

Use of disease analogues to inform health-economic parameters for economic evaluations of rare diseases: a case-study of multiple system atrophy

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Background

- Multiple system atrophy (MSA) is a rare, neurodegenerative disease, with adult onset, characterised by varying combinations of parkinsonian features, autonomic failure, cerebellar syndrome, and pyramidal signs.¹
- Disease progression is rapid, with loss of independent ambulation or intelligible speech happening within 5–6 years and death within 7–10 years of diagnosis.¹
- There are cerebellar (MSA-C) and Parkinson subtypes (MSA-P) which are heterogeneous in nature with diverse symptomatology but ultimately similar loss of function.¹
- In the context of a rare disease, it has been suggested that one way to overcome the scarcity of input parameters in economic evaluations is to explore disease analogues for surrogate data that could potentially be used in cost-effectiveness analysis.^{2, 3} In this case, disease analogues are defined as those who display overlapping disease characteristics with a particular rare disease but have higher prevalence.^{2, 3}

Multiple sclerosis as a potential disease analogue

- Overall, 42 economic evaluations in multiple sclerosis were analysed as a potential source input for modelling in MSA.
- Most modelling in multiple sclerosis was performed using Markov models (n=34) based on the Expanded Disability Status Scale (EDSS) to define health states. A proportion of these models further accounted for on- and off- treatment periods or for disease progression (e.g., remitting/relapsing or secondary progressive multiple sclerosis with and without EDSS scores).
- Of the 42 multiple sclerosis studies reviewed, most were not transferable for MSA modelling as they were stratified by disease-specific health states.
- However, learnings that could be carried over to MSA included the assessment of potential double counting if utility questionnaires are overlapping or if event driven disutility increments are reported together with utilities for health states (e.g. if multiple sclerosis utilities were regressed according EDSS).

Advanced Parkinson's disease as a potential disease analogue

- Overall, only 3 economic evaluations in advanced Parkinson's disease were identified as a potential source input for modelling in MSA.
- This raised suspicion that the 5-year search limit for disease analogues was too limited and indeed a review of publication patterns for indicated a publication peak between 2010 and 2017.⁴
- All three publications used Hoehn and Yahr staging, which is a measure of clinical disease progression, together with ON- and OFF- states to reflect periods of controlled and not controlled motor symptoms, respectively.
- Only one reference was considered as potentially informative for MSA (Table 2).

Amyotrophic lateral sclerosis and spinal cord injury as potential disease analogues

Moreover, exploring economic evaluations for disease analogues may provide important information on decision-analytic model structures, which could help inform a model structure for MSA. To our knowledge, no economic evaluation exists for MSA.

Objective

To determine the usefulness of exploring disease analogues to inform input parameters for an economic evaluation of MSA.

Methods

- Similarly, for costs, including aggregated costs across health states and event driven costs could result in double-counting if not cautiously reported.
- It was found useful to consider analyses with referenced and thorough micro-costing approaches or reporting of clinical events. For example, the cost or disutility of urinary disorders, falling, depression, cardiovascular disorders or walking aids, all of which are relevant events for MSA.
- Overall, 11 references were considered as potentially informative for MSA (Table 1).

Table 1. Multiple sclerosis studies with potential source inputs for MSA

- Two economic evaluations of amyotrophic lateral sclerosis models were reviewed. Both used Markov modelling – the first based on hospitalisation and invasive and non-invasive ventilation and the second based on a functional rating scale. Neither were considered informative for MSA.
- The only spinal cord injury model reviewed used an unclear model structure and was not considered informative for MSA.

