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REVIEW

Quantifying the Value of Introducing an Oral Drug Delivery Option for Edaravone: A Review of Analyses Evaluating the Economic Impact of Oral versus Intravenous Formulations

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Background: Drug formulation and route of administration can have an impact on not only patients' quality of life and disease outcomes but also costs of care. It is essential for decision makers to use appropriate economic modeling methods to guide drug coverage policies and to support patients' decision-making.

Purpose: To illustrate key cost considerations for decision makers in economic evaluation of innovative oral formulations as alternatives to intravenous medication.

Materials and Methods: A structured literature review was conducted using the PubMed database to examine methods used for quantifying the economic impact of introducing a new oral pharmaceutical formulation as an alternative to intravenous medication. To illustrate the methods described in this review, a cost-minimization analysis was conducted to quantify the impact of introducing an oral formulation of a medication originally developed as an intravenous treatment for amyotrophic lateral sclerosis.

Results: We identified 14 published evaluations of oral and intravenous formulations from 10 countries across a variety of disease areas. The identified studies used cost-effectiveness (n=10), cost-minimization (n=2), and cost-calculation (n=2) modeling approaches. All but one (13/14) reported outcomes from payers' perspective, while societal perspectives were also incorporated in 3 of the reviewed evaluations. One study estimated costs from a public hospital's perspective. Only a subset of the identified studies accounted for the effects of safety (n=6) or efficacy (n=8) differences on treatment costs when estimating the costs of a formulation choice. Many studies that omitted these aspects did not include rationales for their decisions.

Conclusion: We found significant design variations in published models that estimated the impact of an additional formulation option on the treatment costs to payers and the society. Models need to be accompanied with clear descriptions on rationales for their time horizons and assumptions on how different formulations may affect healthcare costs from the selected perspectives.

Keywords: cost-effectiveness analysis, cost-minimization, decision makers, formulation comparison, amyotrophic lateral sclerosis

Introduction

Drug formulation, dosing regimens, and route of administration can have an impact on patients' quality of life, disease outcomes, and costs of care. Intravenous (IV), subcutaneous (SC), and intramuscular (IM) injections or infusions of a medication may be medically required or preferred by patients for a variety of reasons. However, due to the need for commitment to more frequent office visits for medication administrations, monitoring for potential injection-site reactions, and other infusion-/injection-specific side effects, many studies have reported patients' preference for oral medications over medications delivered by other routes of administration.[1–3] Because different medication formulations are typically associated with competing benefits and risks, it is critical that patients, providers, and formulary decision makers have a clear path for assessing the value of new formulations.

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A variety of recently developed value assessment framework documents recommends that decision makers account for a new treatment's ability to reduce regimen complexity as part of the contextual considerations for the drug's benefits or disadvantages.[4,5] However, the value of alternative formulations can also be measured quantitatively. For instance, as demonstrated in a review by Stewart et al,[6] the impact of formulation alternatives on patient preference and willingness to pay for treatment has been assessed with the use of discrete choice experiments. Economic models have also played an essential role in guiding payers' coverage policy and to support patients in making the best treatment choice.[7–9] As rising healthcare costs and spending are global concerns to payers and the society, it is essential that decision makers have appropriate economic modeling methods to guide the development of drug coverage policies and support patients in making the most cost-effective treatment choice in a timely manner.

In this study, we conducted a structured literature review to identify and examine methods used in published health economic models that quantified the impact of introducing new pharmaceutical formulations. To ensure comparability across studies, our review focused on studies that compared administrations of an oral formulation with an alternative IV formulation.

We also present a case study to quantify the economic impact of introducing an oral formulation of edaravone (Radicava, approved by the Food and Drug Administration [FDA] in May of 2017), for amyotrophic lateral sclerosis (ALS) using a cost-minimization analysis that we developed. ALS is a fatal neurodegenerative disease with rapid progression of symptoms that directly result from degeneration in motor neurons in the spinal cord, brainstem and motor cortex.[10–12] Despite the significant clinical, humanistic, and economic burden of this disease to patients and their caregivers,[13–15] to date, riluzole and edaravone are the only drugs approved for the treatment of ALS in the United States (US). The case study supplements the literature review and serves as an example to highlight the value of incorporating key cost drivers and importance of describing underlying assumptions in the economic model. This work can inform health outcomes researchers and formulary decision makers regarding what cost attributes to consider when evaluating the value of new formulations.

