

# The Economic Burden of Moderate-to-Severe Multiple Sclerosis Relapse in the United States: Findings From a Systematic Literature Review

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## BACKGROUND

- Multiple sclerosis (MS) is an unpredictable, often disabling disease of the central nervous system that disrupts information flow within the brain, and between the brain and body. The progress, severity and specific symptoms in an individual cannot be predicted.<sup>1</sup>
- Relapses, the clinical hallmark of MS, may also vary by type, severity, and duration and can take a toll on health, daily functioning and quality of life.<sup>2,10</sup> Given MS relapse also impacts family, friends, and caregivers, the societal, economic, familial, and personal burden is enormous.<sup>10</sup>
- Documentation exists on the direct and indirect costs of MS in the United States (US).<sup>3,4</sup> Direct costs are associated with healthcare resource use; indirect costs are incurred from cessation or reduction of work productivity as a result of a disease. Few studies have assessed the associated cost of relapse by severity.
- Low-severity MS relapse is less likely than moderate or severe relapse to be detected, reported and treated.<sup>2</sup> Impact and cost associated can also be expected to vary. Moderate-to-severe relapse, for example, may be more likely to incur use of therapy such as repository corticotropin injection (also known as H.P. Acthar Gel) or plasmapheresis.<sup>5</sup> Similarly, inpatient or emergency department (ED) care may be more prevalent versus outpatient or home care.
- Evaluating MS relapse burden without differentiating by severity may result in diluted understanding of the effects of relapse, including underestimation of impact and cost.

## OBJECTIVE

- To assess whether current literature comprehensively and specifically addresses the economic burden associated with moderate and severe relapse in the US

## METHODS

- A systematic literature review (SLR) of the economic burden of moderate-to-severe MS relapse in the US was conducted. Where relapse severity was unspecified and relapse treatment (i.e., services/prescriptions) was not required, studies were excluded.
- Searches of English-language publications were conducted in MEDLINE, Embase, the Cochrane Library, Econ Lit, and BIOSIS, according to a pre-specified search strategy and protocol. Only full-text publications were considered.
- To manage the large number of studies anticipated, searches for studies of indirect costs (i.e., patient lost productivity and caregiver burden) were limited to those published after 1/1/2010. Because few robust studies on direct costs of MS relapse were anticipated, no date limit was placed on cost and resource-use studies.
- Bibliographic lists of recent relevant SLRs were searched for further studies of interest.
- At level 1 screening, each study title/abstract identified was reviewed by one researcher for eligibility. A second researcher performed a quality check on 10% of these titles/abstracts; any discrepancies were resolved by consensus. At level 2 screening, full-text articles were reviewed following the same process.
- From the studies identified for inclusion, standardized evidence tables presenting the relevant data on the study design and resulting evidence were prepared.
- A qualitative synthesis of data was conducted. Costs were inflated to mid-2016 US dollars<sup>6</sup> based on the original costs provided by the authors.

## RESULTS

- Of 4,263 search results, 24 studies were identified that included estimates of the economic burden related to MS relapse. (The full reference list is available on request.)
- Of the 24 studies, there were 16 database studies, 1 multiple-source cost study, 3 surveys, and 4 clinical trials. After excluding studies where severity was unspecified, 4 studies remained (2 database studies, 1 multiple-source cost modeling study, and 1 survey). (Figure 1)
- Table 1 presents details of the 4 studies with severity data.

### Health Care Direct Costs and Resource Use

#### Total Direct Costs

- Table 2 presents total costs for different severities reported by Parisé et al.<sup>7</sup> and O'Brien et al.<sup>8</sup>

#### Direct Cost Components

- Figure 2 presents the distribution of direct cost components reported by Parisé et al.<sup>7</sup> and O'Brien et al.<sup>8</sup>

#### Resource Use

- Table 3 presents hospital resource use and hospital readmissions used by O'Brien et al.<sup>8</sup> in their cost modeling and estimated by Probasco et al.<sup>9</sup>

