# TREATMENT EXPERIENCE, BURDEN, AND UNMET NEEDS (TRIBUNE) IN MULTIPLE SCLEROSIS STUDY: THE COSTS AND UTILITIES OF MS PATIENTS IN CANADA

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## ABSTRACT

### Background
Multiple sclerosis (MS) is the most common neurological disease among young adults in Canada, but few studies to date have measured the burden imposed by MS on Canadian society.

### Objectives
To estimate the costs and quality of life of MS patients in Canada, while focusing on the burden of relapses and increasing disease severity.

### Methods
MS patients in Canada (N=241) completed a web-based questionnaire which captured information on demographics, disease characteristics, severity (Expanded Disability Status Scale [EDSS]), comorbidities, relapses, as well as resource consumption and quality of life associated with MS.

### Results
Most patients (74%) reported treatment with disease modifying therapies (DMTs). 54% of patients with the relapsing-remitting form of the disease with an EDSS score ≤ 5 had experienced at least one relapse in the past year. The mean cost per patient per year increased with worsening disability, and was estimated at Can $30,836 for patients with mild disability (EDSS score 0-3), Can $46,622 for patients with moderate disability (EDSS 4-6.5), and Can $77,981 for patients with severe disability due to MS (EDSS score 7-9). The excess costs of relapsing-remitting MS patients with EDSS score ≤ 5 that could be attributable to relapse(s) were estimated at Can $10,512. More severe disease and experiencing a relapse were also associated with poorer quality of life of MS patients.

### Conclusions
Costs of MS patients are higher today than shown in previous studies. Disease progression and relapses are associated with increased economic and quality of life burden. Effective treatment that reduces relapse frequency and prevents progression could impact both costs and quality of life and may help to reduce the societal burden of MS.

**Key Words:** *Multiple sclerosis, MS, costs, cost-of-illness, utilities, quality of life, QoL, Canada*

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Multiple sclerosis (MS) is the most common neurological disease among young adults in Canada,[1] and Canada's prevalence rate is one of the highest in the world.[2] An estimated 55,000 to 75,000 people in Canada are currently affected by the disease.[2] MS is more common in women than in men[3] and affects working-age individuals: the age of onset is usually between the ages of 20 and

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50, with a peak around 30. The course of MS is characterized as relapsing-remitting or progressive. Patients with relapsing-remitting MS, the most common type, have periods of symptom remission interrupted by exacerbations. In progressive MS, symptoms and disability steadily worsen with or without exacerbations.[3]

The socioeconomic costs of MS are high for patients, their families, health care systems and society as a whole. The health-related quality of life of patients with MS deteriorates during relapses and as the disease progresses.[4,5] In addition, advancing disease severity and relapses are associated with further increases in indirect costs and informal care costs, which are among the most expensive components of MS-related costs.[5, 6] The Public Health Agency of Canada estimated that the total costs associated with MS were Can $950.5 million in 2000-2001;[7] but, few studies to date have measured the burden imposed by MS on Canadian society.[6-8]

Disease-modifying therapies (DMTs) for MS reduce the frequency of relapses and may slow disease progression. By helping patients with MS reduce the frequency and severity of relapses and stay at a lower disability level for a longer period of time[9], use of DMTs may reduce the burden the disease imposes on society.

The *Treatment Experience, Burden, and Unmet Needs* **(**TRIBUNE) study is an important addition to the currently outdated burden of illness literature for MS in Canada and presents recent local cost and utility data which can be considered in the economic evaluations of DMTs in MS.

The aims of the TRIBUNE study were to measure the burden MS imposes on Canadian society and to contribute detailed cost and health utilities information to the existing literature. In addition, because treatments target progression and prevent relapses, we focused on disease severity and relapses as key contributors to the burden of MS.

## MATERIALS AND METHODS

### Study Design

The TRIBUNE study was a multinational, cross-sectional, retrospective, observational burden-of-illness survey. Data were collected from MS patients in six countries: Canada, France, Germany, Italy, Spain and the United Kingdom. Results for Canada are presented in this paper.

Patients were recruited from six major treatment centres (hospitals with outpatient neurological clinics) in Canada. Patients were required to be diagnosed with MS (ICD-10; G35, ICD-9; 340) and only adult patients were included. Patients with a physical or mental illness leading to inadequate participation in the study and patients currently enrolled in a clinical trial were excluded.

Site staff identified eligible patients by screening patient records, and an invitation to participate in the study was sent to patients who met the inclusion criteria. Only patients who provided their consent to participate in the study were included in the final sample. The study protocol and the questionnaire received ethics committee approval prior to the initiation of the study.

### Assessments

Patients self-completed a questionnaire in English or in French using a web-based electronic data capturing system. They were asked to provide information on their age, sex, living arrangements, educational level, employment status, and to indicate who their informal caregiver(s) was.

Disease information including year of diagnosis, year of first symptoms, type of MS, disease severity (disability), comorbidities, and treatment with DMTs was captured. For the type of MS, short descriptions of relapsing-remitting MS, secondary progressive MS, and primary progressive MS were provided for the patient to select from. Disability was captured using the self-administered Expanded Disability Status Scale (EDSS).[10] EDSS scores range from 0 through 9, with lower scores associated with less disability/disease severity.

Patients were asked to report information related to relapses they had experienced during the past 12 months, including whether or not they had a relapse, number of relapses, number of relapses which required steroid treatment, and the number of days of inpatient care they received due to relapses.

Data on healthcare (inpatient and outpatient care, investigations/tests, consultations with medical practitioners, treatment with DMTs,

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prescribed and over-the-counter medication) and non-medical (investments, professional and informal care) resource consumption, as well as patients' productivity losses (sick leave and retirement due to the disease), was collected using the questionnaire. Different recall periods were used for different resources. Inpatient stays, investigations/tests and investments (e.g., wheelchairs, scooters, or modifications to the house and car) were recorded for the past year. A recall period of 3 months was used for outpatient admissions, consultations with hospital-based or private physicians, use of DMTs, services such as home care and nurses, informal care from family and friends, and absences from work due to sickness. Patients were asked to report use of co-medication and over-the-counter medication during the past month. The health utility of each patient was assessed with the EuroQol 5D (EQ-5D) instrument.[11]

## Costs and Utilities

To obtain the cost per patient per year, the resources used were first annualized assuming that the use during the recall period for each resource was representative of the patients' use over a full year. The annual use of each resource was multiplied by its respective unit cost to get the annual cost.

