimod, and the same author demonstrated alemtuzumab to be dominant over fingolimod in another study³¹ (Table 3).

• Third-line medications:

Bin Sawad *et al.*³⁴ compared IM interferon beta-1a, natalizumab and alemtuzumab with symptomatic management, considering them stages along an increasing therapeutic potency medication journey. They established a cost-effectiveness threshold of USD 50,000-100,000. Although none of the DMTs turned out to be cost-effective with respect to that threshold, alemtuzumab did prove dominant over natalizumab, regardless of the WTP per QALY threshold (Table 3).

Discussion

The results of the present study show that placebo was cost-effective as compared with first-line medications^{26,27}. Only one study, which compared the different drugs to one another, favored the use of teriflunomide over all the other therapies²⁸. For the second line of treatment, dimethyl fumarate proved cost-effective^{29,33}; fingolimod, alemtuzumab and natalizumab were also cost-effective, each in one separate study^{30,32}. Also in the second line, two studies compared dimethyl fumarate with fingolimod, each obtaining different results as a function of the model applied. With respect to the third line, alemtuzumab was found to be dominant over natalizumab³⁴.

Interpretation and application of these results need to be made with caution as ICER values exhibited a wide variability, even within one same treatment and using the same control medication. This variability is heavily dependent on 1) the parameters selected to develop the pharmacoeconomic model; 2) the choice of the control medication; and 3) the WTP per

Table 3. Results of the studies evaluating the incremental cost-effectiveness ratio (cost/QALY)

Study	Cost*	QALY	Threshold**	ICER = Cost/QALY
Studies on first-line therapies				
26	Total lifetime cost per patient: IM interferon beta 1a: USD 154,717.79; SC interferon beta 1a: USD 269,592.47; Interferon beta 1b: USD 321,121.43 Placebo: USD 21,765.47	IM interferon beta 1a: 9,285 SC interferon beta 1a: 9,279 Interferon beta 1b: 9,285 Placebo: 9,081	Random USD 53,649.18 (USD 50,000)	IM interferon beta 1a vs. placebo: USD 651,726.97 SC interferon beta 1a vs. placebo: USD 1,251,651.37 Interferon beta 1b vs. placebo: USD 1,474,660.26
27	Total 10-year cost per patient: IM interferon beta 1a: USD 563,626.85 SC interferon beta 1a: USD 585,462.76 Interferon beta 1b: USD 593,269.22 Glatiramer acetate: USD 573,889.25 Placebo: USD 322,609.95	IM interferon beta 1a: 6,692 SC interferon beta 1a: 6,626 Interferon beta 1b: 6,673 Glatiramer acetate: 6,582 Placebo: 6.5	Unspecified	IM interferon beta 1a vs. placebo: USD 1,255,296.26 SC interferon beta 1a vs. placebo: USD 2,086,133.34 Interferon beta 1b vs. placebo: USD 1,564,504.36 Glatiramer acetate vs. placebo: USD 3,064,381.64
28	Total per patient: IM interferon beta 1a: USD 402,073.95 SC interferon beta 1a: USD 385,053.42 Interferon beta 1b: USD 452,451.97 Glatiramer acetate: USD 408,204.65 Teriflunomide: USD 378,475.60 Dimethyl fumarate: USD 386,018.24 Placebo: USD 368,002.64	IM interferon beta 1a: 7,456 SC interferon beta 1a: 7,595 Interferon beta 1b: 7,063 Glatiramer acetate: 7,475 Teriflunomide: 7,719 Dimethyl fumarate: 7,808 Placebo: 7,331	Unspecified	IM interferon beta 1a vs. placebo: USD 272,570.47 SC interferon beta 1a vs. placebo: USD 64,586.29 Interferon beta 1b vs. placebo: USD -315,109.45 Glatiramer acetate vs. placebo: USD 279,180.66 Teriflunomide vs. placebo: USD 26,992.16 Dimethyl fumarate vs. placebo: USD 37,768.56 Teriflunomide vs. IM interferon beta 1a: USD -89,727.55 Teriflunomide vs. SC interferon beta 1a: USD -53,046.92 Teriflunomide vs. interferon beta 1b: USD -112,768.85 Teriflunomide vs. glatiramer acetate: USD -121,840.37 Teriflunomide vs. dimethyl fumarate: USD 84,748.76 Teriflunomide vs. placebo: USD 26,992.16
Studies on second-line therapies				
29	Total DMTs Dimethyl fumarate: USD 204,270.04 Glatiramer acetate: USD 184,658.08 SC interferon beta 1a: USD 201,795.22	Dimethyl fumarate: 5,885 Glatiramer acetate: 5,357 SC interferon beta 1a: 5,610	USD 42,017.21 (USD 50,000)	Dimethyl fumarate vs. glatiramer acetate: USD 37,074.31 Dimethyl fumarate vs. SC interferon beta 1a: USD 8,968.15
30	Total Natalizumab: USD 491,454.49 Fingolimod: USD 487,663.79	Natalizumab: 6.35 Fingolimod: 6.18	USD 29,123.13-43,684.69 (GBP 20,000-30,000)	Natalizumab vs. fingolimod: USD 22,298.21
31	Total Alemtuzumab: USD 290,189.57 Fingolimod: USD 300,033.77	Alemtuzumab: 4.64 Fingolimod: 4.44	USD 29,030.89-43,546.33 (GBP 20,000-30,000)	Alemtuzumab vs. fingolimod: USD -49,221
32	Total Fingolimod: USD 528,396.27 Dimethyl fumarate: USD 514,065.39	Fingolimod 4.7 Dimethyl fumarate: 3.93	USD 44,487.41 (GBP 30,000)	Fingolimod vs. dimethyl fumarate: USD 18,611.53
33	Total 20-year cost per patient Dimethyl fumarate USD 858,666.84 Glatiramer acetate USD 930,170.91 Fingolimod USD 892,049.88	Dimethyl fumarate: 6,856 Glatiramer acetate: 6,406 Fingolimod: 6,497	Unspecified	Dimethyl fumarate vs. glatiramer acetate: USD -158,897.93 Dimethyl fumarate vs. fingolimod: USD -92,988.97
Studies on third-line therapies				
34	Total 20-year cost per patient: Symptomatic management: USD 164,346.40 Interferon beta 1a: USD 562,639.41 Natalizumab: USD 717,476.43 Alemtuzumab: USD 684,351.11	Symptomatic management: 10.49 Interferon beta 1a: 10.66 Natalizumab: 10.69 Alemtuzumab: 10.71	USD 50,995.99-101,991.98 (USD 50,000-100,000)	IM interferon beta 1a vs. symptomatic management: USD 2,342,900.06 Natalizumab vs. IM interferon beta 1a: USD 5,161,233.95 Alemtuzumab vs. natalizumab: USD -1,656,266.07