	Article	Model type	Utilities	Costs
Clinical experts with extensive experience in managing patients with MSA and other neurological conditions were consulted to identify potential disease analogues for MSA.	Hunter et al., 2021⁵	Markov model with exacerbation/ relapse & remission/ response states.	Utilities sourced from literature by remission/ response, mild-moderate severe and severe relapse.	 Administration costs: central catheter, tubing set and supplies, lab test, plasma exchange, service contract, professional costs, facility costs. Adverse events: asthenia, urinary tract infection, bleeding, catheter occlusion, deep vein thrombosis, infection, fever, increased creatinine, liver
Candidates included: amyotrophic lateral sclerosis, multiple sclerosis, and loss of ambulation through e.g., late-stage Parkinson's disease or spinal cord injury				 tests, stroke. Direct medical costs: ambulatory care, inpatient, physician visit, home health services. Direct non-medical community service, alterations, meals, travels.
Literature searches in MEDI INE and EMBASE together with				 Indirect costs: Absenteeism, presenteeism, disability, informal care, family loss of earnings.
hand searches were conducted for economic evaluations of these disease analogues.	Acosta et al., 2021 ⁶	Markov Model - with responder and non-responder health states	Utilites from trial data as responder analysis (Enhance study). Also, tested data from mobile study.	 Includes costs for urinary tract infection. Other adverse event costs included for falls, back pain, headache, nasopharyngitis, upper respiratory tract infection, cardiovascular disorder,
Articles that contained only aggregated costs and utilities regressed		Markay Madal EDSS with an and	Litility (Opera triale) and digutility data from	and rash. However, most costs were set at the price of GP visit.
	2021 ⁷	off-treatment cycles	Orme et al. ⁸	 Other adverse event costs included for headache, nasopharyngitis, and depression.
Results	Martins et	Markov model with EDSS states	Utility and disutilities by EDSS scores.	 Drug and adverse event costs for urinary tract infection. Other costs included for least administration adverse events, depression.
terature search results		further by relapsing remitting MS and secondary progressive MS.		 Other costs included for local administration adverse events, depression, and respiratory infection. Otherwise, direct costs were by EDSS states
The searches yielded 547 papers, of which 211 hits were uplicates, leaving 335 papers for screening (Figure 1).	Michels et al., 2019 ¹⁰	Markov model with EDSS states, relapse/remitting MS and secondary progressive MS and death	 Utilities across EDSS and caregiver disutilities across EDSS. Disutilities for adverse events, including infusion/injection site reaction, infection, macular oedema, gastroentestinal, hypersensitivity, autoimmune thyroid- related event, influenza-like symptoms, and malignancy 	 Costs by EDSS Direct medical costs, direct non-medical and indirect non-medical costs. Drug costs.
gure 1. Modified PRISMA diagram Identification of studies via databases and registers				
Records identified from: Medline (n = 871) Embase (n = 1455) NHS EED database (n = 0) Records removed before screening: Duplicate records removed (n = 211) Limit to within 5 years (n=1556) Limit to journal articles (n = 223)	Pinheiro et al., 2020 ¹¹	Markov model with EDSS states, remitting MS with disease modifying therapy, remitting MS without disease modifying therapy and secondary progressive MS without disease modifying therapy, and all-cause death	 Utilities by EDSS states. Disutilities for caregivers. Probability of events across two treatment and includes both disutility and costs: serious infection, macular oedema, gastrointestinal disorder, thyroid related event, influenza-like symptoms and malignancy. 	Annual costs stratified by EDSS.
Reports assessed for eligibility (n = 335) Studies included in review (n = 48)	Poveda et al., 2020 ¹²	Markov model with EDSS states stratified by treatment / not treatment or from remitting MS to secondary progressive MS.	 Utilities by EDSS states. Disutilities for caregivers. Probability and disutility for events: serious infections, macular oedema and cancer. 	 Costs based on EDSS. Adverse events: progressive multifocal leukoencephalopathy, serious infections, macular oedema and cancer. Drug costs, administration and monitoring. Other costs included hospital visits, administration, blood count, MRI, consultations.
 Multiple sclerosis (n = 42) Advanced Parkinson's disease (n = 3) Amyotrophic lateral sclerosis (n=2) Spinal cord injury (n=1) 	Stanisic et al., 2019 ¹³	Markov model with EDSS states across RRMS and SPMS, and death. Model was developed by ScHARR	 Utilities by EDSS and for relapse. Included disutility for side effects associated with treatment, varies with treatment. 	 Costs by EDSS. Included a cost for side effects associated with treatment
	Taheri et al., 2019 ¹⁴	Markov models with EDSS states across RRMS (on - off treatment), SPMS, and death	 Utilities by EDSS. Disutility associated with relapse, thyroid dysfunction. Caregiver disutility. 	 Costs by EDSS (nursing, absenteeism). Neurologist visits, psychotherapy, physiotherapy, medicines, hospitalisations, car and house modifications. Adverse events e.g., relapse, PML, thyroid disorder.
CONCLUSION	Walter et al., 2019 ¹⁵	Markov model with 10 EDSS, 4 treatments, relapse,	Utilities by EDSS	 Costs by EDSS Comparator, outpatient costs, monitoring,
Evaluation of potential disease-analogues provided insights		treatment, adverse evets and death.		Adverse event costs.
surrogate data extraction for multiple system atrophy.	Zhao et al., 2022 ¹⁶	Markov model with states: responder, non-responder, best	Utilities for responders and non-responders.	 Costs: drugs, neurologist visits, rehabilitation, outpatient visits, hospitalisations, Adverse events: urinary tract infection, fall and back pain
Potentially useful insights included the broad use of		supportive care and death.		 Walking aids Lost productivity patients and caregivers.

- functional rating scales in health-economic modelling.
- Costs and utilities for disease milestones that have commonality with MSA (e.g., urinary tract disorders, gastrointestinal disorders, caregiver burden and house or car modifications) were identified.



Table 2. Advanced Parkinson's disease studies with potential source inputs for MSA

Kalabina et al., 2018 ¹⁷	Markov model with Hoehn and Yahr states and OFF-states*	 Utilities by regression analysis stratified by Hoehn and Yahr (ON and OFF states). Caregiver disutilities. 	 Regression analysis for health states costs. Service and medication costs e.g., tube insertion, titration, PEG tube removal, follow-ups and tube with or without surgery.
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*OFF states defined as uncontrolled motor symptoms that are non-responsive to treatment

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