Unit costs were derived from public sources for Canada. Unit costs from 2008 and earlier were inflated to 2009 prices using the harmonized price indices reported by the Bank of Canada.[12] The per diem inpatient (Can $911) and outpatient (Can $338) costs for hospitals were based on the tariffs reported by the Ontario Case Costing Initiative,[13] while the cost per day for inpatient stays (Can $1,568) and outpatient visits (Can $29) in rehabilitation centres were derived from sources reported by the Ontario Schedule of Benefits for Physician Services.[14] The cost per day or visit for a nursing home was set at Can $23.[14] Consultation cost was determined per visit (ranging from Can $42 for a visit to a general practitioner to Can $130 for a visit to a psychologist), and investigation/test cost was obtained per procedure (Can $73 per magnetic resonance imaging (MRI) investigation, Can $72 for computed tomography (CT) scan, and Can $75 for one spinal tap test).[14]

MS treatments were assumed to be self-injected, apart from natalizumab, for which a visit to the treatment centre was needed. However, the cost of the visit was not added to the cost of the medication, since in Canada it is fully covered by the company which distributes the drug. The costs per month for DMTs were calculated based on prices per package or dose obtained through the price list of pharmaceuticals available for the province of Quebec,[15] because the price list for Ontario did not include all treatments. DMT prices were: Can $1,350 for intramuscular interferon beta-1a, Can $1,490 for interferon beta-1b, Can $1,296 for glatiramer acetate, Can $1,380 for subcutaneous interferon beta-1a (22 µg), Can $1,680 for subcutaneous interferon beta-1a (44 µg), and Can $2,388 for natalizumab.

The cost of co-medication was estimated based on the recommended daily dose, the price across pack sizes, and the dosage strength. Prices per package were obtained through the Ontario Drug Benefit Formulary.[16] The cost for over-the-counter medication was based directly on patients' reports. The cost per hour for receiving professional assistance from a nurse (Can $26) was obtained through a private provider of home nursing care to Community Care Access Centre in Toronto, Canada.[17] The per hour cost for home or professional help was Can $53.[18] For investments/modifications required due to the disease, the cost per investment was obtained through a private provider (range Can $132-10,257).[19]

The cost of sick leave was calculated by multiplying the patient-reported hours lost from work due to MS by the average gross salary per hour (Can $23).[20] To estimate the productivity losses of early retirement due to MS, the mean annual number of hours worked in 2008 (no 2009 data were available when the analysis was performed) across countries participating in the Organisation for Economic Co-operation and Development (OECD)[21] were multiplied by the gross salary. To allow for comparisons across the countries involved in TRIBUNE, the mean working hours across OECD countries was considered a more relevant estimate than the available per country observations due to differences in the methods used in various countries to obtain the mean working hours (e.g. questionnaires vs. official statistics).

Informal care was valued using the productivity losses of the working caregiver,

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multiplied by the average gross salary.[20] In order to count only the hours leading to the productivity losses of the informal caregiver, the average working hours per week were considered (estimation based on the mean working hours per year) since this information was not captured by the questionnaire. This is a conservative assumption that does not take into account the leisure time lost by the working or non-working caregivers. Therefore, calculations based on alternative methods are provided in this paper as well: hours spent for informal care valued equally for working or non-working caregivers, using the net disposable income for Canada in 2009 (Can $33,170 per year)[22] or productivity losses of the working informal caregiver, valued using the gross salary per hour plus leisure time lost from the working or non-working caregiver values using the net disposable income. The total costs collected in this study were calculated from a societal perspective; all direct and indirect costs incurred by patients and their caregivers were included in the cost calculations.

The excess cost attributable to relapses was calculated as the difference in the mean annual cost (excluding the cost of MS treatments, modifications/investments, and retirement) between patients with the relapsing-remitting form of the disease and EDSS score $\leq 5$ who experienced relapse(s) and those who did not. This method is consistent with earlier burden of illness studies in the US and Europe.[23,24] The cut-off of EDSS $\leq 5$ was considered to be the most medically relevant for the existence of a relapse among patients with relapsing-remitting MS, since most patients beyond this EDSS level have disability progression without experiencing disease exacerbations. The average cost per relapse was estimated by dividing the additional cost attributable to relapses by the mean number of relapses reported by relapsing-remitting MS patients with EDSS $\leq 5$.

A health utility index between 0 and 1 with increasing utility was estimated from the EQ-5D scores for each patient. Utility weights, derived from a normal population in the UK[25] were used because Canadian utility weights were not available.

### Statistical Analysis

Confidence intervals (95%) for costs were estimated by non-parametric bootstrapping.[26] A non-parametric statistical test for independent samples (Wilcoxon-Mann-Whitney Test)[27] was used to determine whether differences between comparisons performed were statistically significant (p-value<0.05). Both methods are commonly used in the analysis of skewed data because the assumptions for parametric estimation do not hold when data is not normally distributed.

## RESULTS

### Patient Characteristics and Disease Information

In total, 241 patients in Canada responded to the questionnaire. One patient was excluded from the analysis of resource utilization and costs due to unusually high values (total cost higher than Can $1,000,000) which could not be attributable to disease severity or other clinical factors. Patient demographics and disease information are presented in Tables 1 and 2.