ICER: Incremental cost-effectiveness ratio; QALY: quality-adjusted life-years.

* Direct costs converted to 2016 United States dollars.

** Threshold converted to 2016 United States dollars and expressed as cost/QALY (threshold published in the study).

QALY threshold established. On the other hand, there are a few similarities such as the use of one same tool to calculate quality of life and discount rate values. First-line drugs were the most commonly analyzed probably because their cost tends to be lower than that of the most innovative therapies. Three publications²⁶⁻²⁸ used placebo, which is usually the least costly of all medications, as the control drug. Studies that evaluated the same drugs took their data from different sources, which may interfere with their comparability. Moreover, different models were used for the economic analysis (Markov's model, decision analysis model and discrete event simulation model). There were also differences in terms of the currencies used in the different cases, the amounts of the costs, the models' time horizons and the outcomes evaluated. All of this poses a significant challenge for the current study in terms of extracting the data and selecting the most relevant of those data making sure they are comparable, at least from a descriptive point of view. All the studies had biases inherent in the model used; there were cases of sponsorship bias, which required a rigorous analysis of both the model itself and the results obtained. The evaluation made using the QHES instrument revealed that the majority of studies were of the highest quality and sought to present information as clearly as possible.

In Colombia, the approval granted to the drugs used to treat relapsing-remitting multiple sclerosis does not preclude their use in the first-line setting, which makes it possible to offer each patient a customized treatment. Based on an understanding that monoclonal antibodies and fingolimod are the most costly of all the drugs in this category, the authorities tend to promote a more rational use of financial resources by separating therapies into different lines so as to gradually increase therapeutic potency according to the patients' requirements and each drug's safety profile. Taking into account this local therapeutic approach (unpublished information), a modification was made to the proposal by Hauser *et al.*²⁰ to execute the information analysis. First-line treatments were considered to include injectable therapies and teriflunomide given their lower effectiveness and higher safety, and the existence of trials with patients with clinically isolated syndrome. The second line included dimethyl fumarate and fingolimod given their higher potency as compared to injectables, regardless of the higher safety profile theoretically associated with dimethyl fumarate. The third line included monoclonal antibodies because of their higher effectiveness, higher risk of adverse effects and higher cost in the country. Regardless of the comparison that could be drawn based on the classification of the different medications, the heterogeneity of the models used inevitably poses a significant limitation on the comparison of the different ICER values.

