UTILITY OF LORENZ CURVES IN EXAMINING PHYSICIAN PRESCRIBING PRACTICES: EXAMPLE OF ONTARIO NEUROLOGIST PRESCRIBING OF MULTIPLE SCLEROSIS DISEASE-MODIFYING THERAPIES IN 2009

By

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A thesis submitted in conformity with the requirements for the degree of Masters of Science,
The Institute of Medical Science,
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Utility of Lorenz curves in examining physician prescribing practices: example of Ontario neurologist prescribing of multiple sclerosis disease-modifying therapies in 2009

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Abstract

BACKGROUND: Differences in disease-modifying therapy (DMT) prescribing patterns between different groups of neurologists have not been explored. HYPOTHESIS: MS-specialist neurologists use a broader range of DMTs in contrast to generalist neurologists who preferentially prescribe Avonex. METHODS: Ontario neurologist demographic and geographical characteristics were linked to 2009 DMT prescription data. Lorenz curves and Gini coefficients were constructed to examine prescribing patterns; separating neurologist characteristics dichotomously and separating Avonex from the other DMTs. Gini Coefficients were compared using jack-knife statistical techniques to derive 95% confidence intervals. RESULTS: Prescriptions are highly concentrated with 12% of Ontario neurologists prescribing 80% of DMTs. High-volume prescribers show a broader range of DMT use while low-volume prescribers tend to use a particular DMT. CONCLUSIONS: The majority of DMTs are prescribed by a small subset of neurologists. High-volume prescribers show more variability in DMT use while low-volume prescribers tend to individually focus on a narrower range of DMTs.
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List of Abbreviations

ARR  annualized relapse rate
BBB  blood brain barrier
CHO  Chinese hamster ovary
CD4  cluster of differentiation 4
CD8  cluster of differentiation 8
CI  confidence interval
CIS  clinically isolated syndrome
CNS  central nervous system
DIN  drug identification number
DMFS  decayed, missing, filled surfaces
DMFT  decayed, missing, filled teeth
DMT  disease-modifying therapy
DNA  deoxyribonucleic acid
EBV  Epstein-Barr virus
EDSS  Expanded Disability Status Scale
EMEA  European Medicines Agency
GP  general practitioner
eod  every other day
FDA  Food & Drug Administration
FSA  Forward Sortation Area
GA  glatiramer acetate
HIV  human immunodeficiency virus
HLA  human leukocyte antigen
HMO  health maintenance organization
ICES  Institute of Clinical Evaluative Sciences
IFN  interferon
IKN  ICES key number
IL2RA  interleukin-2 receptor α gene
IL7RA  interleukin-7 receptor α gene
IPDB  ICES physician database
MIU  million international units
MRI  magnetic resonance imaging
MS  multiple sclerosis
MVA  motor vehicle accident
MX  mitoxantrone
Nab  neutralizing antibodies
NARCOMS  North American Research Committee on Multiple Sclerosis
NK  natural killer
NZ  natalizumab
ODB  Ontario Drug Benefit
ODSP  Ontario Disability Support Program
OHIP  Ontario Health Insurance Plan
OR  odds ratio
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tr>
<td>PML</td>
<td>progressive multifocal leukoencephalopathy</td>
</tr>
<tr>
<td>PPMS</td>
<td>primary progressive multiple sclerosis</td>
</tr>
<tr>
<td>PRMS</td>
<td>progressive-relapsing multiple sclerosis</td>
</tr>
<tr>
<td>PS</td>
<td>propensity scoring</td>
</tr>
<tr>
<td>REB</td>
<td>research ethics board</td>
</tr>
<tr>
<td>RIO2004</td>
<td>Rurality Index of Ontario, 2004</td>
</tr>
<tr>
<td>RRMS</td>
<td>relapsing remitting multiple sclerosis</td>
</tr>
<tr>
<td>RRR</td>
<td>relative risk reduction</td>
</tr>
<tr>
<td>S1P</td>
<td>sphingosine-1-phosphate</td>
</tr>
<tr>
<td>SPMS</td>
<td>secondary progressive multiple sclerosis</td>
</tr>
<tr>
<td>STD</td>
<td>sexually transmitted disease</td>
</tr>
<tr>
<td>Th1</td>
<td>Type 1 helper T cells</td>
</tr>
<tr>
<td>Th2</td>
<td>Type 2 helper T cells</td>
</tr>
<tr>
<td>TDP</td>
<td>Trillium Drug Program</td>
</tr>
<tr>
<td>VCAM-1</td>
<td>vascular cell adhesion molecule 1</td>
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Introduction

The development of the initial injectable disease-modifying therapies (DMTs) for relapsing-remitting multiple sclerosis (RRMS) in the late 1990s was a revolution in the care of multiple sclerosis (MS) patients. At first approximation, the four therapies pioneered at that time, Avonex®, Betaseron®, Rebif® and Copaxone®, may seem more or less interchangeable. However, there are significant differences with respect to efficacy between certain DMTs, the ease of administration for the patient, adverse event profiles, requirements for physician-monitoring and in cost.

No research has examined the interplay between physician (neurologist) characteristics and prescription patterns for the four first-line DMTs. Anecdotal observation at the St. Michael’s Hospital MS Clinic suggested that patients seen in the clinic after starting DMT in the community tended to be on Avonex. This lead to the hypothesis that Avonex was more frequently prescribed by general neurologists whereas MS-specialists would be more likely to use all four DMTs to varying degrees.

Lorenz curves were constructed using the information in the Ontario Drug Benefit prescription database to demonstrate asymmetrical prescribing practices. This analysis showed that ~80% of DMTs in Ontario were prescribed by only ~12% of neurologists. Amongst the prescribing neurologists, high-volume prescribers utilized a wider range of DMTs relative to low-volume prescribers. This dramatic degree of specialization has implications for future DMT access by MS patients. In contrast to the four first-line DMTs studied here, second-line and experimental therapies all require more monitoring.
and have more serious adverse-events. Generalist neurologists are therefore even less likely to prescribe these medications, creating even more of a demand for MS specialist neurologists.
Background/Literature Review

Multiple Sclerosis

Multiple sclerosis (MS) is the most common non-traumatic nervous system disease of young adults with a worldwide prevalence of 30 per 100,000. While MS is a worldwide condition, there are marked geographic disparities in incidence and prevalence reflecting both the genetic predisposition of different populations and local environmental risk factors. The rate of MS in populations of Northern European descent reaches as high as 0.3%. MS is generally thought to be an autoimmune condition in which peripherally circulating autoreactive T-lymphocytes migrate into the central nervous system (CNS). After recognizing and binding self-antigen components of the myelin sheath this lymphocytic migration starts a combined immunological and neurodegenerative cascade of demyelination and secondary loss of the underlying axons and myelin-producing oligodendrocytes.

The name “multiple sclerosis” comes from the German “multiple sklerose”, and supplanted the previous term frequently used in the English-speaking world of “disseminated sclerosis” which itself was derived from Charcot’s original description of “la sclérose en plaques disseminées.” This term is a pathological description of the gross and microscopic pathology of the brains and spines of MS patients which contain sclerotic (gliotic) areas of tissue damage within the white matter corresponding to areas of focal demyelination.
The hallmark of MS is evidence of symptoms and signs secondary to CNS dysfunction that display both “dissemination in space” and “dissemination in time”. This means that the clinical manifestations of MS have to be separated by location (such as inflammation of the optic nerve [optic neuritis] and the spinal cord [transverse myelitis]) and temporally discrete; for example the episodes of optic neuritis and transverse myelitis occurring six months apart.² This spatial and temporal dissemination was noted in the first nineteenth-century descriptions of MS and explicitly stated in the earliest consensus-driven diagnostic criteria for MS.⁶ The most recent diagnostic criteria still maintain this important characteristic; however with the advent of magnetic resonance imaging (MRI) scanning, dissemination in space and time can now also be determined radiologically.⁷

MS typically first presents in the third or fourth decades; although symptoms can begin at any age or even be asymptomatic throughout life and only incidentally detected at autopsy.⁸,⁹,¹⁰ Approximately ninety percent of patients initially have a RRMS characterized by symptomatic relapses separated by periods of remission that last months or years (occasionally decades).⁸,⁹,¹¹,¹² Relapses typically evolve over days and last for weeks before gradually spontaneously resolving. Not all patients experience complete remissions however, with mild residual symptoms common after a relapse.

Relapses reflect acute inflammatory demyelination in eloquent areas of the CNS where other compensatory neural pathways do not exist; hence inflammation in these CNS regions is associated with symptoms.¹³ Typical relapses involve the optic nerves (optic neuritis), brainstem and cerebellar connections (typically extraocular movement
abnormalities and/or ataxia) and the long-tracts within the spinal cord (transverse myelitis with variable patterns of limb sensorimotor disturbance and/or sphincter involvement). Serial MRI studies have demonstrated that for every symptomatic relapse, 5-10 new asymptomatic lesions occur in less eloquent cerebral areas; typically in the subcortical regions.14,15,16

In natural history cohorts, approximately 90% of RRMS patients subsequently develop progressive neurological dysfunction (secondary progressive MS [SPMS]).8,11 While this occurs on average 25 years after symptom onset, there is marked variability with a small subset of patients often exhibiting little clinical and/or radiological activity (so called “benign MS). As discussed below, despite the characterization of MS as a predominantly demyelinating disorder, axon loss also occurs early in the disease and continues throughout the lifetime of the patient.17,18 The onset of the SPMS phase is thought to be the clinical manifestation of compensatory mechanism exhaustion due to this continued axonal attrition. Parenthetically, this “typical” pattern of disease progression from RRMS to SPMS is mirrored in the most widely used index of disease severity and progression called the Expanded Disease Status Scale (EDSS). This scale is heavily weighted towards ambulatory function in the upper region of the scale reflecting the increased reliance of mobility aids typically needed as the SPMS phase develops over years and decades.19

Twenty percent of MS patients do not have a relapsing phase, but instead have insidious progression from onset (primary progressive MS [PPMS]), occasionally with
superimposed relapses (progressive relapsing [PRMS]). PPMS is usually characterized by progressive paraparesis or hemiparesis, although predominantly cerebellar and rarely cognitive progression can also predominant.\textsuperscript{20,21}

In addition to the visual, sensory, motor, coordination and sphincter symptoms describing above, there has been increasing recognition in recent years of other issues including cognitive dysfunction, MS-related fatigue and mood disorders. While less dramatic in appearance, these symptoms can contribute significantly to the morbidity of MS patients.\textsuperscript{22,23} While these issues are more commonly seen in patients with more advanced physical disability, they are frequent in all subtypes and stages of MS. These symptoms likely reflect lesions in cortical-subcortical circuits mediating higher cerebral functions.