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**TABLE 1** Demographic characteristics of multiple sclerosis patients in the study sample

| **Number of patients: n** | 241 | |
|---|---|---|
| **Gender: n (%)** | | |
| Male | 57 | (23.75%) |
| Female | 184 | (76.45%) |
| **Age** | | |
| Mean age (SD) | 44 | (10.3) |
| Patients by age cohorts: n (%) | | |
| 18-29 years | 17 | (7.1%) |
| 30-39 years | 66 | (27.4%) |
| 40-49 years | 88 | (36.5%) |
| 50-59 years | 52 | (21.6%) |
| 60-69 years | 16 | (6.6%) |
| 70-79 years | 2 | (0.8%) |
| **Living situation: n (%)** | | |
| Alone | 53 | (22.0%) |
| With family, spouse/ partner | 187 | (77.6%) |
| Nursing home | 1 | (0.4%) |
| **Education level: n (%)** | | |
| Secondary school | 32 | (13.3%) |
| High school degree | 52 | (21.6%) |
| Professional diploma | 62 | (25.7%) |
| University degree | 95 | (39.4%) |
| **Employment situation: n (%)** | | |
| Employed | 117 | (48.6%) |
| Self-employed | 14 | (5.8%) |
| Home maker | 13 | (5.4%) |
| Retired due to age | 13 | (5.4%) |
| Retired due to MS | 57 | (23.7%) |
| Student | 7 | (2.9%) |
| Unemployed | 20 | (8.3%) |
| **Informal caregiver: n (%)** | | |
| Has at least one informal carer | 102 | (42.3%) |
| Spouse | 80 | (33.2%) |
| Family member | 56 | (23.2%) |
| Friend/ neighbor | 25 | (10.4%) |
| Missing | 4 | (1.7%) |

MS, multiple sclerosis; SD, standard deviation

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**TABLE 2** Disease characteristics of multiple sclerosis patients in the study sample

| **Number of patients: n** | 241 | |
|---|---|---|
| **Onset** | | |
| Mean age at diagnosis (SD) | 35.1 | (10.1) |
| Mean age at first symptoms (SD) | 31.1 | (9.8) |
| **MS type: n (%)** | | |
| Relapsing-remitting MS | 164 | (68.0%) |
| Secondary progressive MS | 31 | (12.9%) |
| Primary progressive MS | 18 | (7.5%) |
| Don't know | 28 | (11.6%) |
| **Comorbidities: n (%)** | | |
| Osteoporosis | 17 | (7.1%) |
| Depression/Anxiety | 89 | (36.9%) |
| Urinary tract infections/Incontinence | 85 | (35.3%) |
| Sleep problems | 117 | (48.5%) |
| Arthritis | 26 | (10.8%) |
| Hypertension | 26 | (10.8%) |
| Cognitive problems | 117 | (48.5%) |
| **Disease severity** | | |
| Mean EDSS score (SD) | 3.0 | (2.1) |
| *Number of patients by EDSS cohorts (%)* | | |
| EDSS 0 - 1 | 69 | (28.6%) |
| EDSS 2 - 3 | 77 | (32.0%) |
| EDSS 4 - 5 | 51 | (21.2%) |
| EDSS 6 - 6.5 | 38 | (15.8%) |
| EDSS 7, 8 & 9 | 6 | (2.5%) |
| **Treatment for MS** | | |
| Number of patients (%) | | |
| Treated | 177 | (73.4%) |
| Not treated now but received treatment in the past | 27 | (11.2%) |
| Never treated | 32 | (13.3%) |

EDSS, Expanded Disability Status Scale; MS, multiple sclerosis; SD, standard deviation.

When dividing the patients according to disease severity (EDSS score), a sufficiently large sample was identified for mild and moderate-severity subgroups (38-69 patients), but only 6 patients with advanced disability levels (EDSS 7-9) participated in the study (Table 2). Patients with mild disability were younger than moderate or severe MS patients (p-value=0.002 and p-value=0.049 respectively). No statistically significant differences were observed when comparing the age of disease onset and symptom onset across the three severity groups (p-values > 0.05). The majority of MS patients were experiencing the relapsing-remitting form of the disease (68%). Responses regarding employment status indicated that more than half of the sample (54%) was currently employed or self-employed; 11% of patients with mild disability (EDSS score 0-3) had retired due to the disease, compared with 43% and 40% of patients with moderate (EDSS score 4-6.5) and severe (EDSS score 7-9) disability, respectively. The average age at retirement for these patients was 48 years. Many of the MS patients reported having comorbidities (Table 2). Almost half of patients reported sleep problems or cognitive problems, and depression/anxiety and urinary tract infection were both reported by more than one-third of patients. As shown in Table 2, nearly three-quarters of patients received DMTs during the

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past 3 months while 11% reported treatment with DMTs in the past, but not during the recall period. Approximately 13% of the patients in the study sample indicated that they had never been treated with MS therapies. Eighty-one patients experiencing relapsing-remitting MS and having an EDSS score ≤ 5, approximately 54% of the relapsing-remitting MS sub-group, had experienced at least one relapse during the past year. The number of relapses experienced by these individuals ranged between 1 and 8. No statistically significant differences were observed with regards to the age, years since disease onset and MS symptoms, education, living arrangements, and employment status when comparing the relapsing-remitting patients with EDSS score ≤ 5 with and without relapse(s) (p-values > 0.05). On average, the underlying severity of relapsing-remitting patients with EDSS score ≤ 5 that did experience a relapse(s) was higher compared to the same sub-group of patients that did not report any disease exacerbations during the past 12 months (mean EDSS score 2.4 vs. 1.9 respectively; p-value = 0.032).

## Resource Utilization

Among all patients in the study, 5% required a hospital admission and/or an inpatient stay at a rehabilitation centre due to MS in the past year. The proportion of patients who had inpatient care increased across disability severity subgroups, as shown in Table 3.

**TABLE 3** Use of healthcare and non-medical resources by patients with multiple sclerosis, and productivity losses by disease severity