Three previous systematic reviews looked into pharmaco-economic outcomes in the context of multiple sclerosis treatment⁴⁹⁻⁵¹. Clegg *et al.* set about investigating the effectiveness of therapies used within the different lines of treatment, including such non-disease-modifying drugs as methotrexate, cyclophosphamide and azathioprine⁴⁹. They only found pharmaco-economic cost-effectiveness and cost-utility studies for interferon beta-1a, interferon beta-1b and glatiramer acetate, with significant variabilities and highly heterogeneous outcomes that are difficult to interpret out of context. As regards the reviews by Yamamoto *et al.*⁵⁰ and Iannazzo *et al.*⁵¹, although findings are similar to those of the present study, the authors included studies with a social perspective, which further increased the heterogeneity of results and limited the strength of any conclusions drawn¹³. Additionally, in Iannazzo *et al.*⁵¹, the method used to convert prices is not ideal. Although the present review specifies the difficulties inherent in working with heterogeneous information, it, at the same time, identifies a full range of therapeutic options as well as further studies with active control medications. The present study therefore seeks to analyze the whole range of DMTs authorized by the two most important regulatory agencies worldwide (EMA and FDA).

From the patient's point of view, the most interesting thing to determine would be each drug's potential to reduce disability, improve quality of life and extend the individual's productive lifespan. Accordingly, an effective pharmaco-economic assessment should include outcome measures that are important for both the patient and the payer in the long term. Unfor-

tunately measuring these indirect costs is not easy given the scarcity of data and the vagueness of values and utilities. For this reason, a decision was made to limit the scope of the present paper in order to obtain results that would be comparable across different studies. The payer's perspective is usually narrower, with outcomes that tend to be of greater interest to the healthcare system, which reduces the social impact created by the conclusions obtained. One of the most significant limitations of the present study is the inability to determine the real economic and social impact of the different therapies given the large number of variables to be considered. Indeed, none of the studies reviewed achieved such a large scope, especially in Latin America where no cost-effectiveness evaluation was found for the local population. Adapting and extrapolating the information obtained to other countries' models and currencies is difficult and could even be inappropriate. This means that apart from the results that could be obtained, it is not feasible to generate a healthcare policy for a specific country without local data. Another limitation of this study is the selection bias resulting from having excluded studies written in languages different from Spanish and English. Only one (Russian language) manuscript (repeated three times) was excluded from the analysis, but given the model used (mentioned in the abstract) it is unlikely that it would have affected the results. Restricting searches to the period between 2010 and 2017 could also be construed as another limitation of the present paper, but taking into account that currencies tend to fluctuate significantly over time and that adjustments for inflation are not always correctly made, including older studies would have a strong impact of a cost-effectiveness model.

Further studies are required, designed on the basis of as homogeneous a set of models as possible (in terms of perspective, currency, time horizon, discount rate, target population, model cycles, interventions to be evaluated, outcomes to be measured), which are free from sponsorship bias and which take into consideration the factors that have the greatest impact on patients' lives such as disability and productive life years.

The present study shows that, in spite of the effort to homogenize the high level of methodological variability of cost-effectiveness studies, it is not possible to determine which DMTs are the most cost-effective in the multiple sclerosis relapsing-remitting setting. Some of the studies in the literature even provide mutually contradictory results. Given the dearth of evidence available to answer the research question, further and more methodologically uniform studies are required to provide reasonable and effective cost-related recommendations to patients and to the healthcare system at large.

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Conflict of interest

No conflict of interest.

Contribution to the scientific literature

The present study looks into the most recent payer-perspective cost-effectiveness analyses of the different disease-modifying therapies for relapsing-remitting multiple sclerosis in an attempt to provide a clear overview of the findings obtained (same currency, same perspective, same outcomes).

Given the methodological variability across the different studies, it is not possible to determine which drug is the most cost-effective.

Methodological uniformity is required to come up with a recommendation that supports decision-making with respect to cost-effectiveness.

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