The classic T-lymphocyte-driven paradigm of MS pathogenesis described above does not fully account for the constantly evolving body of neuro-immunological and neuro-pathological observations which have lead to an increased appreciation of the biological complexity of this disorder. Other immune-system constituents, including B-lymphocytes and natural killer (NK) lymphocytes, have been shown to have pivotal roles in the neuroimmunology of MS.\textsuperscript{3,24,25} There is also some intriguing neuropathological and neuroimaging evidence that oligodendrocytes might, at least in some individuals, undergo a primary neurodegenerative process or apoptotic failure with the immune system involvement being a secondary reaction.\textsuperscript{26,27} Axonal loss is an ongoing process throughout the course of the disease. It occurs early in acute inflammatory MS lesions, possibly through a “bystander effect” in the toxic milieu of such active lesions and also to
a lesser degree in long-established lesions.\textsuperscript{17} This continued axonal attrition results from both the ongoing mild degree of active inflammation that persists in chronic lesions and also more importantly, from metabolic and/or mitochondrial failure in the remaining overactive axons.\textsuperscript{28}

Additionally, while MS is traditionally thought of as a “white-matter” disease given the primary role accorded to demyelination, there is an evolving body of evidence demonstrating widespread cortical lesions in MS patients with both demyelination of cortical axons and cortical neuron and oligodendrocyte loss.\textsuperscript{29,30} MRI and pathological studies have also demonstrated that the normal appearing white matter (NAWM) surrounding the plaques is not physiologically normal in MS patients.\textsuperscript{31,32}

MS is most common in individuals of Western-European descent, although it is a global disease present in varying degrees in all parts of the world and ethnic groups.\textsuperscript{1,2,33} The variable worldwide prevalence of MS is thought to reflect the complex interaction between environmental factors which “trigger” the disease in those with an inherited genetic predisposition to develop autoimmunity. Familial aggregation studies, including the seminal series of papers from the Canadian Collaborative Study have clearly established that the risk of family members developing MS drops exponentially as genetic similarity decreases from a ~30% risk in the monozygotic twin of an MS patient to ~3% in a parent or child to the background risk of ~0.3% in a adopted sibling.\textsuperscript{2,34,35}

With the exception of the HLA locus where alleles such as \textit{DRB1*1501} signify an increased risk (odds ratio [OR] 5.42 for homozygotes) and other alleles such as
DRB1*1401 signify a decreased risk, the contribution of other individual genes is relatively small.\textsuperscript{36,37} Recently, for example, strong evidence from detailed linkage studies has pointed to alleles of both the interleukin-2 receptor α (IL2RA) and interleukin-7 receptor α gene (IL7RA) genes being linked with MS.\textsuperscript{38} However, these interleukin receptor allelic variants can only explain ~0.2% of the variance in risk. The genetic predisposition to MS is likely conferred by small additive effects of numerous common allelic variants each of which is insufficient in isolation to cause MS. Each variant is also carried by a large segment of the population, only a minority of whom will develop MS.\textsuperscript{39} Large linkage analyses involving thousands of patients in various populations have failed to find other significant genetic risk factors. Given the power of these studies, it has been concluded that no other genes exist which independently contribute to MS risk with the same magnitude as HLA.

Environmental factors have a significant role in MS pathogenesis as shown by migration studies where individuals who move from an area of low to high prevalence (or the converse) acquire the risk of their new region if the migration occurs in early life; although more modern studies have suggested that the age cut-off of fifteen derived from one study of immigrants to South Africa might have been too simplistic.\textsuperscript{40} Studies of the rates of paediatric MS in first-generation Canadian children relative to adult immigrants also demonstrate the age-dependent impact of environmental change in altering the risk of MS.\textsuperscript{41} Such epidemiological studies provide intriguing circumstantial evidence that the environmental factors which contribute to MS need to interact with a developing immune system to lay the foundation for the development of MS either in childhood or as
an adult. The nature of the specific environmental factors at play in MS pathogenesis are still incompletely understood. Nevertheless, low serum vitamin D levels and childhood Epstein-Barr virus (EBV) infection are consistently reproducibly risk factors. In addition, childhood obesity, smoking and an earlier spring (especially May) month of birth confer an increased risk of MS, although the magnitude of the effect is less than that of vitamin D and EBV. The combined genetic and environmental body of evidence suggests that specific interactions/influences of environmental factors in genetically predisposed individuals’ results in MS; a synthesis which has culminated in early efforts to combine these inherited and acquired risk factors into an aggregate risk scoring algorithm.

_Treatment of MS_

Treatment of MS can be conceptualized as utilizing a multimodal approach with drug (medical) therapy needing to be combined with occupational/physical therapy, psychotherapy, speech-language pathology and social work expertise depending on individual patient needs. The goals of therapy as outline by Compston and Coles are to:

1. reduce relapse rates
2. prevent fixed disability directly attributable to relapse
3. provide symptomatic management of fixed neurological deficits
4. prevent disability acquired through progression
5. treat established progression.

With respect to treatment of relapses, corticosteroids have been in use for decades. They are effective in speeding up recovery from relapses, however the degree of recovery is not altered by corticosteroid use. Plasma exchange is commonly used for severe,
debilitating relapses. Rarely, immunosuppressants such as cyclophosphamide are used for fulminating relapses in conjunction with corticosteroids and/or plasma exchange.

MS symptoms such as weakness, dysesthesia and bladder dysfunction can be treated with varying degrees of success through a combination of pharmacological and nonpharmacological approaches. Dysesthesia, bladder dysfunction, pain, depression and fatigue for example can benefit from medical interventions. Physical, occupational and psychotherapy interventions can also augment or complement pharmacological agents.

Immunosuppressants such as azathioprine and cyclophosphamide have been used for over forty years in MS. This use has been sparingly however because of the scant evidence of effectiveness (partially reflective of the poor quality of the early clinical trials) and their significant side effects. Nevertheless, one potent immunosuppressant, the anthracenedione antineoplastic agent mitoxantrone (MX), was shown to be modestly effective in preventing disability progression in aggressive RRMS and SPMS. (To date, this remains the only drug with any demonstrable efficacy in SPMS patients who are not having relapses). In Canada, MX use in MS remains off-label (it is licensed in Europe and the United States). However, there are growing concerns with this agent’s propensity to cause heart failure and haematological malignancies. Of the other immunosuppressive agents, only cyclophosphamide is currently used with any great frequency. Although the evidence from the main clinical trials to date has not been uniformly positive, this agent has been shown to be effective in patients with rapidly
progressive MS as well as patients with significant RRMS not responsive to the first-line therapies addressed below.\textsuperscript{53,54,55}

The era of so-called “disease-modifying therapy” (DMT) in MS began with the results of the IFNB Multiple Sclerosis Study Group trial of subcutaneous interferon (IFN) β1b (Betaseron®) in RRMS, initially published in 1993\textsuperscript{56,57} with the final study results reported in 1995.\textsuperscript{58} This was quickly followed by similar positive results with the related compound IFNβ1a (Avonex®\textsuperscript{59} and Rebif®\textsuperscript{60}) and with glatiramer acetate (GA) (Copaxone®).\textsuperscript{61} These drugs were classified as “DMTs” because they were all shown to alter the natural history of the disease; at least over the relatively short time-frame studied in the initial pivotal clinical trials. Table 1 summarizes the main endpoints of the pivotal trials for the four first-line injectable DMTs.

IFNβ1b is produced in an \textit{Escherichia coli}-based expression system resulting in structural differences from the wild-type human IFNβ. As a result of the prokaryotic system it is not glycosylated. Additionally it was engineered with a deletion of methionine at position 1 and a substitution of serine for cysteine at position 17, both of which were introduced to increase the yield of drug.\textsuperscript{62,63} IFNβ1b and the two formulations of IFNβ1a discussed below all have an incompletely understood mechanisms of action. In reality, these agents likely act in multiple ways: blocking T-cell activation, promoting activity of T-regulatory cells, causing apoptosis of autoreactive T-cells and preventing autoreactive T-cells from entering the CNS through blood-brain barrier (BBB) stabilization are all potential mechanisms of IFNβs biological effects on MS.\textsuperscript{63,64}
Table 1: Summary of four first-line DMTs

<table>
<thead>
<tr>
<th>Medication</th>
<th>Route/Frequency</th>
<th>Mean Reduction in Relapse Rate</th>
<th>Mean Reduction in Progression</th>
<th>New MRI T2 lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFNβ1a (Avonex)</td>
<td>IM/weekly</td>
<td>-18% (p≤0.05)</td>
<td>-37% (p≤0.05)</td>
<td>-36% (p≤0.01)</td>
</tr>
<tr>
<td>IFNβ1a (Rebif)</td>
<td>SC/tiw</td>
<td>-32% (p≤0.001)</td>
<td>-30% (p≤0.05)</td>
<td>-78% (p≤0.001)</td>
</tr>
<tr>
<td>IFNβ1b (Betaseron)</td>
<td>SC/qod</td>
<td>-34% (p≤0.001)</td>
<td>-29% (NS)</td>
<td>-83% (p≤0.01)</td>
</tr>
<tr>
<td>GA (Copaxone)</td>
<td>SC/daily</td>
<td>-29% (p≤0.01)</td>
<td>-12% (NS)</td>
<td>-38% (p≤0.01)</td>
</tr>
</tbody>
</table>

NB: All reductions are relative to placebo
IFN interferon, IM intramuscular, NS not significant, SC subcutaneous, qod every other day, tiw three times per week
Adapted from reference (65).