| | | EDSS 0-3 (n=146) | | | EDSS 4-6.5 (n=89) | | | | EDSS 7-9 (n=5) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | ***Unit*** | % of patients using resources | Mean (SD) use per patient per year | | % of patients using resources | Mean (SD) use per patient per year | | % of patients using resources | Mean (SD) use per patient per year | |
| Inpatient care | days | (3%) | 2.6 | (30.2) | (7%) | 0.9 | (5.6) | (0%) | 0.0 | (0.0) |
| Outpatient care | times | (18%) | 1.4 | (3.9) | (20%) | 12.4 | (55.6) | (0%) | 0.0 | (0.0) |
| Consultations | visits | (66%) | 7.2 | (12.0) | (78%) | 11.0 | (17.1) | (100%) | 55.2$^{\dagger}$ | (59.0) |
| Investigations | tests | (36%) | 0.4 | (0.7) | (33%) | 0.4 | (0.5) | (20%) | 0.2 | (0.4) |
| MS Treatments | n.a. | (80%) | n.a | n.a | (64%) | n.a | n.a | (40%) | n.a | n.a |
| Prescribed co-medication | days | (43%) | 182.3 | (293.8) | (71%) | 414.6* | (429.3) | (100%) | 741.6$^{\dagger}$ | (406.8) |
| OTC drugs | n.a. | (60%) | n.a | n.a | (63%) | n.a | n.a | (60%) | n.a | n.a |
| Investments/ Modifications | n.a. | (5%) | n.a | n.a | (40%) | n.a | n.a | (60%) | n.a | n.a |
| Professional care | hours | (3%) | 1.0 | (11.9) | (9%) | 38.8* | (221.3) | (60%) | 393.6$^{\dagger}$ | (665.5) |
| Informal care | hours | (30%) | 125.3 | (337.2) | (61%) | 389.3* | (760.0) | (60%) | 748.8$^{\dagger\ddagger}$ | (701.0) |
| Sick leave | days | (14%) | 15.6 | (50.2) | (16%) | 16.4 | (52.9) | (20%) | 48.0 | (107.3) |
| Retirement | n.a. | (11%) | n.a | n.a | (43%) | n.a | n.a | (40%) | n.a | n.a |

* Difference is statistically significant compared to the mild subgroup of patients (p-value<0.05)

$^{\dagger}$ Difference is statistically significant compared to the mild subgroup of patients (p-value<0.05)

$^{\ddagger}$ Difference is statistically significant compared to the moderate sub-group of patients (p-value<0.05)

EDSS, Expanded Disability Status Scale; MS, multiple sclerosis; n.a., not applicable; OTC, over-the-counter; SD, standard deviation.

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All together, 71% of patients reported having at least one medical visit. Among all patients, 64% visited a neurologist, 26% visited a general practitioner, 6% visited a psychologist, 5% visited a physiotherapist, 14% visited a nurse, 8% visited an optician, and 4% visited an occupational therapist. The majority of relapsing-remitting MS patients with EDSS score ≤ 5 that reported having a medical visit (65%) had at least one relapse during the past 12 months.

Informal care was more frequently reported than professional care among patients with mild or moderate disability (Table 3), and professional assistance by a nurse, personal assistant, and/or home help was not often needed, especially during the early stages of the disease. Use of professional or informal care increased across the severity subgroups (Table 3). The mean number of informal care hours and sick leave for relapsing-remitting patients with EDSS score ≤ 5 who reported having at least one relapse were much higher than the mean hours of informal care for non-relapsed patients within the same sub-group (259 hours vs. 49 hours for informal care; p-value=0.001, 211 hours vs. 48 hours of sick leave; p-value=0.007) (Figure 1).

**Costs**

The mean total cost per MS patient per year from a societal perspective was measured at Can $37,672, of which 46% was attributable to direct healthcare costs. The cost of treatment with MS therapies represented 33% of the total costs. The cost due to patients' sick leave and retirement due to MS was an important component, comprising 32% of total costs.

As shown in Table 4, total costs varied among severity subgroups, with the lowest cost for patients with mild disease severity. The relative contributions of the cost components differed among the subgroups; for example, indirect costs comprised a larger proportion of total costs in moderate compared to mild disability subgroups.

**FIG. 1** Mean hours of informal care and sick leave per multiple sclerosis patient per year according to relapse status

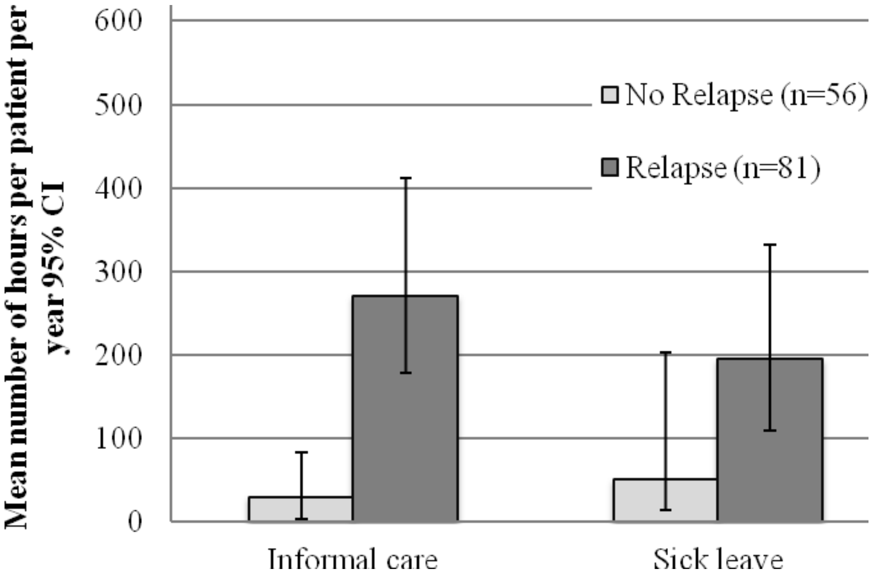

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**TABLE 4** Direct medical, non-medical, indirect, and total costs per multiple sclerosis patient per year (2009 Can $), by disease severity