### Productivity Loss and Indirect Costs

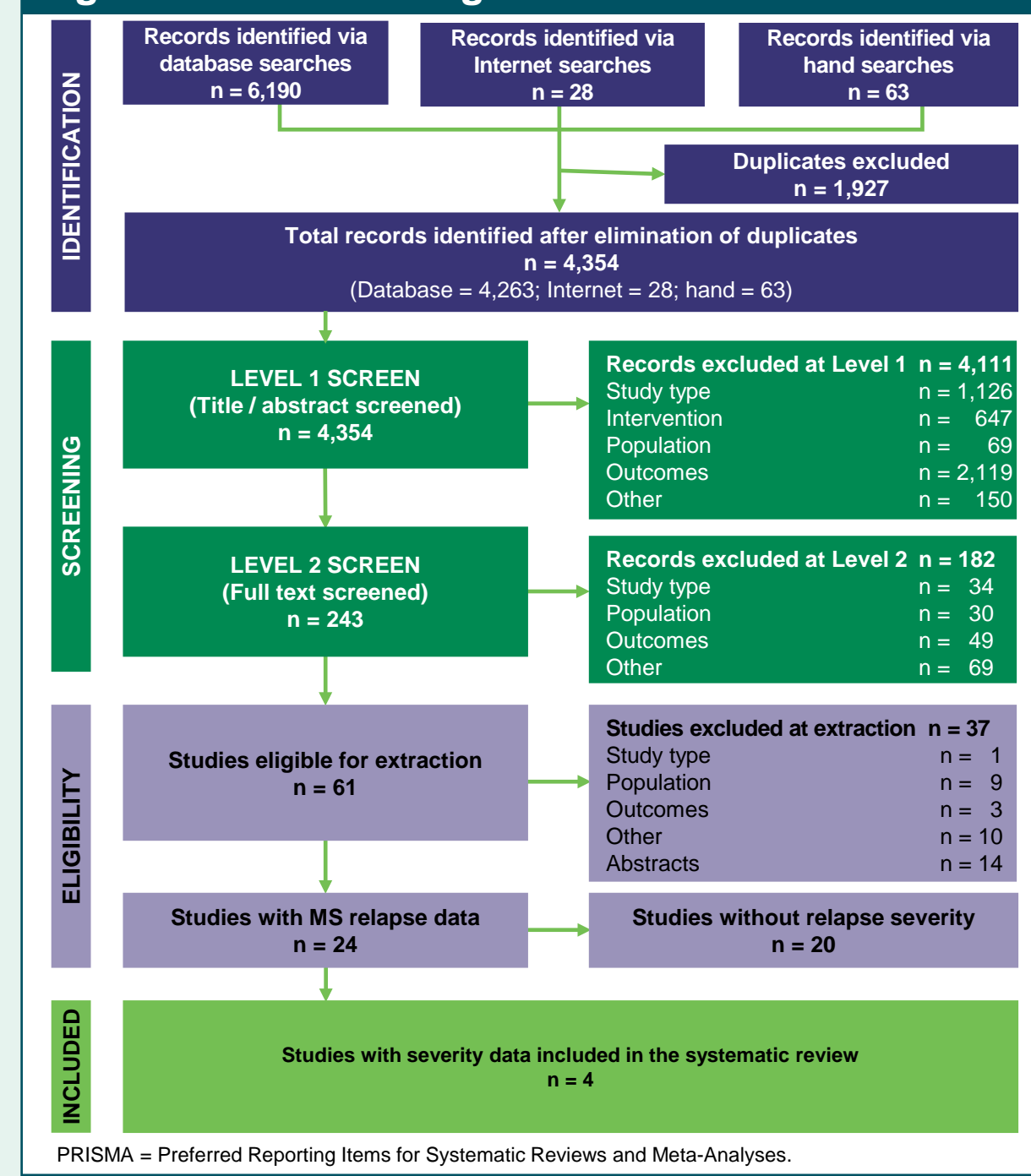
- In addition to providing estimates of direct costs, Parisé et al.<sup>7</sup> estimated indirect costs by MS-relapse severity. Nickerson et al.<sup>10</sup> conducted a survey of MS relapse patients and reported missed work or school due to relapse, which was perceived by most patients to be of moderate severity.
- No study was identified that reported caregiver burden by frequency of relapse. The per-caregiver per-year costs associated with more frequent relapses were higher compared with the costs for less frequent relapses.
- Parisé et al.<sup>7</sup> estimated indirect cost burden over 12 months for a subset of MS patients with disability coverage from a claims database. These costs were estimated from an employer's perspective; other costs, such as those associated with productivity loss and early retirement, were not included. For the 322 low/moderate severity relapse MS patients, the indirect cost due to disability were \$1,992 per patient per year. For the 84 MS patients with high-severity relapse, the indirect cost due to medically-related absenteeism was \$2,565 per patient per year.
- From the cross-sectional survey of MS patients who described their most recent relapse, Nickerson et al.<sup>10</sup> found 55% of patients reported missing work or school. Of those who missed work or school, missed days from work or school ranged from a half day to 90 days, with a mean of nearly 13 days. Most patients (n = 229) reported that their most recent relapse was of a "moderate" severity. Estimates of missed work or school days were not presented by relapse severity.