IFN β1b was the first agent shown to have a disease-modifying effect in a phase III trial.56,57,58 In the pivotal trial, two doses of Betaseron (50μg or 1.6 million international units [MIU] and 250μg or 8 MIU) administered subcutaneously every other day (eod) were compared with placebo over a 2 year period in the core study, with some endpoints also assessed at 3 years and the final dataset consisting of subjects enrolled in the trial for between 3.5 to 5 years.57,58,59 The 2-year annualized relapse rate (ARR) was 1.27 in the placebo arm, 1.17 in the 1.6 MIU arm (p=0.01 versus placebo) and 0.84 (p=0.0001 versus placebo) in the 8 MIU arm.56 MRI disease activity (defined as the percentage change of new, recurrent or enlarging lesions) over 3 years was also significantly less in the 8 MIU arm relative to placebo (-6.2% relative to 17.1% respectively, p=0.002) with the 1.6 MIU arm having an intermediate value of 0.2% (significance not reported).57 At the conclusion of the study, these endpoints again favoured IFNβ but there was only a trend towards prevention of disability progression in the 8 MIU arm (35% progressed by ≥1 EDSS point sustained for 3 months relative to 46% in the placebo arm, p=0.096).58 The higher 8 MIU dose is the one that was approved for use by regulatory bodies worldwide.
Subsequently, two other formulations of IFNβ, intramuscular and subcutaneous IFNβ1a (Avonex and Rebif respectively) were reported to also be efficacious in RRMS. Unlike IFNβ1b, these molecules have the same amino acid sequence as human IFNβ and are manufactured in Chinese hamster ovary (CHO) cell lines so they are glycosylated. The pivotal trial of the intramuscular IFNβ1a product Avonex 30μg (6 MIU) once weekly published in 1996 reported a lower rate of disability progression after two years of therapy (34.9% on therapy versus 21.9% on placebo, p=0.02). The ARR of 0.67 in the treated patients was also significantly lower than the rate of 0.82 in the placebo arm (18% reduction, p=0.04) with inconsistent MRI results. Of note, this trial has been criticised because it was stopped prematurely. As such, the primary endpoint analysis only utilised 57% of the enrolled patients and subsequent analysis of this group of “2-year completers” suggested that these patients were not representative of the study population as a whole.

In the final pivotal IFNβ trial, two doses of Rebif, 22μg (6 MIU) and 44μg (12 MIU), administered subcutaneously eod were compared with placebo over the course of two years. A dose-response effect was seen with the primary endpoint of mean relapse number over two years being 2.56, 1.82 and 1.73 in the placebo, low- and high-dose arms respectively (both comparisons with placebo p<0.005). Dose-dependent slowing of disability progression and MRI lesion accumulation were also seen.

In addition to the three IFNβ formulations, the phase III results of a different compound, glatiramer acetate, were published in 1995. Glatiramer is a collection of random polymers of the amino acids glutamic acid, lysine, alanine and tyrosine in a fixed molar ratio. It was paradoxically designed to produce encephalitic symptoms in animal models.
but was discovered to actually be protective. Similar to IFNβ, the precise mechanism of action in MS is incompletely understood, however it likely that the predominant disease-modifying effect is through shifting autoreactive CD4+ T-cells into expressing an anti-inflammatory cytokine profile (ie: CD4+ Th2-type T-cells) in addition to stimulation of regulatory T-cells and CD8+ T-cell mediated killing of autoreactive Th1 CD4+ T-cells. In the pivotal trial, subcutaneous Copaxone 20 mg injected daily reduced the relapse rate over 2 years to 1.19 versus 1.68 in placebo treated patients (p=0.007). MRI endpoints were not reported in the pivotal trial, however a subsequent study demonstrated an 83% decrease in the cumulative number of T2-lesions developing relative to placebo.

Subsequent trials unsurprisingly demonstrated that Avonex, Rebif, Betaseron and Copaxone all delay the development of clinically definite MS in clinically isolated syndrome (CIS) patients. (CIS refers to patients who have had a single clinical relapse at risk of subsequently developing RRMS). IFNβ has also been shown to reduce relapse rates and slow progression in SPMS patients, however importantly this effect was only seen in those individuals who were still experiencing superimposed relapses and not in patients with a purely progressive clinical course. 

Similar to the dose-effect response seen in the pivotal trials of both Betaseron and Rebif, subsequent trials comparing various IFNβ formulations and doses also suggested high-dose IFNβ produces greater therapeutic benefits. The “Once Weekly Interferon for MS Study” (OWIMS) used single weekly doses of Rebif (22µg/6MIU and
44μg/12MIU) which were chosen specifically to bracket the weekly dose equivalent of Avonex (30μg weekly) used in the pivotal trial described above. This placebo-controlled trial demonstrated a dose-response effect on the primary endpoint of MRI disease activity at 24 weeks and other secondary MRI (but not clinical) endpoints at 24 and 48 weeks. The “Independent Comparison of Interferon” (INCOMIN) study performed in Italy compared the Betaseron and Avonex formulations of IFNβ over a two year period without a placebo arm. The primary endpoint of relapse freedom was achieved in 51% of the Betaseron and 36% of the Avonex-treated patients (p=0.03). INCOMIN was conducted in an open-label fashion, creating a significant bias affecting the primary endpoint in addition to the secondary clinical endpoints. The MRI results however, which were interpreted by blinded radiologists, also all showed significant benefits of high-dose IFNβ at both 1- and 2-years. The “Evidence of Interferon Dose-Response: European North American Comparative Efficacy” study (EVIDENCE) compared Avonex and Rebif administration over 6 months. In this trial, the clinical and MRI evaluators were blinded to treatment allocation however subjects were not, which again could have biased the self-report of relapses. Taking into account these methodological issues, the proportion of relapse-free patients at 6 months (the primary clinical endpoint) was significantly higher in the Rebif-treated patients relative to Avonex (75% versus 63%; hazard ratio of 0.70, p=0.003). Similar to INCOMIN, the blinded MRI assessments (which would not be influenced by the subject’s knowledge) also favoured the high-dose IFNβ.
While the evidence from both the randomized, fully-blinded pivotal trials that tested multiple doses of IFNβ and the follow-up OWIMS, INCOMIN and EVIDENCE trials all indicate that a dose-response effect exists, this apparent benefit may be offset to some degree by the higher likelihood of neutralizing antibody (NAb) production found relative to that in patients with low-dose IFNβ (Avonex). NAbs bind to exogenously administered IFN, removing it from the systemic circulation and thereby rendering the drug biologically inactive. Patients who are NAb-positive have been reproducibly demonstrated to have higher rates of clinical and MRI activity than NAb-negative patients. Antibodies to Copaxone, in contrast, do not interfere with the effectiveness of this DMT.

The two most recent head-to-head clinical trials of the established DMTs comparing Copaxone with either Rebif or Betaseron did not demonstrate a clinical advantage of either drug over the other. Interestingly, both of these trials suggested that MRI markers of MS progression may respond more to IFN than GA therapy, but these differences were still modest and were not seen across all of the secondary MRI endpoints evaluated. These two trials were very important in demonstrating that high-dose IFNβ and GA are equally effective on an aggregate level in RRMS. Individual patients however may certainly respond better to one medication over another.

The second-wave of DMTs was heralded by the approval of natalizumab (NZ) (Tysabri®) for use in RRMS. This second-wave is characterized by two inter-related trends. The first trend is that of higher potency agents which are more effective in
preventing both clinical and radiological progression relative to IFNβ and GA at a cost of more significant side effects. The second trend is the development of oral DMTs which will hopefully translate into better tolerability and compliance. These two trends intersect/overlap to a certain extent. Two of the oral agents studied recently, fingolimod and cladribine, are likely more potent than the four conventional first-line DMTs, although only fingolimod has been studied in a head-to-head trial. However these agents are also associated with more serious, albeit rare, side effects.

Natalizumab was shown to be effective in RRMS subjects in two separate double-blinded trials published simultaneously in 2006.\(^{90,91}\) NZ is a humanized monoclonal antibody directed against the α4 subunit of α4β1-integrin present on circulating T-lymphocytes. Binding of NZ prevents α4β1-integrin from binding to vascular-cell adhesion molecule 1 (VCAM-1) which is expressed on endothelial cells. This interaction therefore blocks a necessary step in lymphocyte transmigration, preventing NZ-laden T-lymphocytes from entering the CNS.\(^{92}\) The first study was a placebo controlled trial which demonstrated a relative risk reduction [RRR] of 68\% (p<0.001) in the ARR after 1 year and a RRR of 42\% (p<0.001) of treatment in disability progression after 2 years.\(^{90}\) Significant results were also obtained with the MRI endpoints, including an 83\% reduction in the development of new T2-lesions. In the second trial, NZ or placebo was added-on to subjects’ pre-existing Avonex therapy.\(^{91}\) Similar RRRs in the 1- year ARR (54\%, p<0.001) and disability progression (24\%, p=0.02) were seen as in the placebo-controlled trial.\(^{91}\)
Despite not being studied in a head-to-head fashion with the conventional DMTs, it was initially expected that the apparent increased efficacy and relative ease of administration (monthly IV infusions) would make NZ supplant IFN/GA therapy. However, shortly after the drug was licensed, two cases of progressive multifocal leukoencephalopathy (PML) were diagnosed in two of the NZ-treated patients enrolled in the add-on Avonex trial and another in a Crohn’s disease trial patient. In the post-marketing setting to date there have been a total of 95 cases of PML and 20 deaths. The approximate rates of PML are 0.01, 0.41 and 1.64 per 1000 patients in the first, second and third years of therapy respectively with an overall risk of 1.16 per 1000 patients. Currently, therefore, this drug is typically only recommended for patients who have an unsatisfactory response to IFN or GA treatment. In such patients with significant breakthrough disease, the risk/benefit ratio would suggest that the low risk of PML is exceeded by the higher risk of ongoing/worsening disability secondary to MS itself.