| | **EDSS 0 - 3 (n=146)** | | | **EDSS 4 - 6.5 (n=89)** | | | **EDSS 7 - 9 (n=5)** | | |
|---|---|---|---|---|---|---|---|---|---|
| | **Mean** | **SD** | **(95% CI)** | **Mean** | **SD** | **(95% CI)** | **Mean** | **SD** | **(95% CI)** |
| Inpatient care | 4020 | 47362 | (75-19669) | 982 | 5713 | (113-2916) | 0 | 0 | n.a. |
| Outpatient care | 395 | 1136 | (247-637) | 749 | 1977 | (420-1324) | 0 | 0 | n.a. |
| Consultations | 515 | 821 | (403-683) | 809 | 1352 | (602-1252) | 3 810[†] | 4228 | (1622-8615) |
| Investigations | 39 | 64 | (29-51) | 34 | 60 | (23-49) | 14 | 32 | (0-58) |
| MS treatments | 13910 | 7908 | (12588-15102) | 10222* | 10100 | (8145-12413) | 3576[†] | 7996 | (0-14304) |
| Prescribed medications | 319 | 580 | (243-431) | 743* | 828 | (581-946) | 1175[†] | 576 | (590-1490) |
| OTC medications | 641 | 4492 | (239-2117) | 520 | 1066 | (345-844) | 902 | 1083 | (144-1766) |
| **Total direct medical costs** | **19837** | **48419** | **(15366 - 33108)** | **14058** | **12008** | **(11757 - 16617)** | **9478** | **9955** | **(3462 - 20084)** |
| Investments/ Modifications | 289 | 1343 | (111-542) | 2645* | 5120 | (1784-3954) | 5838[†‡] | 7642 | (2103-18675) |
| Professional care | 52 | 632 | (0-261) | 2058* | 11726 | (515-6975) | 18528[†] | 35486 | (2246-81408) |
| Informal care | 3506 | 10305 | (2113-5548) | 8009* | 15989 | (5509-12790) | 19656 | 31137 | (5400-62424) |
| **Total direct non-medical costs** | **3848** | **10693** | **(2358-5927)** | **12712*** | **20872** | **(9121 - 18455)** | **44022**[†] | **54408** | **(9751 - 102718)** |
| Sick leave | 2811 | 9028 | (1682-5075) | 2945 | 9515 | (1464-5792) | 8640 | 19320 | (0-34560) |
| Retirement due to MS | 4340 | 12413 | (2712-6781) | 16908* | 19699 | (13348-21802) | 15840[†] | 21690 | (7920-39600) |
| **Total indirect costs** | **7151** | **14526** | **(5065 - 9952)** | **19853*** | **19439** | **(15816 - 24148)** | **24480**[†] | **22395** | **(7920 - 41760)** |
| **Total costs** | **30836** | **51791** | **(25128 - 43259)** | **46622*** | **34231** | **(39854 - 54576)** | **77981**[†] | **62307** | **(40945 - 135740)** |

* Difference is statistically significant compared to the mild subgroup of patients (p-value<0.05)

† Difference is statistically significant compared to the mild subgroup of patients (p-value<0.05)

‡ Difference is statistically significant compared to the moderate sub-group of patients (p-value<0.05)

EDSS, Expanded Disability Status Scale; MS, multiple sclerosis; n.a., not applicable; OTC, over-the-counter; SD, standard deviation.

Note: Cost components may not sum to total costs due to rounding.

Informal care was valued in the base case analysis using only the productivity losses of the working caregiver; the mean cost calculated per patient per year for informal care for the entire sample was Can $5,513. When changing the method to calculate this cost item, taking into consideration the loss of leisure time of the working and non-working informal caregiver valued using the net disposable income, the cost of informal care increased to Can $8,072 per patient per year. When all hours invested by the informal caregivers in assisting the patients were valued using the net disposable income only, the cost due to informal care was Can $4,452 per patient per year.

## Additional Cost due to a Relapse

Relapses contributed to excess costs among patients with MS. The additional cost attributed to relapses among patients with the relapsing-remitting form of the disease with EDSS $\leq 5$ was estimated at Can $10,512 per patient per year (p-value $< 0.001$). The severity of relapse(s) was a factor resulting in higher costs (p-value $= 0.081$) for relapsing-remitting MS patients with EDSS $\leq 5$ who required steroid treatment due to their relapse(s) and/or hospitalization, compared with patients from the same sub-group who were not treated with steroids or who were hospitalized during their relapse(s) (see Figure 2).

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**FIG. 2** Mean cost per relapsing-remitting patient with EDSS score ≤ 5 per year, by relapses and relapse severity, OTC, over-the-counter

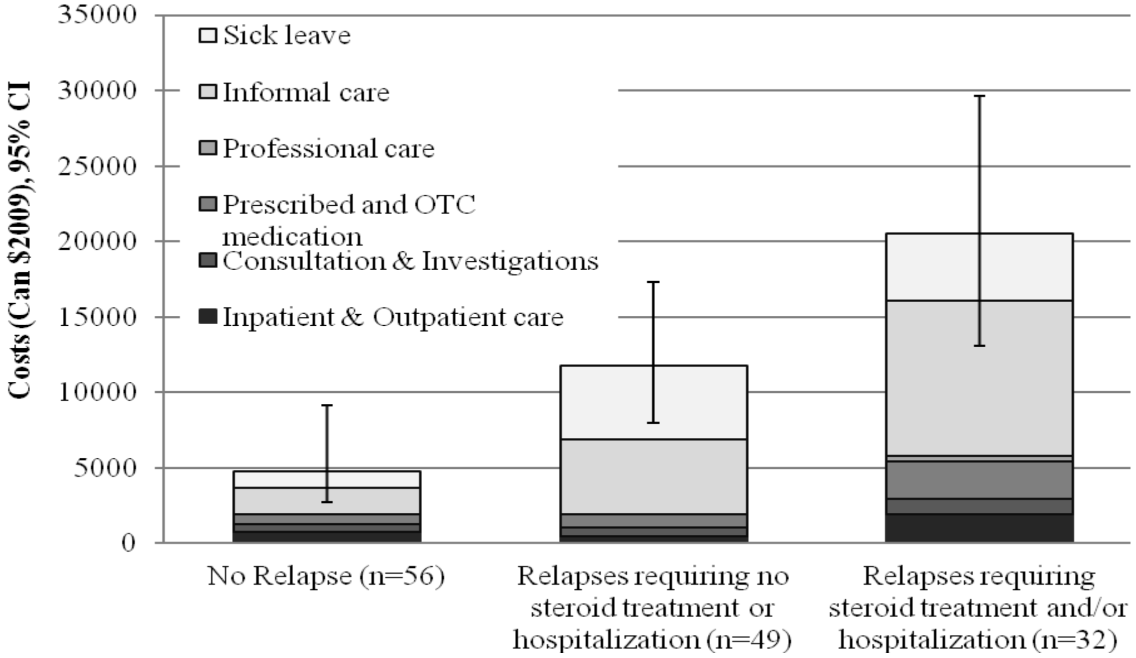
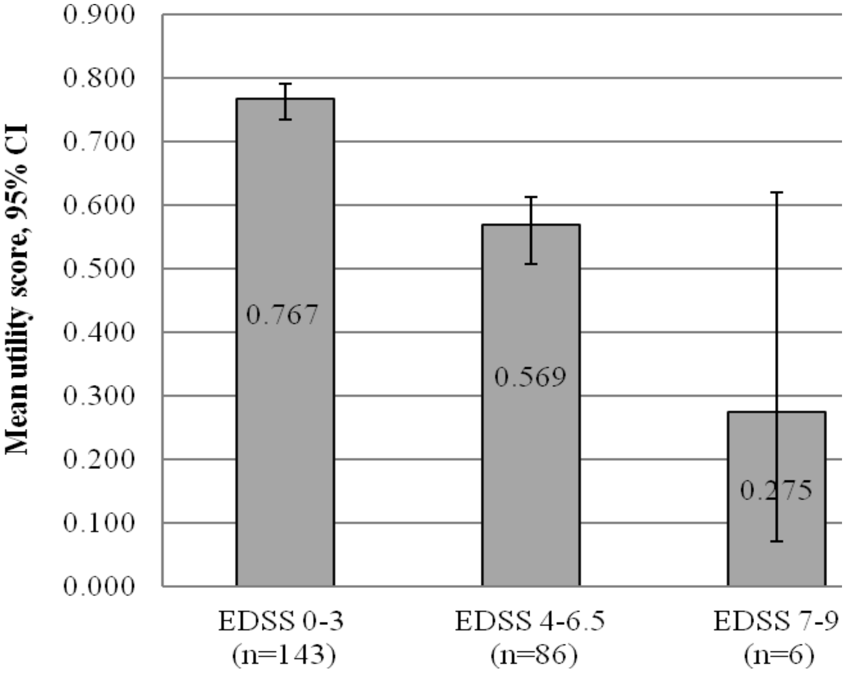