Materials and Methods

An electronic keyword search of articles published from January 2000 to May 2021 was performed using the PubMed database. The literature search strategy targeted articles that included economic analyses comparing oral versus IV formulations of pharmacotherapy indicated for any condition. The following search terms were used to identify potential studies for inclusion: ("oral"[Title/Abstract] AND "versus"[Title/Abstract] AND "intravenous"[Title/Abstract] AND "cost"[Title/Abstract] AND "benefit"[Title/Abstract] OR "effectiveness"[Title/Abstract] OR "offset"[Title/Abstract] OR "minimization"[Title/Abstract]). From an initial review of the abstracts identified in the electronic searches, a subset of articles was selected for full review. The initial selection of studies was evaluated by another reviewer to confirm inclusion or exclusion. Review studies, articles published in a non-English language, and studies that did not explicitly estimate the economic impact of a treatment due to the formulation difference were excluded. The search strategy and each step of the search process are outlined in Figure 1.

In each of the studies, the design, perspective, interventions, and presence or absence of the key cost and healthcare resource measures were reported. Data were extracted from the identified studies, including information about publication year, country, disease area, study comparators, model type, model perspectives, time horizon, and key model outcomes. Outcomes related to healthcare resource use were further classified by the type of resource (eg, related to drug administration, IV maintenance, disease management, efficacy/adherence difference, or adverse events), and cost-related outcomes were grouped into categories of indirect and direct costs. To compare design features across the identified studies, we organized the data into two tables that present key study characteristics. The first table was organized by the methodology used to conduct the analyses and by the country of the study. The second table highlights a subset of studies that captured specific types of healthcare resources and unique types of cost drivers.

Case Study

As a case study illustrating methods described in the literature review, we developed a cost-calculator model that quantifies the effect of introducing an oral formulation of a marketed intravenous treatment for ALS, edaravone, on the costs to

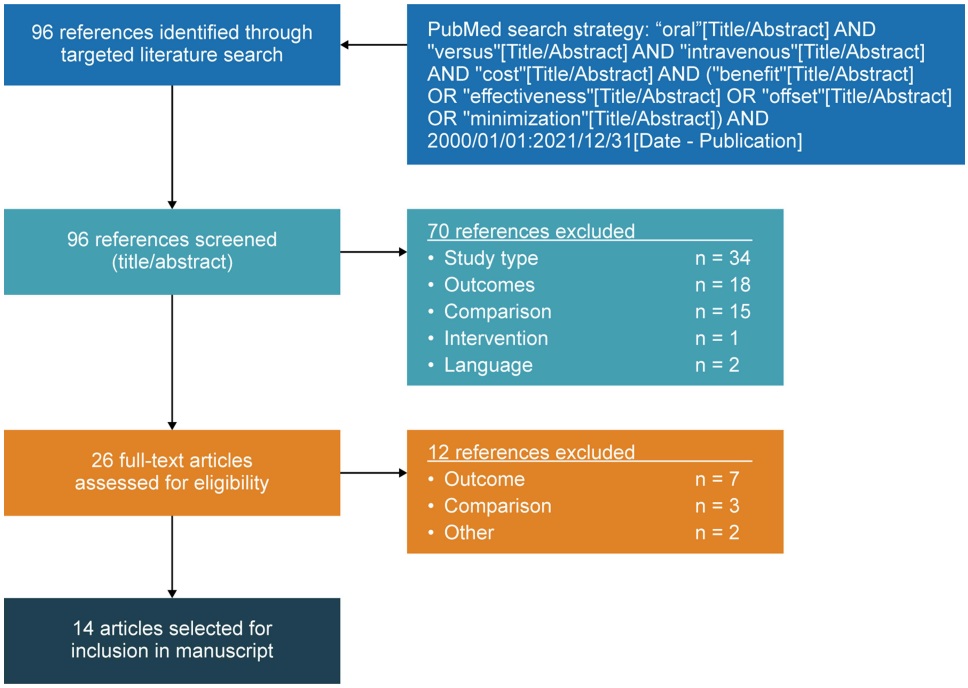

Figure 1 PRISMA flow chart and the literature search strategy.
Abbreviation: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

payers and the society. An IV form of edaravone was approved as a treatment for ALS by the US FDA in May of 2017[16] and an oral formulation was approved in May of 2022.[17] This example was selected as a case study for several reasons. First, because similar efficacy outcomes between the oral and IV formulations were anticipated, the model could be simplified to assume equal efficacy between treatments, justifying a simple cost-minimization analysis (vs a cost-effectiveness analysis) as an appropriate approach. Second, to estimate the potential societal impact of the availability of a new formulation on patients and their caregivers, an ideal case study involved a situation where a currently available treatment required a substantial time commitment from patients and their caregivers. In the model, IV edaravone was administered for 14 consecutive days, 60-minutes each day, followed by a 2-week treatment-free period. Then, subsequent treatment cycles were repeated as a daily treatment for 10 of the next 14 days, followed by 2 weeks without treatment. We compared and contrasted the methods used to develop the ALS cost calculator to the methods identified in the literature.