In March of 2011, fingolimod (Gilenya®) became the sixth drug to be licensed in Canada for use in RRMS. This is a significant step forward in treatment as this is the first oral DMT available. Fingolimod is an oral sphingosine-1-phosphate (S1P) receptor modulator felt to have an antagonist function as fingolimod binding to S1P downregulates the receptor on lymphocyte cell surfaces. As binding of endogenous S1P to the S1P1 receptor is a requisite step in lymphocytic egress from secondary lymphoid organs and lymph nodes, fingolimod’s ultimate mechanism of action is to trap these cells within the lymphoid tissues.
The two pivotal phase III trials of fingolimod were published simultaneously in 2010.\textsuperscript{102,103} The first was a two-year long, three arm trial comparing two doses of fingolimod to placebo. At the conclusion of the trial, ARRs were decreased by 54% and 60% in the low and high-dose treatment arms respectively relative to placebo (p<0.001 for both comparisons).\textsuperscript{102} Accumulation of disability and MRI secondary endpoints were also significantly lower in both groups of fingolimod treated patients. The second fingolimod trial is also notable because this is one of the few head-to-head trials conducted in MS, and the first to be a phase III trial explicitly designed to launch a novel agent. In this one-year long study, both low and high-dose fingolimod reduced the ARR to a greater extent than Avonex (p<0.001).\textsuperscript{103} Secondary MRI endpoints also favoured fingolimod, although no differential effect on disability progression was seen.

Although fingolimod’s side-effects do not seem to be of the same magnitude as PML, it still carries with it greater risk than the conventional DMTs. Bradycardia, mild increases in blood pressure and decreases in forced expiratory volume typically occur early in the treatment course.\textsuperscript{102,103} Of more concern, single fatal cases of disseminated varicella and herpes simplex encephalitis have occurred in addition to an unusual and unexplained case of hemorrhagic encephalitis in which the subject was left with significant neurological deficits.\textsuperscript{103,104}

The results of the phase III trial of the oral agent cladribine was reported simultaneously with those of fingolimod in 2010.\textsuperscript{105} Cladribine causes a profound and long-lasting lymphopenia through selective targeting of lymphocytic DNA repair proteins, triggering
apoptosis. The ARR was significantly reduced over the course of the trial in both treatment arms (p<0.001 for both comparisons) with significant reductions in disability progression and MRI activity as well. Cladribine is a very appealing treatment from a convenience perspective as only a few tablets are required each year. However, the development of unusual cancers (both malignant and benign) in 2.2% of treated patients coupled with concerns about whether the profound and irreversible immunosuppression created by the drug would cause delayed complications led to the licensing application being rejected by both the European Medicines Agency (EMEA) and the Food and Drug Administration (FDA). This decision has led the manufacturer to cease production of the drug and it is has been withdrawn from the market in the two jurisdictions (Australia and Russia) where it was licensed (EMD Serono Canada, personal communication).

Other therapies which are in the developmental pipeline include the oral agents teriflunomide, laquinimod, and fumarate and the monoclonal antibodies ocrelizumab, daclizumab and alemtuzumab. With the exception of alemtuzumab, these therapies have not been associated with worrisome side-effect profiles in the phase I/II trials to date, although PML has occurred with administration of rituximab, a similar molecule to ocrelizumab, in rheumatological patients. Alemtuzumab is associated with a ~20% risk of autoimmune thyroid disease and 6 patients in the phase II RRMS trial developed idiopathic thrombocytopenic purpura.
Returning to the four first-line “conventional” DMTs (Avonex, Rebif, Betaseron, Copaxone); the trial evidence to date would suggest that on a population level, Betaseron, Rebif and Copaxone are all essentially equally efficacious. Avonex in contrast, is likely less effective than the higher-dose Betaseron and Rebif formulations, albeit with the caveats detailed above. It is important to acknowledge that these trials have all examined patients for a relatively short time-span (typically 2-3 years) of what is a decades-long disease process. Extrapolation of this clinical trial data has been problematic at best as it is impossible to prove that these agents prevent the development of fixed disability over the lifetime of the patient—which is the real outcome of interest to both patients and clinicians.

Long-term extension studies using the original pivotal trial patient populations have been performed for all four of the first-line therapies with follow-up extending for upwards of 16 years. These trials provide some limited information on the long-term safety of these DMTs and also that the subjects who have remained on DMT have done well on therapy. However these extension studies are inherently biased to generate “positive” efficacy results because of the self-selection of subjects who are tolerating therapy and doing well: those subjects who have significant break-through disease activity and/or side-effects will leave the extension study and are lost to follow-up. In contrast, one extension study that was able to assess ~70% of the subjects originally enrolled in the initial Betaseron study did not find any difference in either clinical or MRI outcomes between those initially randomized to the placebo or active treatment arms after 16 years. The exception was a seeming dose-dependent decreased
mortality in treated patients, although the overall number of deaths was quite small and this finding could have been due to chance. Given that the subjects initially treated with placebo or Betaseron over the five-year long trial were both later treated with multiple different therapies for varying lengths of time over this 16-year period, any beneficial effect of Betaseron treatment could easily have been obscured by the heterogeneity of the data. In the same way that the other extension studies cannot “prove” long-term efficacy, this study cannot “disprove” it.

Propensity scoring (PS) is a statistical technique that attempts to replicate the randomization of RCTs when examining nonrandomized, “real-world” observational datasets. PS methods have been used to suggest that IFNβ helps slow disease progression in RRMS, and that early treatment is beneficial. PS matches treated/untreated patients on known confounders using regression analysis to create a “virtual” control group: essentially using statistical manipulation of the dataset to create control/treatment groups that are balanced with respect to demographic and other characteristics. This mimics the effect of randomization in a RCT which (usually) serves to balance confounders. The main disadvantage of PS is that it cannot be used to balance either unknown or unmeasurable confounders (ie: genetic determinants of MS severity). This was demonstrated in the long-term extension study of Copaxone in which the authors showed that dropouts and long-term DMT users could be matched in a PS analysis; however the dropouts still developed more severe MS and left the study.
Statistical modelling of patient outcomes in the DMT era relative to the time-period before these agents were available has also been performed using the 25-years of data available in the Dalhousie Multiple Sclerosis Research Unit database.\textsuperscript{127,128} These studies suggest that there has been a change in the “natural history” of MS since the introduction of DMTs. Such research can only be considered hypothesis-generating however due to the selection bias leading only some patients to take DMT, that MS care has evolved in general over the years, and that the demographics of MS are changing due to earlier diagnosis at milder stages of disease.

The discussion of long-term effectiveness is also complicated by the question of whether or not the clinical and MRI measures used in the trials to date are valid surrogates for the main outcome of interest (prevention of fixed disability over the long-term).\textsuperscript{129,130} All of these factors has lead to great debate as to the real-world utility of DMTs over the long-term matches the demonstrable effectiveness noted in the clinical trials.\textsuperscript{131,132,133}

\textit{Treatment of MS: Use of DMT in Routine Clinical Practice}

Given that the MS treatment landscape is set to dramatically alter with the introduction of the novel agents reviewed above, it would be worthwhile to assess current DMT utilization patterns. Along with the debate over whether low-dose (less NAbs) or high-dose (dose-response effect on efficacy outcomes) IFNs are superior, there are ongoing differences of opinion amongst MS-specialists both over the relative merits of the three IFNs and Copaxone (hereby grouped as the “first-line DMTs”) and over their effectiveness as a group in forestalling/preventing the development of irreversible
disability. Consensus guidelines acknowledge the apparent IFN dose-response effect seen but do not explicitly argue for IFN dose-escalation as a strategy for treatment failure.\textsuperscript{50} Expert opinion papers written after the introduction of natalizumab due suggest that this agent, in addition to mitoxantrone or cyclophosphamide chemotherapy, should be used in aggressive MS).\textsuperscript{99,134}

Table 2: DMT Costs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Brand Name</th>
<th>Annual Cost\textsuperscript{*}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interferon</td>
<td>Avonex®</td>
<td>$20,170</td>
</tr>
<tr>
<td></td>
<td>Betaseron®</td>
<td>$20,830</td>
</tr>
<tr>
<td></td>
<td>Rebif® (22 \textmu g)</td>
<td>19,800</td>
</tr>
<tr>
<td></td>
<td>Rebif® (44 \textmu g)</td>
<td>24,000</td>
</tr>
<tr>
<td></td>
<td>RebiSmart® autoinjector</td>
<td>$22,630</td>
</tr>
<tr>
<td>Glatiramer acetate</td>
<td>Copaxone®</td>
<td>$16,580</td>
</tr>
<tr>
<td>Natalizumab</td>
<td>Tysabri®</td>
<td>$30,280</td>
</tr>
</tbody>
</table>

\textsuperscript{*}Canadian Dollars; from reference\textsuperscript{135}

From a societal level, the issue of how the evidence (including the lack of evidence) for DMT use is being applied by neurologists is of great importance. The first line DMTs all cost in the order of $20,000 dollars annually (range ~$16,000—$24,000), with natalizumab exceeding these costs by approximately a third (Table 2).\textsuperscript{135} The worldwide prevalence and incidence of MS is also increasing.\textsuperscript{136} This increasing prevalence would suggest that the need for DMT and the associated societal cost will also continue to increase.