**FIG. 3** Quality of life (mean utility score) of multiple sclerosis patients, by disease severity. EDSS, Expanded Disability Status Scale



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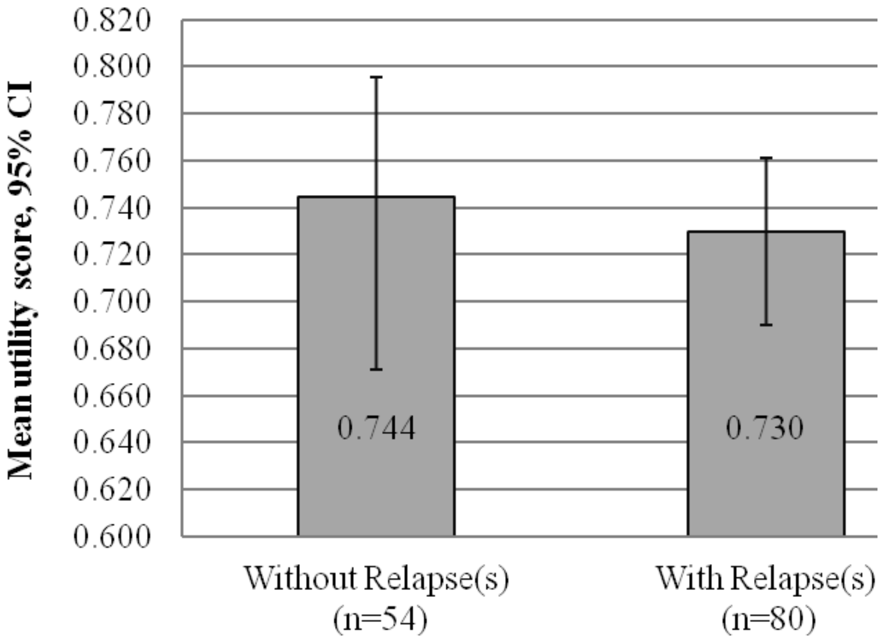
The mean cost per relapse among relapsing-remitting MS patients with EDSS ≤ 5 was estimated at Can $6,402 by dividing the excess burden that could be attributable to disease exacerbations by the mean number of relapses during the past 12 months reported by relapsing-remitting MS patients with EDSS ≤ 5 who experienced a relapse.

**Utilities**

More severe disease, experiencing a relapse, and presence of comorbidities were all associated with poorer quality of life as measured by the EQ-5D instrument. The mean utility score decreased across the EDSS score-based severity subgroups (see Figure 3). Patients with comorbid depression, sleep disorders, urinary tract infections/incontinence, or cognitive problems reported lower mean utility scores (0.591, 0.614, 0.599, 0.632, respectively) than patients with no such comorbidities (0.734, 0.747, 0.727, 0.728, respectively); all differences were statistically significant (p-values <0.001).

Patients with relapsing-remitting MS and EDSS ≤ 5 who experienced at least one relapse during the past 12 months reported lower utilities compared with relapsing-remitting MS patients with EDSS ≤ 5 who did not report a relapse (p-value = 0.058) (see Figure 4).

**FIG. 4** Quality of life (mean utility score) of relapsing-remitting multiple sclerosis patients with EDSS score ≤ 5, according to relapse status. EDSS, Expanded Disability Status Scale



## DISCUSSION

The first aim of the TRIBUNE study was to measure the societal burden of MS and to contribute with detailed cost and quality of life information to the existing literature in Canada. In addition, the study focused on the association of the societal burden with disease severity/disability and relapses. The study shows that MS imposes a significant economic burden on Canadian society.The mean cost per patient with MS was estimatedat Can $37,672, which is comparable to the cost per patient with mild to moderate disability. This cost estimate increases if the assumption for valuing informal care changes to include the loss of leisure time of the informal caregiver in addition to their productivity losses (Can $40,231 per patient per year).