Results

Figure 1 illustrates a PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) diagram of the search strategy, and the number of articles identified and/or excluded at each step in the search process. A total of 96 unique abstracts were retrieved from the PubMed database search. The dual review of these abstracts identified 26 articles that met the inclusion criteria for our review. After reviewing the full text of the selected 26 articles, 12 were excluded because of issues regarding the types of outcomes reported (n=7), comparisons made (n=3), and documentation of study methods and outcomes (n=2).

Table 1 presents a summary of the study characteristics, organized by study countries, interventions compared, and model design. Of the 14 studies reviewed, 5 were conducted in North America (3 in the US, 2 in Canada), and each of the remaining 9 studies were from different countries across Europe, Asia, and the Middle East (the United Kingdom, France, Italy, Taiwan, China, Japan, Thailand, and Qatar). Four of the 14 reviewed studies were in oncology, and 3 examined treatments of infections. The remaining 7 studies pertained to treatments for a rare autoimmune disease (antibody-associated vasculitis), anemia in patients with chronic kidney disease, anemia in patients with inflammatory bowel disease, a gastrointestinal disease (peptic ulcer hemorrhage), osteoporosis, a retinal disease (cytomegalovirus retinitis), and an infancy heart defect (patent ductus arteriosus).

Table 1 Summary of Identified Studies[a]

Study	Country	Disease Area	Indication	Comparators	Model Type	Time Horizon	Perspective	Drug Acquisition	Drug Admin and IV Maintenance	Disease Monitoring	AE	Adherence Issues	Efficacy Differences	Travel	Productivity Loss
McMeekin et al[7]	UK	Infectious disease	Bone or joint infection	Oral vs intravenous antibiotics	CEA based on trial data	1 year	NHS perspective	x	x	x			x		
Montante et al[8]	France	Rare autoimmune disease	Antibody-associated vasculitis	IV rituximab vs oral azathioprine	CEA based on trial data	28 months	French social health insurance perspective	x	x	x	x		x		
Riccio et al[9]	Italy	Anemia	Anemia in patients with ND-CKD	Sucrosomial iron (oral) vs IV iron supplement	CMA	3 months	Payer and societal perspective	x	x	x				x	x
Hsu and Wang[20]	Taiwan	Oncology	Stages II and III colorectal cancer	Oral uracil-tegafur/ leucovorin (LV) vs IV 5-fluorouracil (5-FU)/LV	CMA	25 weeks	National health insurance perspective	x	x	x	x				
McCrea et al[19]	US	Oncology	Advanced renal cell carcinoma	IV nivolumab vs oral everolimus	CEA	25 years	US payer perspective	x	x	x	x		x		
Zhang and Hu[23]	China	Infectious disease	Acute lower respiratory tract infection in elderly patients	IV levofloxacin vs IV levofloxacin followed by oral levofloxacin	CEA	10 days	Healthcare provider perspective	x	x	x			x		
Spiegel et al[21]	US	GI disease	Peptic ulcer hemorrhage	Oral proton pump inhibitor (PPI) vs IV PPI and IV histamine receptor antagonist therapy	CEA and BIA	1 year	Third-party payer perspective	x	x	x			x		
Ferko et al[24]	Canada	Bone disease	Osteoporosis	Risedronate and ibandronate (oral) vs IV zoledronate	CEA	1 year	Managed care organization perspective	x	x	x			x		
Pettigrew et al[25]	Canada	Infectious disease	MRSA infection	IV and oral linezolid vs IV vancomycin	Cost-calculator model	4 weeks	Quebec healthcare system perspective	x	x	x					

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Shiroiwa et al[18]	Japan	Oncology	Stage III colorectal cancer	Oral capecitabine vs IV 5-FU/LV	CEA	Short term (1 year) and long term (15 years)	Japanese healthcare payer perspective	x	x	x	x				
Teerawattananon et al[22]	Thailand	Retinal disease	Cytomegalovirus retinitis in patients with HIV/AIDS	Intravitreal injection, vs IV, oral, and intraocular implantation formulations of ganciclovir	CEA	1 year	Healthcare providers' perspective and societal perspective (base case)	x	x		x			x	x
Hillner et al[26]	US	Oncology	Advanced metastatic melanoma	Oral temozolomide vs IV dacarbazine	CEA	1 year	Health system or centralized payer perspective (base case) and societal perspective (scenario)	x	x	x					x
Abushanab et al[27]	Qatar	Heart defect	PDA	Intravenous ibuprofen vs oral ibuprofen	Cost-calculator model	1 year	Public hospital perspective	x	x	x	x		x		
You et al[28]	China	Bone disease	Osteoporosis	IV zoledronic acid vs oral alendronate	CEA	Lifetime	Healthcare payer perspective	x	x	x		x	x		

Notes: [a]None of the reviewed studies incorporated cost differences due to differences in adherence to certain types of drug formulations. Two studies[21,25] acknowledged the potential cost due to higher discontinuations due to drug formulations. Symbol: x = included in study.