**Table 1. Characteristics of Included Studies**

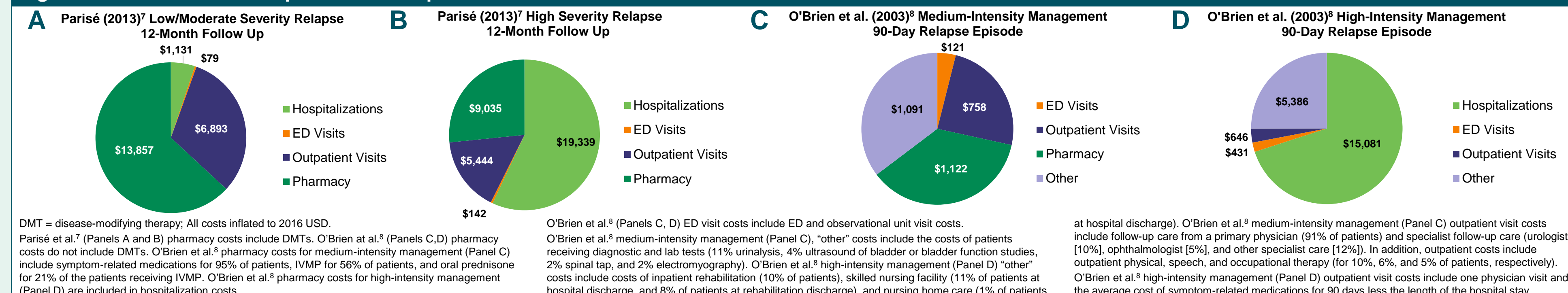
	Parisé et al. <sup>7</sup> (2013)	O'Brien et al. <sup>8</sup> (2003)	Probasco et al. <sup>9</sup> (2015)	Nickerson et al. <sup>10</sup> (2015)
<b>Relevant outcomes reported</b>	Direct and indirect costs	Direct costs and resource use	Resource use among hospitalized patients	Missed work or school
<b>Study design</b>	Retrospective analysis	Cost modeling	Prospective intervention (admission order set and checklists) cohort was compared with a retrospective, preintervention cohort	Cross-sectional survey
<b>Data source</b>	Health care claims database	Multiple data sources including various US state administrative databases, fee schedules, government reports, published literature	Electronic administrative databases and electronic medical records from the acute care units at the Johns Hopkins Hospital	Patients participating in the NARCOMS registry
<b>Definition of relapse severity</b>	High severity: hospitalization at index with principal diagnosis of MS Low/moderate severity: outpatient/ED claim at index with a listed diagnosis of MS followed by a pharmacy or medical claim for a corticosteroid within 7 days of visit	High-intensity management: hospitalization Medium-intensity management: no hospitalization; ED or observational unit visit, or relapse requiring formal intervention (e.g., IVMP) provided in home or outpatient setting	APR-DRG severity of illness level (clinical scale used for inpatient hospitalizations)	Self-reported severity (mild, moderate, or severe)
<b>Time period for cost evaluation</b>	12 months and 36 months (latter not reported here)	90-day relapse period	Pre-intervention: 6 months Post-intervention: 7 months	No requirement

APR-DRG = All Patient Refined Diagnosis Related Groups; IVMP = intravenous V methylprednisolone; NARCOMS = North American Research Committee on Multiple Sclerosis.

**Figure 1. PRISMA Diagram**



**Figure 2. Distribution of Relapse Costs Components**



## DISCUSSION

- Across the four studies, differences in outcomes definitions, study designs, data sources, patient populations, definitions of relapse severity, and durations of follow-up make it difficult to compare the studies and synthesize findings.
- Differences of note include the following:
  - Diverse perspectives and outcomes definitions: direct costs in 2 studies,<sup>7,8</sup> resource use in 2 studies,<sup>8,9</sup> productivity loss in 2 studies (Parisé et al.<sup>7</sup> from an employer perspective, Nickerson et al.<sup>10</sup> from a patient perspective)
  - Distinct study designs and data sources: retrospective claims data analysis,<sup>7</sup> multiple-source cost modeling,<sup>8</sup> hospitalization records,<sup>9</sup> and survey data<sup>10</sup>
  - Distinct criteria for defining relapse severity: based on hospitalization at index,<sup>7</sup> hospitalization during follow-up,<sup>8</sup> use of clinical criteria within inpatient hospitalizations,<sup>9</sup> and patient self-report<sup>10</sup>
  - Distinct reporting timeframes: 12- and 36-month (latter not reported here) per-person per-year costs,<sup>7</sup> 90-day resource use and costs,<sup>8</sup> hospitalization-related resource use within past 6 months pre-intervention and within 7 months of follow-up post-intervention,<sup>9</sup> and missed work or school associated with the last relapse (no time period specified)<sup>10</sup>
- Nine of the originally identified 16 database analyses, including Parisé et al.,<sup>7</sup> examining the economic burden of MS relapse identified patients with MS relapse used a claims-based algorithm developed by Ollendorf et al.,<sup>11</sup> with positive predictive value of 67.3%.<sup>12</sup> The algorithm does not address patient functioning and disability, nor relapse duration.
- As illustrated in Figure 2, there appears to be no standardized method for assessing economic burden of a relapse (overall, or by severity), which would facilitate comparison of cost estimates across studies.

## CONCLUSIONS

- The majority of studies on the economic burden of MS relapse do not address nor differentiate severity. The few studies that differentiate by severity indicate the cost and impact of relapse increases with severity level. These study results cannot be further integrated towards a more comprehensive understanding due to inherent differences, complicating synthesis and interpretation of data.
- Effects of MS-relapse severity on patient functioning and disability, caregiver burden, and relapse duration are difficult to measure, incorporate, and translate into overall burden; therefore, despite being a well-established area of focus, an unmet need still exists and the impact of moderate-to-severe relapse remains underappreciated.
- Implications for relapse awareness, characterization and management, including careful consideration of all available treatment options, should be considered.

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## DISCLOSURE

- Funding for this study was provided by Mallinckrodt Pharmaceuticals.