As it was shown, direct and indirect costs generally increased with disease severity, which can be explained by a higher need for medical and non-medical care associated with progressing disability. The mean cost per patient per year was estimated at Can $30,836 for patients with mild disability (EDSS score 0-3), Can $46,622 for patients with moderate disability (EDSS 4-6.5), and Can $77,981 for patients with severe disability due to MS (EDSS score 7-9). It should be noted that not all cost differences across severity groups were statistically significant, most probably due to the low sample size in the moderate and severe sub-groups. Nevertheless, the interpretation of the statistical hypothesis testing and significance levels is not the same within the context of economic evaluations when compared to the clinical trial framework. The objective of the economic evaluations is to estimate the socioeconomic burden imposed on the healthcare systems and society as a whole due to a disease, rather than hypothesis testing. Point estimates of costs may be of relevance for decision-makers irrespective of statistical significance.

The TRIBUNE findings regarding costs are consistent with conclusions of previous cost-of-illness studies of MS in Canada. The Canadian Burden of Illness Study Group[6], which reported results of a similar study in 1998, indicated that the mean societal cost among 198 MS patients increased with disability: Can $14,523, Can $21,698, and Can $37,024 for patients with mild (EDSS ≤2.5), moderate (EDSS 3.0-6.0) and severe (EDSS ≥6.5) disability, respectively. The most recent Canadian study, reported by Grima and colleagues[8] in 2000, estimated that the mean cost per patient for relapse-free patients ranged between Can $10,598 and Can $51,698 in 1997 prices (Can $13,459 and Can $65,656 in 2009 prices) and increased with disease severity. Indirect costs were identified as major contributors to total costs in both of these studies[6,8], as in the TRIBUNE study.

The overall annual costs per patient in the TRIBUNE study are higher when compared with the previous cost estimates for MS in Canada. To explore whether this increase could be attributable to the higher cost of treatments observed in our study, we compared costs other than costs for DMTs between the studies,[8] and found that the costs from TRIBUNE are lower for most of the disability levels. Although this suggests that changes in the contribution of treatment costs partially account for the overall increase we observe, it is not possible to draw a conclusion regarding the cost variation between the studies given the differences in the methodologies used to estimate the costs and the different characteristics of the patient populations (in the study by Grima et al.,[8] cost refers to patients in remission whereas in the TRIBUNE study both relapsed and non-relapsed patients are taken into account in the calculation of mean costs).

Studies similar to TRIBUNE that were conducted in the US and Europe concluded as well that the annual per patient costs are higher for advanced disability levels. The average per patient per year costs for MS were US $47,215 in 2004 prices[24] (Can $56,582 in 2009 prices) in the US and €23,695 in 2004 prices[23] (Can $36,430 in 2009 prices) in Europe, and costs increased with increasing disability. Differences in the numerical values of the costs can be partially attributed to the differences in the underlying disease severity of the study populations in the studies as well as the cost of DMTs. Key factors for the estimation of the cost of DMTs are the availability of DMTs at the time of the study and the distribution of their use among MS patients. Differences among the healthcare systems and the patterns of care across countries also help to explain the variation in the costs reported by these studies.

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In addition to the trends in economic costs associated with MS severity, the TRIBUNE study estimated that there is a decrease in mean utility scores as the disease progresses. This finding is consistent with previously published literature in Canada[8], the US and Europe[23,24] and suggests that slowing disease progression can reduce the patient burden of MS in terms of health-related quality of life. It should also be noted that the utility scores derived from the EQ-5D, while useful for international comparisons, may underestimate the true burden of MS-related illness.[28]

The TRIBUNE study results showed that relapses impact the economic burden and the quality of life of patients with MS. Compared with relapse-free patients with relapsing-remitting MS and EDSS $\leq 5$, the mean utility score was lower for patients who experienced a disease exacerbation during the past 12 months. In addition, relapses had a significant impact on both direct and indirect costs, with a higher number of hours devoted to professional care and more productive hours lost by informal caregivers and patients for those patients who reported experiencing a disease exacerbation. Informal care is an important component of the care received by patients with MS,[5,6,29] and lessening the need for additional informal care by reducing the frequency of relapses could reduce the burden on friends and family as well as society.

In addition, based on methodology which was previously used in the US and European studies,[23,24] the economic impact of relapses on total burden was estimated by calculating the excess cost attributable to relapses per patient per year and the cost of one relapse. The additional economic burden attributed to relapses among patients with the relapsing-remitting form of the disease with EDSS $\leq 5$ was estimated at Can $10,512 per patient per year. The average cost per relapse was estimated at Can $6,402. For relapses of short duration, this could be considered an overestimation because the difference in costs may be attributed to factors other than relapse, such as differences in disease severity. However, one could also argue that since the study design did not allow capture of the full period of increased costs for patients who experienced multiple relapses, this average cost is an underestimation of the excess economic burden imposed on patients and society due to disease exacerbations. Our results are consistent with previous findings in Canada by Grima and colleagues[8] even though different methodology was used. They reported a range between Can $1,722 and Can $5,764 in 1997 (Can $2,187 and Can $7,320 in 2009 prices) for the additional cost due to a relapse. In the US, the cost of a relapse was estimated at US $1,561 in 2004 prices (Can $1,871 in 2009 prices),[24] which was lower than the cost of a relapse calculated in this study. Variations in the estimates may be attributed to the differences in the characteristics of the patient populations included in the studies and the methodologies used to calculate the additional cost due to relapses.

The main contribution of this study to the existing literature for MS in Canada is the important update that it provides for the burden associated with the disease in terms of costs and utilities in an era of more widespread use of MS therapies. The whole disability spectrum is covered in the patient sample, and thus the comparability of results with a general MS population is reinforced. However, even though this study measured the burden of MS in Canada based on a larger sample of MS patients than previous studies,[6-8] very few patients with severe disability were included, and a larger sample is needed to generalise the results according to disease severity.

Another limitation of this study, which is rather common among cost-of-illness studies, relates to the fact that the cost estimates are likely to reflect how the sample of MS patients was derived. Cost estimates would probably have been lower if the sample had included MS patients recruited from the community rather than from specialized clinics, because patients in the community are likely to have less severe disease and are treated with DMTs less frequently. Indeed, the proportions of patients in our sample who reported receiving treatment with DMTs or having a relapse were relatively high. In addition, if patients from nursing homes/chronic care institutions had been included in the sample, the costs attributed to the use of DMTs would have been lower; however other costs may have been higher in comparison with patients living in the community.