Abbreviations: AE, adverse event; BIA, budget-impact analysis; CEA, cost-effectiveness analysis; CMA, cost-minimization analysis; GI, gastrointestinal; NHS, National Health Service; IV, intravenous; MRSA, methicillin-resistant staphylococcus aureus; ND-CKD, non-dialysis chronic kidney disease; PDA, patent ductus arteriosus; UK, United Kingdom; US, United States.

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All but one (13/14) study, which assessed three different formulations of the same drug (ie, intravitreal injection, IV or oral [or IV followed by oral], and intraocular implantation formulations), compared an oral drug with another drug in an IV formulation indicated for the same condition. With regard to the type of model selected, 8 studies used the decision analytic modeling approach to conduct a cost-effectiveness analysis, 2 studies conducted a cost-effectiveness analysis alongside clinical trials, and the remaining 4 studies used a cost-minimization (n=2) or cost-calculation (n=2) approach. Of the 14 studies, 10 evaluated the economic impact of a formulation choice in a time horizon within 1 year. One study reported outcomes at two different time horizons (at 1 year and at 15 years). The remaining 3 studies had a time horizon of 28 months, 25 years, and lifetime.

Approximately 20% of the studies reviewed (3/14) reported the societal costs of the formulation choice, and the rest of the studies focused on costs to third-party payers (10/14) or hospitals (1/14) only. All reviewed studies incorporated the costs of drug administrations and IV maintenance to estimate the impact of selecting oral versus alternative formulations on direct healthcare costs. Most studies accounted for the time for healthcare providers to administer the IV drug and the resources required for inserting and removing IV lines. Only a subset of the reviewed studies considered the costs of adverse events (n=6) or the different treatment or disease management costs due to differential efficacy (n=8). One study accounted for costs due to differences in treatment adherence based on the formulation choice.

Tables 2–4 summarize studies that included the societal perspective, studies that incorporated costs of treating adverse events, and studies that account for the impact of efficacy differences on direct costs, respectively. Of the three studies that examined results from the societal perspective, all accounted for the wages lost because of reduced productivity, while only two accounted for the cost of travel expenses (Table 2). One study reported the contribution of indirect costs to the overall incremental costs; in a cost-minimization analysis of patients with non-dialysis chronic kidney disease, Riccio et al[9] compared differences in costs for treating patients with oral or IV iron supplements for anemia and found that approximately 69% of the total costs were non-direct medical costs (€65.75 [travel costs], €757.44 [productivity loss] vs €1191.25 [total costs]).

Less than half (6/14) of the reviewed studies accounted for the costs of adverse events (Table 1). Of the eight studies that did not account for adverse events, only one explained the study's rationale to assume the equal or similar safety profiles between the treatments. In studies that incorporated the costs of treating adverse events, the proportion of the

Table 2 Studies That Incorporated a Societal Perspective (3 of 14)

Study	Country	Study Comparators	Model Type	Time Horizon	Travel Costs	Productivity	Proportion of Societal Costs vs Total Costs
Riccio et al[9]	Italy	Sucrosomial iron (oral) vs IV iron supplement	CMA	3 months	Distance-based estimate from survey translated to cost/km	Productivity loss for patients and caregivers estimated based on wage losses	Approximately 69% of the total costs (€65.75 [travel costs], €757.44 [productivity loss] vs €1191.25 [total costs])
Teerawattananon et al[22]	Thailand	Intravitreal injection vs IV/oral and intraocular implantation formulations of ganciclovir	CEA	1 year	Travel costs for patients and family members	Wage loss for patients and family members	Not reported
Hillner et al[26]	United States	Oral temozolomide vs IV dacarbazine	CEA	1 year	Not included	A caregiver's lost wage (half a day) for each IV evaluation office visit	Not reported

Abbreviations: CEA, cost-effectiveness analysis; CMA, cost-minimization analysis; IV, intravenous.