No study has comprehensively assessed the incidence or prevalence in Canada as a whole. However, the predominantly provincially-based studies to date have demonstrated some of the highest burdens of MS in the world.\textsuperscript{137,138,139,140,141} The most recent published Canadian study reported an age-adjusted prevalence of 226.7 per 100,000 population in Manitoba in 2006.\textsuperscript{141} Using the same methodology as the
Manitoba study, the prevalence of MS in Ontario was found to be 178 per 100,000 population (unpublished data acquired simultaneously with this research project from the Institute for Clinical Evaluative Sciences [ICES] Health Care Databases).

While such administrative database studies can be used to determine the number of MS patients, determining the number with RRMS or the number who should (or could) be on DMT is more problematic. Even amongst the RRMS population, some patients with “benign MS” might not need to be treated, some might have aggressive disease requiring therapy with second-line agents such as cyclophosphamide, some might refuse treatment even if clinically indicated and others might not tolerate therapy. These issues have all complicated assessments of DMT “cost-effectiveness” which need to make numerous assumptions including how effective DMTs are over the long-term, leading to wildly divergent calculations.142,143,144,145,146,147,148

A recent study examined prescriptions of the four first-line DMTs in Canada between 2002 and 2007.149 The authors demonstrated that the annualized prescription rate climbed from 3.9 to 5.1 per 1000 Canadians over that time period; corresponding to an increase in cost from $187 to $287 million dollars per year. In 2007, Ontario had one of the lower provincial prescription rates at 3.9/1000 (in contrast to the lowest rate of 2.0/1000 in Nova Scotia and the highest at 9.0/1000 in Manitoba).149 While such data are important, they do not assess the specifics of how these DMTs are utilized on an individual level: namely what prescriber and patient characteristics are associated with DMT prescribing?
Given the similarities and differences detailed above between the four first-line RRMS DMTs; without any clinical evidence to support one particular drug over the others in all circumstances and the lack of a evidence-based “treatment algorithm” to dictate where, when and in whom each specific DMT is best used, the question of how these medications are prescribed naturally arises. Individual patients may favour certain treatments (eg: Avonex because fewer needles, Copaxone because no bloodwork is needed, high-dose IFN over low-dose IFN because of perceived efficacy benefit). Prescribers may also favour certain therapies because of perceived better risk/benefit ratios. Non-MS-specialist neurologists may also focus on one or two of the four first-line DMTs that they feel more comfortable prescribing. In contrast, specialists may be expected to treat liberally with all four first-line DMTS even if they have an individual preference purely because of the high-volume of patients seen in MS clinics.

In MS, prescribing patterns have usually been examined from the patient perspective by examining which patient characteristics are associated with receiving a script for DMT. Some of these analyses have used administrative databases collected by health maintenance organizations (HMOs) in the United States or the American Medicare program. Others have been performed through direct interviews of MS patients or through analysis of the North American Research Committee on Multiple Sclerosis (NARCOMS) registry (an online repository of information from MS patients who input their own clinical data). These latter studies are useful in showing gaps in patient care or patient access to neurologists in general and/or
DMTs, however they all suffer from the limitations of selection bias and inaccurate reporting inherent in questionnaire or interview based research protocols.

In contrast, little research has been done looking at prescribing from the physician or neurologist perspective: namely what characteristics of the prescriber are associated with higher rates of DMT use, either in aggregate or on an individual DMT level. One study examined how female neurologists in the US and Canada counsel female patients on DMT discontinuation during pregnancy.\textsuperscript{157} This study was performed using a mailed questionnaire (35% response rate), examined only one issue related to prescribing and did not compare whether male and female neurologists counselled female MS patients differently as only female neurologists were studied.

Administrative databases have also been used to research physician prescribing practices to MS patients in Nova Scotia, Wales and Norway.\textsuperscript{158,159,160} The Norwegian study attempted to indirectly assess the uniformity of neurologist DMT prescribing by matching data from the national Norwegian Prescription Database to the estimated MS prevalence rates in the eight counties where this information was available.\textsuperscript{158} The other eleven counties in Norway were excluded from the analysis. The authors found markedly variable rates of DMT, ranging from 19-47% of patients (average 28%), across the country. The authors concluded that probably some neurologists were either over- or under-prescribing DMTs. This study however has serious limitations including the fact that neurologists in certain counties may be prescribing for patients who live in other regions of the country. The percentages of MS patients in certain counties who are
candidates for DMT may also vary (ie: more patients with active RRMS may live in the counties with higher prescription rates). This study also only examined DMTs in aggregate and did not examine whether individual DMTs were more commonly prescribed by certain neurologists.

The Welsh study examined the rates of general medications (ie: not DMTs) by Welsh general practitioners. This case-control study compared the rates of prescriptions given to MS patients to those given to non-MS-patients. The Nova Scotia study linked the records of senior citizens with MS seen at the Dalhousie Multiple Sclerosis Research Unit to the provincial pharmacare program to contrast the cost of medications in this population to that of seniors without MS. They found that pharmacare costs were 65% higher for seniors with MS. While these two latter studies used administrative databases, they studied prescriptions in aggregate and did not focus on neurologists (indeed, the Welsh study only looked at GP prescribing). Furthermore, none of these three studies attempted to examine how DMT prescribing correlated with the characteristics of the prescribing physician.

Given the combination of different efficacy information and side-effect profiles, coupled with a significant cost-differential between the four first-line DMTs, it would be useful to know if prescribing practices vary by prescriber-characteristics including basic demographics, geographical location and degree of MS specialization. No population-based study has assessed if neurologist practice settings or demographic characteristics are associated with different DMT-prescribing patterns.
This research was specifically spurred by the anecdotal observation that Avonex seemed to more commonly prescribed by community neurologists who subsequently referred patients to the St. Michael’s Hospital MS Clinic in Toronto, Ontario. If indeed there was a markedly disproportionate use of the lowest-dose IFNβ formulation, this would suggest that MS patients in Ontario would benefit to increased access to MS specialists to ensure that appropriate DMT choices were being made. To study this issue in the province of Ontario required access to individual DMT prescription data and the ability to link such prescriptions to physician-provider information. The next sections detail how this information is available through the Institute for Clinical Evaluative Sciences (ICES) databases and the methodological techniques used to analyze the data.

Institute for Clinical Evaluative Sciences Health Care Databases

ICES is an independent research facility focused on studying health care resource utilization and health outcomes in the province of Ontario. ICES’ data holdings consist of a series of health care databases covering physician-visit claims (Ontario Health Insurance Plan [OHIP]), acute care, rehabilitation hospital and emergency room information including responsible diagnosis, length of stay and outcome data and drug prescription data. All of these databases can be linked anonymously through patient and physician record numbers to provide a more comprehensive picture of health care in the province.
Prescription claim data is stored in the Ontario Drug Benefit (ODB) program database. The ODB program records all claims for medications made at a pharmacy for drugs covered by the ODB program. Each claim represents in essence a visit to the pharmacy to either pick up a new prescription or a refill of an existing prescription. Therefore, a year-long prescription written by a physician as one-month’s worth of drug with eleven refills would be entered into the ODB database as a total of twelve claims.

Three separate government-funded prescription-drug programs are included within the overall umbrella of the ODB. The first consists of all prescriptions filled by Ontario residents 65 years or older as this group has fully publicly-funded prescription coverage. Since this database covers virtually all the scripts filled in the province by those 65 years or older, this is the typical group studied in previous ICES research studies of drug utilization because it allows for a more comprehensive sampling. Secondly, Ontario residents who are on social assistance (the Ontario Disability Support Plan [ODSP]) are also automatically enrolled in the ODB. The third important group of prescriptions included is those funded through the Trillium Drug Program (TDP). The TDP will cover the costs of medications that are listed in the general Ontario drug formulary and also ones (such as the DMTs) which are not on the formulary but can be requested specifically by a physician through the Exceptional Access Program (EAP). The TDP and EAP exist to defray the costs of expensive medications for Ontario residents younger than 65 years old not on social assistance who do not have adequate private drug coverage. These Ontario residents would otherwise not be able to start such therapies because either they do not have full private drug coverage (ie: through their workplace) or the drug coverage
they do have is insufficient to cover the costs of their medications. The TDP deductible is 4% of the patient’s net household income. Given that the annual cost of DMT ranges from $16,000 to $24,000, the TDP is an important program to ensure that cost does not prevent patients from using necessary medications. For MS patients without 100% private drug coverage, application for funding to the TDP allows for the financial cost to the patient and his/her family to be minimized. This occurs either through full TDP drug coverage of the drug cost, minus the deductible, for someone who is self-employed with no private drug plan or jointly through the TDP and a private drug plan in someone who has partial private coverage. As an example, a single MS patient with a net household income of $60,000 would have a deductible of $2,400. Assuming 80% private drug coverage and a DMT cost of $20,000, by applying to the TDP the patient would be saving $1,600/year as they would only be paying the $2,400 deductible and not the full $4,000 amount not covered by his/her private drug plan.

Given that DMTs are only used in RRMS, which tends to be the predominant clinical phenotype early in the course of MS as described previously, very few patients would be expected to be in the “medicare” group of 65 years old or older. The vast majority of DMT scripts available for analysis in the ODB database originate from either the ODSP for MS patients on social assistance or through the TDP. When a patient picks up a script from the pharmacy, if that medication is being funded solely through a private drug plan, paid for directly by the patient or jointly by private/self-pay these scripts would not be captured by the ODB database. The latter group of private/self-pay would include those whose income levels are high enough that the 4% deductible to pay for TDP coverage is
equal to the cost of paying the remainder of the drug cost themselves. The implications of this with respect to data integrity, database comprehensiveness and generalizability are addressed in more detail in the discussion. Figure 1 outlines the various DMT payment methods in Ontario and whether a given script will be captured by the ODB database.