In conclusion, the TRIBUNE study contributes to and updates the limited and

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outdated information on costs and health utilities of MS patients currently available in Canada. Considering that total costs of MS increase and health utilities decrease with worsening disability, and also that exacerbations impose an additional burden in terms of both costs and quality of life, slowing progression and reducing the frequency of exacerbations presents an opportunity to reduce the burden of MS. Treatments for MS can significantly slow the progression of disability associated with the disease and restrict the number of relapses patients experience.[9] Further research is needed to explore the precise relationship between relapse rate reduction and long term benefits of MS treatments. This study suggests that use of effective and readily-useable treatments may lead to a reduction in both the clinical and socioeconomic costs of MS.

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## REFERENCES

1. Multiple Sclerosis Society of Canada. *About MS.* (2010) http://mssociety.ca/en (Access date: November 18, 2010).
2. Multiple Sclerosis International Federation. *Atlas of MS Database.* (2009) http://www.atlasofms.org/index.aspx (Access date: November 10, 2010).
3. Compston A, Coles A. Multiple sclerosis. Lancet 2008;372:1502-17.
4. Burden of illness of multiple sclerosis: Part II: Quality of life. The Canadian Burden of Illness Study Group. Can J Neurol Sci 1998;25:31-8.
5. Henriksson F, Fredrikson S, Masterman T, Jonsson B. Costs, quality of life and disease severity in multiple sclerosis: a cross-sectional study in Sweden. Eur J Neurol 2001;8:27-35.
6. Burden of illness of multiple sclerosis: Part I: Cost of illness. The Canadian Burden of Illness Study Group. Can J Neurol Sci 1998;25:23-30.
7. Canadian Institute for Health Information. *The Burden of Neurological Diseases, Disorders and Injuries in Canada.* (2007) http://mssociety.ca/en/pdf/banhc-impactreport-200706_EN.pdf (Access date: March 12, 2010).
8. Grima DT, Torrance GW, Francis G, Rice G, Rosner AJ, Lafortune L. Cost and health related quality of life consequences of multiple sclerosis. Mult Scler 2000;6:91-8.
9. Sormani MP, Bonzano L, Roccatagliata L, Mancardi GL, Uccelli A, Bruzzi P. Surrogate endpoints for EDSS worsening in multiple sclerosis. A meta-analytic approach. Neurology 2010;75:302-9.
10. Kurtzke JF. A new scale for evaluating disability in multiple sclerosis. Neurology 1955;5:580-3.
11. The EuroQol Group. EuroQol--a new facility for the measurement of health-related quality of life. Health Policy 1990;16:199-208.
12. Bank of Canada. *Harmonized Price Indices.* (2010) http://www.bankofcanada.ca/pdf/nrma09-12.pdf. (Access date: April 14,2010)
13. Ontario Ministry of Health and Long-Term Care. *Ontario Case Costing Initiative. (OCCI).* (2008) www.occp.com (Access date: April 12, 2010).
14. Ontario Ministry of Health and Long-Term Care. *Ontario Schedule of Benefits for Physician Services.* (2009) http://www.health.gov.on.ca/english/providers/program/ohip/sob/physserv/physserv_mn.html (Access date: April 12, 2010).
15. Price List of Pharmaceuticals in Quebec. *Liste de medicaments publiee par la Regie de l'assurance maladie du Quebec.* (2010) http://www.ramq.gouv.qc.ca/fr/professionnels/medicaments/listmed/pdf/modification/liste_medicaments.pdf. (Access date: April 12, 2010).
16. Ontario Ministry of Health and Long-Term Care. *Ontario Drug Benefit Formulary.* (2010) http://www.health.gov.on.ca/english/providers/program/drugs/odbf_eformulary.html. (Access date: March 11, 2010).
17. Community Care Access Centre. Toronto Central. (2009) www.toronto.ccac-ont.ca (Access date: May 6, 2011).
18. London Health Sciences Centre. *Case Costing Fiscal Year 2009.* (2009)

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http://www.lhsc.on.ca/About_Us/Case_Costing/index.htm (Access date: May 6, 2011).

19. Shoppers Home Health Care, New Street Burlington, Ontario. 3-5-2010.
20. Statistics Canada. *Average hourly wages of Canadian employees in January 2010.* (2010) http://www40.statcan.ca/l01/cst01/labr69a-eng.htm (Access date: March 11, 2010).
21. Organization for Economic Co-operation and Development (OECD). *Labour Force Statistics: Average annual hours actually worked per worker, 2008.* (2011) http://stats.oecd.org (Access date: May 6, 2011).
22. Organization for Economic Co-operation and Development (OECD). *Social and Welfare Statistics: Income Distribution, 2008.* (2011) http://stats.oecd.org (Access date: May 6, 2011).
23. Kobelt G, Berg J, Lindgren P, Fredrikson S, Jonsson B. Costs and quality of life of patients with multiple sclerosis in Europe. J Neurol Neurosurg Psychiatry 2006;77:918-26.
24. Kobelt G, Berg J, Atherly D, Hadjimichael O. Costs and quality of life in multiple sclerosis: a cross-sectional study in the United States. Neurology 2006;66:1696-702.
25. Dolan P, Gudex C, Kind P, Williams A. A Social Tariff for EuroQol: Results from a UK General Population Survey. York: Centre for Health Economics, University of York, 1995.
26. Davison A, Hinkley D. *Bootstrap Methods and their Application (8th Edition). Cambridge University Press, Cambridge, UK. 2006.*
27. Fay MP, Proschan MA. Wilcoxon-Mann-Whitney or t-test? On assumptions for hypothesis tests and multiple interpretations of decision rules. Stat Surv 2010;4:1-39.
28. Fisk JD, Brown MG, Sketris IS, Metz LM, Murray TJ, Stadnyk KJ. A comparison of health utility measures for the evaluation of multiple sclerosis treatments. J Neurol Neurosurg Psychiatry 2005;76:58-63.
29. McCrone P, Heslin M, Knapp M, Bull P, Thompson A. Multiple sclerosis in the UK: service use, costs, quality of life and disability. Pharmacoeconomics 2008;26:847-60.

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