Table 3 Studies That Accounted for Costs of Adverse Events (6 of 14)[a]

Study	Country	Study Comparators	Model Type	Time Horizon	Included AEs	Importance of AE Costs
Montante et al[8]	France	IV rituximab vs oral azathioprine	CEA based on trial data	28 months	Hospital discharge diagnoses with a reasonably possible causal relationship with the treatment (eg, infectious events) were included in the economic evaluation	Approximately 30% of the difference in total direct costs In 1-way sensitivity analyses, presence of severe AEs was one of the top (third among all model parameters) drivers of the ICER
Hsu and Wang[20]	Taiwan	Oral uracil-tegafur/leucovorin (LV) vs IV 5-fluorouracil (5-FU)/LV	CMA	25 weeks	Physician consultations and resource use for treatments of AEs obtained in a physician survey	Approximately 10% of the difference in total direct costs
McCrea et al[19]	United States	IV nivolumab vs oral everolimus	CEA based on trial data	25 years	Not broken out by type of AE	<1% of the difference in total direct costs
Shiroiwa et al[18]	Japan	Oral capecitabine vs IV 5-FU/LV	CEA	1 year and 15 years	Medication for adverse events for four frequent chemotherapy-related toxicities (ie, diarrhea, nausea/vomiting, infectious diseases, and hand-foot syndrome)	<1% of the difference in total direct costs
Teerawattananon et al[22]	Thailand	Intravitreal injection vs IV/oral and intraocular implantation formulations of ganciclovir	CEA	1 year	Cost of treatment of endophthalmitis, retinal detachment, cytomegalovirus infection in other organs, treatment of sepsis	Not reported
Abushanab et al[27]	Qatar	Intravenous ibuprofen vs oral ibuprofen	Cost-calculator model	1 year	Spontaneous intestinal perforation, necrotizing enterocolitis, thrombocytopenia	<1% of the difference in total direct costs

Notes: [a]Hillner et al[26] explained their study did not include AE costs because no AE observed required hospitalization. Additionally, there was no difference between grades 3 and 4 between treatments.
Abbreviations: AE, adverse event; CEA, cost-effectiveness analysis; CMA, cost-minimization analysis; ICER, incremental cost-effectiveness ratio.

total costs that accounted for treatment of adverse events varied by studies, but it was typically less than 10% (Table 3). For instance, in a study comparing the costs of oral capecitabine and IV 5-fluorouracil in patients with stage III colorectal cancer in Japan, the researchers found an incremental cost from the treatment of adverse events associated with the oral formulation, but it was less than 1% of the total direct cost savings from the selection of the oral formulation.[18] A similar outcome was reported in a US-based cost-effectiveness analysis of IV nivolumab versus oral everolimus for patients with advanced renal cell carcinoma.[19] However, a Taiwanese study of stages II and III colorectal cancer reported that the cost savings from lower costs for adverse events were approximately 10% of the total cost savings from patients receiving oral uracil-tegafur.[20] Finally, in a comparison of IV rituximab versus oral azathioprine, Montante et al[8] estimated the total cost savings for patients who select oral azathioprine instead of IV rituximab for the treatment of antibody-associated

Table 4 Studies That Accounted for Efficacy Differences (8 of 14)

Study	Country	Study Comparators	Model Type	Time Horizon	HCRU Due to Efficacy Differences	Importance of Efficacy Differences
Montante et al[8]	France	IV rituximab vs oral azathioprine	CEA based on trial data	28 months	Relapse issues (inpatient costs)	Up to 27% of per-patient total costs
Zhang and Hu[23]	China	IV levofloxacin vs IV levofloxacin followed by oral levofloxacin	CEA	10 days	Different efficacy	Not reported
Spiegel et al[21]	United States	Oral proton pump inhibitor (PPI) vs IV PPI and IV histamine receptor antagonist therapy	CEA and BIA	1 year	Recurrent hemorrhage	In the sensitivity analysis, the study identified that the model was highly sensitive to only 3 variables; 2 of these 3 variables were related to the rebleed rate (the efficacy variables included)
McMeekin et al[7]	United Kingdom	Oral vs IV antibiotics	CEA based on trial data	1 year	Inpatient stays by treatment	Approximately 1% of the total incremental direct costs (-£37 vs £2727)
McCrea et al[19]	United States	IV nivolumab vs oral everolimus	CEA	25 years	Different costs for progressed and progression-free health states	Approximately 1.5% of the per-patient total incremental direct costs
Ferko et al[24]	Canada	Risedronate and ibandronate (oral) vs IV zoledronate	CEA	1 year	Fracture costs differentiated by efficacy	The difference in total costs is mainly driven by costs due to efficacy difference (fracture costs)
Abushanab et al[27]	Qatar	Intravenous ibuprofen vs oral ibuprofen	Cost-calculator model	1 year	Probability of closure success	Significant difference in duration of overall course of treatment impacts costs
You et al[28]	China	IV zoledronic acid vs oral alendronate	CEA	Lifetime	Fracture costs differentiated by efficacy	Not reported

Notes: Two of the six studies that did not differentiate costs based on efficacy differences[9,20] supported their equal efficacy assumption based on similar efficacies observed in previous studies.