![Figure 1: Private and public drug coverage schemata](image)

Patients can apply directly to the TDP program, but to get funding for specific medications through the TDP, they have to meet certain eligibility criteria established by the Ontario government. With respect to the DMTs, these criteria have evolved over the years, most recently with the addition of natalizumab to the EAP in late 2009. A patient’s treating physician fills out paperwork stating the clinical reason for prescribing a
DMT and how the patient meets the criteria for TDP coverage. An independent physician reviewer for the Ontario Ministry of Health then either approves or rejects the request for funding. Table 3 lists the criteria for first-line DMT funding in Ontario. Of note, the criteria for reimbursement rely solely on clinical and not MRI characteristics.

It is important to emphasize that this limitation of the drug database information available in Ontario at the individual-patient level is one of the reasons why previous ICES studies of drug utilization have focused on Ontarians aged 65 years or older. One of the objectives of this research on a practical methodological level was to assess whether studies of prescribing in those younger than 65 years are feasible despite the limitations of the Ontario ICES drug-database. If this were to be the case, it would extend the ability of ICES researchers to study prescribing in younger populations in Ontario.

The main purpose of this research was to assess how neurologist characteristics correlate with DMT prescribing patterns. Examination of the ICES ODB data would allow this to be done on a provincial level. Given that this study was interested in examining the distribution of DMT prescriptions by physician characteristics, a decision was made to use Lorenz curves. Lorenz curves allow for the degree of inequality in a population (in this case the inequality in neurologist DMT prescribing rates) to be compared. There are very few published studies using Lorenz curves to examine drug utilization. A further methodological aim therefore was to demonstrate the utility of Lorenz curves in studying prescribing patterns.
## Table 3: EAP "Section 16" Reimbursement Criteria for first line MS DMT

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Criteria for reimbursement</th>
<th>DMTs covered</th>
</tr>
</thead>
</table>
| Clinically Definite Multiple Sclerosis (CDMS): | Initial Application:  
  - date and details of the most recent neurological exam (≤ 90 days); and  
  - dates and details (e.g., exam findings) of ≥2 clinical attacks, including 1 clinical attack within the past year; and  
  - EDSS ≤ 6*  

  Renewals:  
  - description of the patient’s clinical course in the last year, including details of all attacks; and  
  - date and details of the most recent exam (≤ 90 days); and  
  - EDSS ≤ 6*  | Avonex®  
  Betaseron®  
  Rebif®  
  Copaxone®* |
| Clinically Isolated Syndrome (CIS) | • date and details of the most recent neurological exam (≤ 90 days); and  
  • date and description of CIS within the last 12 months; and  
  • EDSS ≤ 6. | Avonex®  
  Betaseron®**  
  Copaxone®** |

*EDSS ≤ 5 cutoff for Copaxone  
** Betaseron added to formulary for CIS in 2008, Copaxone in 2011  
NB: requests for patients with CDMS/CIS are reviewed by external medical experts to determine that the clinical information provided meets these criteria  
Adapted from Ontario Ministry of Health formulary.163

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**Lorenz Curves and Gini Coefficients**

What have become known as “Lorenz curves” were initially described by M.O. Lorenz in a short 1905 paper explaining their potential use in assessing the income or wealth distribution of a population.164  
Lorenz curves are constructed by plotting the cumulative population along the x-axis and the cumulative wealth along the y-axis.  
A sample Lorenz curve is shown in Figure 2 (in the original manuscript, Lorenz had the axes flipped from...
the conventional usage that is depicted in the figure). In a population where each individual has the same income or wealth, the two cumulative proportions would both increase at the same rate and the Lorenz curve would fall along the so-called line of equality. As the degree of income inequality increases, the Lorenz curve will skew or bow further away from the line of equality, approaching the theoretical “line of inequality” (which is typically not shown on Lorenz curves) where one individual would have 100% of the income or wealth in that population. The elegant simplicity of the Lorenz curve has made it the most commonly used income inequality measure in the economics literature and has been described as “the workhorse of income inequality analysis.” As Dalton acknowledges, the Lorenz curve was described independently by Séailles in 1910 and was sketched out in the same year as Lorenz, although not as completely, by Sir Leo Chiozza Money.

Nested Lorenz curves representing different populations are an excellent visual representation of differential inequality. In addition, as the curves are constructed using proportions or percentages, different size populations can be easily compared to one another, with the “inner curve” closer to the line of equality representing a population with a more egalitarian distribution of wealth.

Lorenz himself did not describe in detail the mathematics behind constructing his curves and no quantitative measure of the degree of income inequality that was visually depicted in the curve bowing was provided. In 1912, Corrado Gini described how to represent the degree of inequality as the ratio of the area between the line of equality and the curve and
the total area under curve (Figure 2). This is called the Gini coefficient or Gini index where \( G = \frac{A}{A+B} \), and is typically recorded as a number in range 0-1. Gini’s Italian-language monograph was not widely cited until Dalton’s key paper in 1920 which was the first English discussion of Gini’s contribution to the analysis of Lorenz curves.

![Lorenz Curve Diagram](image)

**Figure 2: Basic Lorenz curve (adapted from De Maio)**

The Gini coefficient provides a quantitative measure to compare and contrast different Lorenz curves, with a larger Gini representing a greater degree of skew and subsequently a greater inequality in the distribution of wealth. In addition to, or in place of the Gini co-efficient, Lorenz curves are often interpreted by selecting any quantile along the x- or
\( y \)-axes to characterize the concentration of the value of interest in the population (ie: “\( y \% \) of wealth is held by \( x \% \) of the population”). 172

To describe the mathematics behind the construction of a Lorenz curve and its associated Gini coefficient in more detail, the traditional income inequality usage will serve as an example. For a population of \( n \) population units (in this generic formulation, this “unit” may be an individual, family, city or other grouping) ranked in order by wealth from the poorest to richest, each population unit as represented by \( x_i \) has a wealth given by \( y_i \) where \( i=1,2,\ldots,n \), such that \( y_{i-1} < y_i < y_{i+1} \). To construct a Lorenz curve for such a population, the cumulative proportion of the total population will be plotted along the \( x \)-axis and the cumulative proportion of the total wealth will be plotted along the \( y \)-axis. The Lorenz curve will be the interpolation of the points \( L(X_i, Y_i) \) where \( X_i \) is the cumulative proportion of the population at the \( i \)th population unit and \( Y_i \) is the cumulative proportion of wealth held by all the population units up to and including the \( i \)th population unit. These can be formally depicted as

\[
X_i = \frac{x_1 + x_2 + \ldots + x_i}{x_1 + x_2 + \ldots + x_n}
\]

\[
Y_i = \frac{y_1 + y_2 + \ldots + y_i}{y_1 + y_2 + \ldots + y_n}
\]

The total area between the line of inequality and the Lorenz curve constructed from these interpolated points can be calculated by adding the areas of all the individual trapezoids created between the line of equality and the Lorenz curve.173,174 This area can be used to
calculate the Gini index as above. The overall formula for the Gini can be reduced algebraically to 

\[ G = \sum_{i=1}^{n} (X_i \times Y_{i+1}) - \sum_{i=1}^{n} (X_{i+1} \times Y_i) \]

using the coordinates \( X_i \) and \( Y_i \)\(^{175}\).

Alternatively, rather than use the cumulative proportion \( X_i \), the Gini can be calculated using the proportion or fraction of the total population associated with each \( y_i \) value denoted here as \( x'_i \) where \( x'_i = \frac{X_i}{x_1 + x_2 + \ldots + x_n} \). The Gini can therefore be calculated as

\[ G = 1 - \sum_{i=1}^{n} [x'_i \times (Y_i + Y_{i-1})] \]

Of note, when each “unit” of the population is one individual, this second equation for the Gini coefficient is easy to calculate as each value of \( x'_i \) is equal to \( \frac{1}{n} \) where \( n \) is the number of individuals in the population.

Calculation of the standard error and associated 95% confidence intervals (CIs) for Gini coefficients has been described by various authors, all of whom have used some variation on bootstrapping or jack-knifing methods.\(^{176,177,178,179,180,181,182}\) The method used by Ogwang is to construct multiple Lorenz curves based on the sample data with each curve not using one of the individuals in the sample population. The distribution of the Gini coefficients (termed “pseudo-Gini coefficients”) generated from these Lorenz curves can be used to calculate 95% CIs and the standard error of the Gini coefficient.\(^{179}\) Ogwang gives the formula for the variance of the Gini as

\[ \text{var}(G) = \left( \frac{n-1}{n} \right) \sum_{i=1}^{n} \left( G(n,i) - \overline{G}(n) \right)^2 \]

where \( G(n,i) \) is the pseudo-Gini coefficient calculated with the \( i \)th point removed from the Lorenz curve calculation and \( \overline{G}(n) \) is the
mean of all the $G(n,i)$ terms. From this, the standard error of $G$ can be calculated simply as $SE(G) = \sqrt{\text{var}(G)}$. The standard error can be used to calculate the 95% CIs under the assumption that $G(n,i)$ follows the normal distribution using the formula

$$95\% \text{CIs} = G \pm \left( \frac{Z_{\alpha}}{2} \times SE(G) \right)$$

where $\alpha = 0.05$ and $Z_{0.05} = 1.96$.

Despite the intuitive visual appeal of the Lorenz curve as a measure of inequality in a population and the development of the mathematical techniques to compare these curves as discussed above, they do have some limitations. It is unclear how to compare Lorenz curves that cross each other. Differently shaped Lorenz curves can also have the same Gini coefficient. Furthermore, no one has yet developed a useful technique to allow multivariate modelling of Lorenz curves.