Abbreviations: CEA, cost-effectiveness analysis; CMA, cost-minimization analysis; HCRU, healthcare resource use; IV, intravenous.

vasculitis, but the incremental cost of treating serious adverse events because of an oral azathioprine was estimated to be approximately 30% of the total cost difference.

More than half (8/14) of the identified studies accounted for the effects of efficacy differences on treatment costs when estimating the costs of a formulation choice (Table 1). Among the studies that incorporated efficacy differences, some studies reported a sizable impact of such efficacy differences on the overall direct costs (Table 4). For instance, in a French study comparing IV rituximab with oral azathioprine in patients with antibody-associated vasculitis, 27% of the total costs were driven by efficacy differences.[8] Furthermore, in a US-based analysis investigating the cost-effectiveness of an oral versus IV proton pump inhibitor in patients with peptic ulcer hemorrhage,[21] two of the three model parameters that were reported to be drivers of the incremental cost-effectiveness ratios were the efficacy variables. Among the remaining studies (6/14) that did not account for efficacy differences, only four explicitly explained that they would be assuming the same efficacy between the comparators; two of these four studies indicated that the compared regimens were shown to have similar efficacy in previous studies.

Case Study – The Economic Impact of Introducing Oral Edaravone to Patients With ALS

In this case study, we illustrate a process of designing a cost-calculator model that estimates the costs of introducing an oral formulation of edaravone as a treatment for ALS over a 3-year time horizon. To estimate the differences in direct costs of treatment of ALS among patients receiving IV edaravone and oral edaravone, we first identified key resources required for the administrations and maintenance of IV edaravone. For IV administrations and maintenance (IV line replacement and removals), we accounted for the hours required for healthcare providers, patients, and their caregivers. Because the hours required for healthcare providers, patients, and their caregivers varied based on whether the IVs were administered at home or outpatient facilities, these resource requirements were separately identified. In addition, the resource requirements for IV removals and reinsertions vary by the methods of catheterization (a peripherally inserted central catheter [PICC] line, implantable port, or a peripheral line). Therefore, these resources were weighted by the distribution of patients who receive each type of IV treatment.

The base-case analysis focused on costs associated with US payers only. However, patients who are prescribed the IV formulation of edaravone devote a significant amount of time to receiving IV infusions. Therefore, the model allowed for an option to account for the direct costs associated with the change in administration only as well as an option to incorporate a broader societal perspective, accounting for indirect costs from the lost productivity of patients and their unpaid caregivers. Figure 2 depicts the overall structure of this model. All key model inputs and their sources are presented in Supplementary Table S-1. Because of the 3-year time horizon, all cost results were undiscounted. We assumed both formulations provide similar efficacy outcomes given the oral formulation's dose was selected to deliver a similar exposure to edaravone as the IV infusion (MTPA data on file, 2020). Additionally, only infusion-related safety events were differentiated between the formulations, as completed toxicology studies for the oral formulation demonstrated no new safety findings at the selected dose (MTPA data on file, 2020). The model accounted for indirect costs because of lost wages as a result of travel and appointment time for IV administrations and maintenance only.

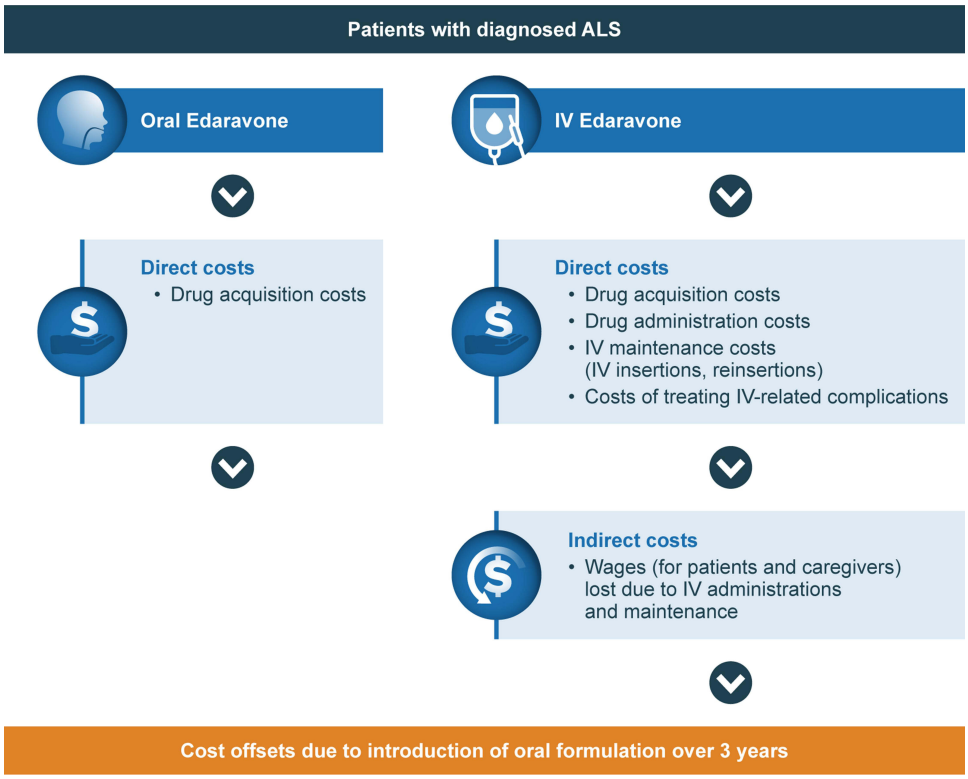

Figure 2 ALS case study model design.
Abbreviations: ALS, amyotrophic lateral sclerosis; IV, intravenous.

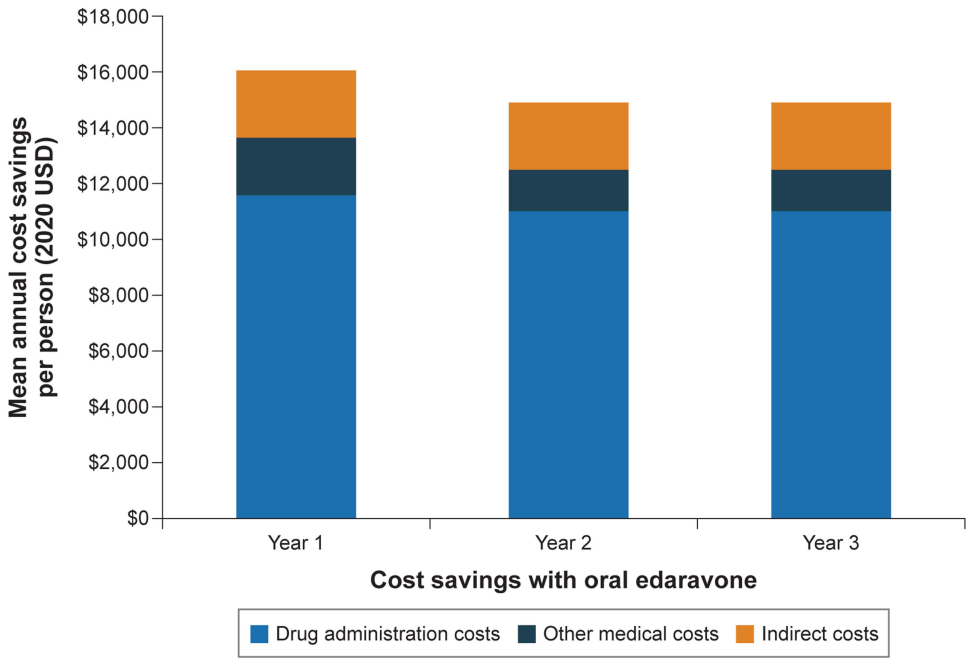

Figure 3 Mean average cost savings per person with oral edaravone.
Abbreviation: USD, United States dollars.

As presented in Figure 3, the cost-calculator model estimated oral edaravone would save each patient and his or her caregivers approximately $13,700 in direct costs in year 1. Including indirect costs, the cost savings in year 1 were approximately $16,000. The number of IV administrations (approximately 134, 130, and 130 infusions in years 1, 2, and 3) drove the economic burden of administrations in office and hospital settings. Although the cost of each insertion was lower with peripheral line compared with PICC line and implantable port, the number of reinsertions each year (approximately 27 in year 1 and 26 each year in years 2 and 3) drove the costs of peripheral-line maintenance. In addition to administration and insertion/removal, IV-related adverse events also had a small contribution to the total cost of selecting the IV formulation compared with switching to the oral formulation.

Discussion

In our review of studies that quantified the economic impact of introducing an oral formulation drug as an alternative regimen to an IV formulation, we confirmed that all 14 studies we identified accounted for the costs of providers' time to administer IV medications. Most studies used a simple model structure with a time horizon of 1 year or less, estimating the high-level economic impact of choosing a different formulation. Most studies we reviewed (11 of 14) accounted for costs that may stem from differences in safety or efficacy profiles associated with changes in formulations. However, when studies did not account for these differences, few (1 of 8 that omitted safety considerations, 2 of 6 that omitted efficacy considerations) explained the reasons why the study assumed similar efficacy or safety outcomes between treatments. In studies that incorporated efficacy and/or safety differences between treatments, these differences often contributed to the economic impact of selecting a certain formulation over another. Therefore, to ensure economic models to be reliable sources for a variety of stakeholders to estimate the value of a new formulation, a transparent explanation on the rationale for key assumptions on efficacy and safety between treatments is critical.