*Application of Lorenz Curves in Biomedical/Epidemiology Research*

After its initial introduction in the field of economics, the Lorenz curve was utilized in other social sciences to measure health inequality, population geographical concentration and population segregation. Over time however, this statistical methodology has been used in a wide variety of other fields including basic science and health care resource distribution or utilization. This section will review the literature on these applications of the Lorenz curve, culminating in a discussion of the work published to date using Lorenz curves to examine medication prescribing practices.
Lorenz curve and Gini coefficient statistical techniques have been used quite extensively to evaluate the geographical distribution of physician and other healthcare providers. These analyses have adapted the traditional “cumulative percentage of the population” x-axis information in the original economics formulation of the Lorenz curve to calculate the rural/urban distribution of medical practitioners. Two papers have examined this issue in Alberta. In the first, Northcott found that between 1956 and 1976 general practitioners (family doctors, paediatricians) were more evenly distributed across the province relative to a more urban concentration of specialists—interestingly these results did not change much over the two-decade period examined. In a subsequent analysis of Alberta health-care practitioners, including dentists and physicians, similar findings were noted between 1987—1991. Similar research has been done worldwide, variously exploring the distribution of specific types of physicians or other medical resources at the local county or country level or comparing and contrasting different jurisdictions.

Lorenz curve analysis has also been used to examine health care resource utilization, or alternatively what changes would need to be made to health care delivery to ensure more equitable access. For example, one study examining coronary revascularization procedures in London, England found that the distribution of publicly funded procedures was markedly more equitably distributed across the city (Gini = 0.12) than privately funded procedures (Gini = 0.35). The latter were more common in regions of the city with the lowest need, which the authors indicated demonstrated that private health care did not act to “relieve” stress on the public health system.
Lorenz curve analysis has also been proposed as a useful epidemiological tool to examine exposure/disease associations at the population level. The authors of these two papers created hypothetical Lorenz curves that depicted projected “disease” rates at different “exposure” levels. They then demonstrated how these curves could be used to complement standard relative and attributable risks and also how these risks could be calculated from the Lorenz curve itself.

Dental health research has made extensive use of the Lorenz curves to map the distribution of tooth disease within populations. One early application in Danish teenagers demonstrated that the skew in the distribution of diseased, missing or filled surfaces (DMFS) per mouth increased over time with 20% of the population having 40% of the caries in 1980 but 70% in 1985. Regional and temporal skews have been identified in other countries and linked to both socioeconomic status and tapwater fluoridation status.

Lorenz curves have also been used to explore geographical patterns of infectious disease. Studies of sexually transmitted disease (STD) rates across Manitoba and of Seattle, Washington both showed dramatic geographical skewing. These studies suggest that prevention strategies need to be optimized geographically depending on the specific disease (ie: targeted interventions in certain communities versus a more-broadly implemented campaign). Italian researchers calculated the cumulative burden of tick infestations in a wild mouse population as part of a study to assess variables influencing
tick-borne encephalitis rates in sheep and humans. They found that approximately 20% of mice carried 80% of the tick parasite burden in the population. Lorenz curves have also been used to study rates of campylobacter infections across Manitoba, patterns of malarial cases in Peru and STD risk in Britain and Pakistan. Other research groups have also adapted the basic Lorenz technique to investigate other population health issues. This research has variously examined fertility and contraception in Jordan, obesity rates across Canada, motor vehicle accidents (MVAs) in the United States, Dubai and Qatar.

One paper from a German hospital used Lorenz curves to calculate the cumulative number of surgical procedures performed against the cumulative number of indications/diagnoses using the standard International Classification of Diseases 9th revision (ICD-9) coding of patients’ charts. They found that the Lorenz curves for general surgery, trauma surgery and neurosurgery were all markedly skewed towards the line of inequality (visual inspection, no Gini coefficients were calculated). The authors’ concurrent chart review indicated that this skew was an artefact of the ICD-9 coding system which did not reflect the breadth of different operations and types of conditions treated surgically.

Another paper used Lorenz curves to assess the degree of equality of clinical trial patient recruitment at different study sites. Trials with a greater number of participating study sites, more prolonged recruitment periods and longer follow-up periods were all
associated with more unequal patient recruitment with a minority of sites contributing a greater proportion of patients.

**Lorenz Curves in the Analysis of Medication Prescribing**

The first application of Lorenz/Gini inequality testing to drug utilization was performed by Hallas and Nissen who examined prescription drug consumption in a single Danish county.\(^{225}\) The authors had access to a central registry of all prescriptions filled in that region. They were able to show a marked skew with 20% of adults filling over 90% of the scripts. Through linking these medications to the specific prescriber and medication they were able to show that individual “heavy users” tended to utilize a specific class of medications and tended to overwhelmingly obtain these scripts from a single prescribing physician. This implied that the marked skew seen was because most medications were given to the minority of the population with significant medical issues rather than because of inappropriate prescribing practices. Another paper from the same research group constructed Lorenz curves plotting the cumulative percentage of users against the cumulative percentage of drug volume for 22 different classes of medications.\(^{226}\) While Gini coefficients were not calculated, the authors reported the cumulative number of scripts filled for the 1\(^{st}\) and 50\(^{th}\)-percentiles of patients using that particular class of medication. Interesting differences were seen with some medications (such as thyroid replacement and oral anticoagulants) having more uniform distributions than others (such as inhaled beta-agonists and opioids). A South African study of drug adherence
examined the uniformity of methylphenidate dispensation amongst those patients prescribed the drug. The authors found little skew with the Lorenz curve approximating the line of equality (70% of patients used 66% of the prescribed drug). Lorentz curves were used in a study of antibiotic exposure in a Hungarian county which plotted cumulative antibiotic exposure against the cumulative number of patients prescribed antibiotics. The authors reported that 1% of antibiotic users consumed 6.9% of the total amount of antibiotics prescribed, however no Gini coefficient was calculated.

The study of medical prescribing in Nova Scotia seniors with MS described previously also used Lorenz curve analysis. The total medication costs for the 52 seniors with MS in 1993-1994 (average $975/patient) was unequally distributed with a Gini coefficient of 0.489, however this value was similar to the Gini in those seniors without MS of 0.508 (average $599/patient). This meant that while average medication costs were higher in the MS patients, the skew in medication cost distribution was comparable to that seen in the general population of seniors in that province.

**Summary and Purpose**

As mentioned previously, the initial observation which prompted this work was the anecdotal impression that Anovex prescriptions were disproportionately over-represented in the group of RRMS patients who were started on a DMT by a community neurologist and only later referred to the St. Michael’s Hospital MS Clinic. The main clinical and health resource utilization purpose of this work was therefore to assess how neurologist characteristics correlate with DMT prescribing patterns with the main hypothesis being
that Avonex prescriptions would be over-represented amongst non-MS-specialist neurologists relative to the other three first-line DMTs. Analysis of the ICES ODB data would allow this to be done on a provincial level. Of note, unlike other provinces, Ontario—being the most populous—has the largest number of dedicated MS clinics. Additionally, unlike other provinces where DMT prescribing can only occur in these MS clinics, community neurologists can prescribe DMT and apply for EAP/Trillium funding. Ontario therefore provides a unique opportunity to assess geographical prescribing patterns in addition to specialist/generalist neurologist prescribing.

Besides this specific disease-related issue, the methodological interest was in expanding ICES database analysis by assessing the feasibility of analyzing DMT: if this research generated meaningful results despite not being able to track every script in the province, this could open up ICES analyses more broadly to assess prescription use in other diseases of younger adults or other populations apart from the 65 years and older cohorts that have been typically examined. An inter-related methodological objective was to explore the utility of Lorenz curves in testing hypotheses about drug prescribing/utilization patterns given that this technique has been used only sparingly for this purpose in the published literature to date.
Research Aims and Hypotheses

MS is treated by a wide spectrum of neurologists ranging from community-based generalist neurologists to academic MS-specialists who are affiliated with tertiary hospital based MS Clinics. Differences in DMT prescribing patterns between different groups of neurologists have not been previously explored. This is of interest given the differences in efficacy, cost and side effects of the four first-line DMTs (Avonex, Betaseron, Rebif and Copaxone). Of the three interferons, Avonex has the advantage of fewer injections, however the dose-response effect seen in the comparator trials suggests it is not as beneficial as Betaseron or Rebif. Copaxone in contrast has been shown to be equally effective as Betaseron and Rebif, however it costs approximate $4000 to $8000 dollars/year less.

This project was therefore designed to examine how DMT is prescribed for RRMS patients in Ontario and to try and elucidate if any correlations exist between prescribing neurologist characteristics and patterns of DMT prescriptions. To accomplish this task, the anonymized, linked Ontario health-care resource databases stored at ICES were used to retrospectively link demographic and geographical characteristics of Ontario neurologists to DMT prescription data obtained from the ODB Plan for the year 2009.

In particular, this research sought to assess the distribution of DMT prescriptions amongst all neurologists and to analyze if prescription patterns varied between specialist and generalist neurologists. Based on the anecdotal experience seen in the St. Michael’s Hospital MS Clinic, if was hypothesized that general community neurologists
preferentially prescribed Avonex. Being only a single weekly injection, Avonex might be perceived as less onerous on patients and therefore easier for community neurologists to monitor. The specific hypotheses tested were that:

1. The majority of DMT prescriptions are filled by a minority of Ontario neurologists (MS-specialists).

2. Amongst the cohort of all Ontario neurologists who prescribed any DMT, the four first-line DMTs are not equally prescribed with a preferential trend towards Avonex prescriptions specifically.

3. Prescribing patterns correlate with neurology sub-specialization with general neurologists preferentially prescribing Avonex and MS Clinic-based, MS-specialist neurologists demonstrating a broader range of DMT prescriptions.

4. Neurologists who prescribe a relatively low number of DMT prescriptions preferentially prescribing Avonex while high-volume DMT-prescribing neurologists use a broader range of DMT prescriptions.