There was heterogeneity across studies in terms of how and whether researchers accounted for costs of IV insertions and removals. This may be due to differences in the way these resources are reimbursed in different countries. For future studies, we recommend researchers ensure that their analyses account for all resources used for drug administrations and maintenance paid by key stakeholders relevant to the selected perspective of the analyses and include a rationale for excluding costs from the analysis when this occurs.

Only 3 of the 14 studies we reviewed accounted for how a formulation choice may affect the indirect costs of treatment. In these published models and in our case study, although the total indirect costs were relatively small compared with the direct costs, the estimated impact of a formulation selection on patients and their caregivers' ability to work was sizable. For instance, our case study estimated that over 600 hours would be lost for patients and their family members due to IV administration and maintenance per year. Two studies also highlighted the potential barrier to nonoral treatments due to the cost of traveling.[9,22] Therefore, although these outcomes are typically not required for inclusion in analyses reviewed by third-party payers, given how these factors are important determinants of quality of life among patients and their family members, payers may be interested in reviewing a co-analysis that accounts for these societal outcomes and costs to make coverage decisions based on patient-centered outcomes goals.

Furthermore, the three identified studies that incorporated indirect costs did not differentiate the estimates for lost wages by patients' demographics. In the case study, it was critical for the model to reflect the expected earnings among people in the typical age group of patients with ALS because ALS often affects older patients who typically have higher earning potentials but may be nearing the age to retire from the workforce. Researchers who are developing a model that incorporates indirect costs should consider how the treatment may impact the earning potentials of the population with the typical demographic characteristics associated with the condition of their interest.

There are several limitations to this study. First, our literature review was targeted to understand the designs used to quantify the economic impact of using an oral formulation compared with a different formulation. However, our review of the literature was structured with a search strategy that has been documented and is fairly reproducible. Second, we reviewed only English-language articles; despite this limitation, we identified 14 studies from 10 different countries. Readers who are interested in understanding how to conduct an economic analysis of switching from an IV to an oral formulation in a non-English speaking country may want to conduct further analysis including articles written in that country's native language. Finally, although we focused on reviewing approaches used for estimating the economic impact of formulation choice, there are many other factors beyond cost that are important to patients when they are choosing between different formulations. For instance, factors such as patients' preference, distance to healthcare providers, level of independence, and disease severity may have a strong impact on how patients value certain formulations over others. Although this is outside the scope of the current study, further research on the value of new formulations is warranted.

Key limitations of the modeled case study analyses pertain primarily to assumptions required because of a lack of data. Specifically, there may be potential indirect costs associated with IV administrations other than lost earnings from IV administrations and maintenance, such as lost earnings from time required to manage IV-related adverse events, interrupted educational pursuits for provider visits, or costs for making different living arrangements to care for family members. Further, published data on the frequency of edaravone IV reinsertions is limited. The assumptions made to estimate IV maintenance costs may need to be updated as new data become available. Additionally, the current evidence on hours lost because of IV administration and maintenance in this population is limited. Finally, researchers should be careful not to use the cost-minimization approach unless there is a strong clinical foundation that justifies an assumption of equal efficacy across treatment.

Conclusion

We examined published studies to compare methods for assessing the economic value of additional formulation options from a variety of perspectives. We found significant variations in the impact of an additional formulation option on treatment efficacy, safety, and ease of use by patients, depending on the treatments of comparison across all analyses. Models need to be accompanied by clear descriptions of the rationales for the model time horizon and assumptions on how different formulations may affect healthcare costs according to selected perspectives in the model. Additionally, while the economic consequence of the societal burden due to selecting a certain formulation may not be sizable, we found it is important to consider and report the societal burden such as time spent by patients and caregivers. A standardized approach to formulation comparisons may help improve such comparisons in the future.

Abbreviations

5-FU, 5-fluorouracil; AE, adverse event; ALS, amyotrophic lateral sclerosis; BIA, budget-impact analysis; CEA, cost-effectiveness analysis; CMA, cost-minimization analysis; FDA, Food and Drug Administration; GI, gastrointestinal; HCRU, healthcare resource use; ICER, incremental cost-effectiveness ratio; IM, intramuscular; IV, intravenous; LV, leucovorin; MRSA, methicillin-resistant staphylococcus aureus; ND-CKD, non-dialysis chronic kidney disease; NHS, National Health Service; PICC, peripherally inserted central catheter; PPI, proton pump inhibitor; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SC, subcutaneous; US, United States; UK, United Kingdom.

Data Sharing Statement

Only published data were used in this study; all references reviewed are presented in Table 1. All sources for model inputs are reported in Supplementary Table S-1.

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Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

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Disclosure

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