In addition, secondary investigations sought to assess if other neurologist demographic characteristics were associated with differential prescribing practices. Rural neurologists (who would also be expected to be general neurologists) might also favour Avonex. Additionally, neurologists as a whole (ignoring specialization for the moment) who have been in practice for a shorter length of time may be more comfortable with prescribing relatively novel immunomodulatory therapies and have a broader DMT prescription repertoire. Since there has been a shift towards a higher proportion of female
neurologists graduating over time, a gender correlation may also occur along with the presumptive age-effect on prescribing patterns.

The specific secondary hypotheses related to these issues were that:

5. Prescribing patterns have a geographical correlation with the rural neurologists who have prescribed any DMT preferentially prescribing Avonex and urban neurologists demonstrating a broader distribution of DMT prescriptions.

6. Prescribing patterns have an age-related correlation with older Ontario neurologists (defined as being more than 20 years since graduation) favouring Avonex and younger neurologists (defined as being 20 years or less since graduation) demonstrating a broader distribution of DMT prescriptions.

7. Prescribing patterns have a gender correlation with male Ontario neurologists who have prescribed any DMT favouring Avonex and female neurologists demonstrating a broader distribution of DMT prescriptions.
Methods

All data was collected from the linked, anonymized public health services databases for the province of Ontario maintained at ICES (Sunnybrook Hospital, Toronto, Ontario). The data was collected after appropriate regulatory approval from the Sunnybrook Hospital/ICES research ethics board (REB) was obtained and all data manipulation involving the raw dataset was performed in-house at ICES in accordance with regulatory requirements.

All DMT prescriptions obtained by ODB recipients through the EAP (Trillium program) between January 1st, 2009 and December 31st, 2009 inclusive were obtained from the ODB claim database. All drug identification numbers (DINs) (see Table 4) corresponding to the various formulations of the four DMTs were obtained. All scripts without valid associated ICES Key Numbers (IKNs) were excluded as these were required to link scripts to the ICES Physician Database (IPDB). Each DMT script was linked to the corresponding prescribing physician (and his/her demographic and geographical characteristics) via the IPDB. All physicians not classified as “NEUROLOGIST” in the IPDB were excluded from the main analysis. (Scripts obtained from non-neurologists were also separately tabulated for completeness, but these prescribers were not utilized in the calculations below). Additionally, if the required demographic characteristics of gender, graduation date and postal code were not listed in the IPDB for a neurologist, any associated scripts were also excluded from the main analysis.
The Brogan commercial database of pharmacy claims in the province of Ontario was also queried to extract the total number of private and publicly funded DMT scripts filled in the province in 2009. This database will list an individual script (either new prescription or refill) twice if the DMT is being paid for partially through Trillium and partially through a person’s private drug coverage. This means that the total number of DMT scripts in the province cannot be calculated by simply adding the two categories of scripts together.

### Table 4: List of all DINs for DMTs

<table>
<thead>
<tr>
<th>DMT</th>
<th>DINs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avonex</td>
<td>02237770 02269201</td>
</tr>
<tr>
<td>Betaseron</td>
<td>02169649</td>
</tr>
<tr>
<td>Rebif</td>
<td>02237317 02237319 02237320 02318253 02318261 02277492 02281708</td>
</tr>
<tr>
<td>Copaxone</td>
<td>02233014 02245619</td>
</tr>
</tbody>
</table>

Neurologist practice location was defined in two ways. First, all Ontario neurologists were characterized by whether they worked in a geographical area corresponding to an MS Clinic (labelled as “MSCLINIC”) or not (labelled as “nonMSCLINIC”). This was done by querying the IPDB to see whether each physician’s practice location postal code forward sortation area (FSA), the first 3 alphanumeric characters of the postal code, corresponded to any of the six adult hospital-based Ontario MS clinics (as listed on [http://mssociety.ca/en/help/clinics.htm#ontario](http://mssociety.ca/en/help/clinics.htm#ontario)) in Toronto, Ottawa, Kingston, London, Hamilton and Thunder Bay. By necessity therefore, all non-MS-specialist neurologists with a practice address corresponding to an MS clinic (namely all neurologists working in
a hospital with one of the MS clinics listed above) were classified as “MSCLINIC”.

Although all the specific MS-specialists working in Ontario were known by name, privacy issues prevented the analysis from utilizing these names directly to define the “MSCLINIC” cohort of physicians. (The implications of this are reviewed further in the discussion). Conversely, since the IPDB only lists each physician’s primary practice address, any neurologist who had a primary practice outside of the tertiary hospital MS Clinic postal code FSAs above who also spend time working in one of these MS clinics would be classified as “nonMSCLINIC” despite their sub-speciality interest in MS.

The potential association between geographical localization and prescribing patterns was also explored by splitting all Ontario neurologists into either urban or rural practitioners using the practice location FSAs available in the IPDB. “RURAL” and “URBAN” was defined by the 2004 version of Rurality Index of Ontario (RIO2004) using the standard methodology employed by ICES. The RIO2004 was initially devised to establish a quantitative way to define how “rural” a community was to allow for better allocation of resources with respect to physician recruitment within the province of Ontario. The RIO2004 scale ranges from 0 to 100. Scores less than 45 are considered to represent a “urban” region of the province. Each Ontario neurologist’s FSA was linked with the appropriate RIO2004 number through the corresponding census subdivision for that particular community using standard ICES linkage algorithms.

Specialization was also indirectly examined using the number of DMT scripts prescribed by a physician as a surrogate for MS sub-speciality interest. An arbitrary decision was
made to classify individual Ontario high-volume prescribing neurologists as MS specialists if they prescribed greater than one hundred DMT scripts in 2009.

To make comparisons based on how long Ontario neurologists had been in practice, the age at medical school graduation recorded in the IPDB was used as a surrogate marker. The physician population was split into those who had been practising for less than or equal to twenty years and those who had been practicing for longer than twenty years. Physician gender is also recorded in the IPDB, allowing the prescribing patterns of male and female neurologists to be compared.

The ICES analysts created a Microsoft Excel 2003 (Microsoft Corporation, Redmond, WA, USA) file which listed all of the neurologists in Ontario, the number of scripts for each DMT that each neurologist prescribed and the demographic information for each neurologist (Table 5). The IPDB numbers were removed and each neurologist was given a sequential identification number. This file was then used to create individual Excel spreadsheets which were used separately to analyze each of the hypotheses.

<table>
<thead>
<tr>
<th>ID</th>
<th>MS Clinic (Y/N)</th>
<th>Rural (Y/N)</th>
<th>&gt;100 DMT scripts</th>
<th>Male (Y/N)</th>
<th>Grad &gt;20 yrs (Y/N)</th>
<th>#DMT scripts</th>
<th>#Avonex scripts</th>
<th>#Betaseron scripts</th>
<th>#Rebif scripts</th>
<th>#Copaxone scripts</th>
<th>#nonAvonex scripts</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>2</td>
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</tbody>
</table>

Lorenz curves and Gini coefficients were constructed to examine prescribing patterns; separating neurologists dichotomously as listed above and separating Avonex from the other DMTs depending on the specific analysis being performed. All Lorenz curves were constructed in Excel and Gini coefficients were calculated from the Excel spreadsheet data. The Gini coefficients derived from the shape of different Lorenz curves were used
to compare how unequally DMTs were prescribed by different populations of Ontario neurologists.

To generate each Lorenz curve, a separate spreadsheet was made containing only those particular Ontario neurologists being examined in that specific curve (for example, all “MSCLINIC” neurologists). In the spreadsheet, each row corresponded to one neurologist and initially continued two columns: that neurologists’ anonymous ID number (ID) and the number of DMT scripts (DMT) of the specific type being graphed (for example, all “non-Avonex scripts”) that the neurologist prescribed. The rows were sorted sequentially by DMT with the highest prescribing neurologist listed in the last row.

To calculate the cumulative percentage of neurologists (MD) on the x-axis, two columns were then created. The first column, labelled $f_{MD}$, contained the same value $(1/n)$ in each row where $n$ was the total number of rows (or neurologists) in that particular spreadsheet. The second column, labelled $F_{MD}$, contained the sum of the cumulative fractions $(1/n)$ above and including that row where $F_{MD} = \sum_{i=1}^{n} f_{MD} = \frac{i}{n}$ and thereby extended from the numeric values of $(1/n \ldots 2/n \ldots 3/n)$ in the first three rows to $n/n$ (or 1) in the last row of the spreadsheet.

To calculate the cumulative percentage of DMT scripts, three further columns were created. The first, $DMT$, contained the number of scripts prescribed by each neurologist. (This column was a duplication of the column used to sort the spreadsheet from the lowest to highest prescriber). In the second column, labelled $f_{DMT}$, the absolute number
of scripts in that row (ie: prescribed by that single neurologist) was converted to a
fraction of the total of DMT scripts of that type prescribed by all the neurologists in that
data set such that for the \( i \)th neurologist; 
\[
 f_{DMT_i} = \frac{y_i}{\sum_{i=1}^{n} y_i} \]
where \( y_i \) was the
DMT value for that neurologist. The third column, labelled \( F_{DMT} \), contained a cumulative
total of the fractions of scripts dispensed by all the preceeding neurologists in previous
rows added to the fraction prescribed by the neurologist in that row;
\[
 F_{DMT_i} = \frac{\sum_{j=1}^{i} y_j + y_i}{\sum_{i=1}^{n} y_i} \]
Similar to the data used to generate the information for the \( x \)-
axis, this final column used to generate the \( y \)-axis also had a numeric value of “1” in the
final row, ie: 
\[
 F_{DMT_n} = \frac{\sum_{j=1}^{n} y_j}{\sum_{i=1}^{n} y_i} \]
indicated that this was the total fraction of
DMTs prescribed. Each Lorenz curve was formed from the interpolation of the
points \( L(F_{MD}, F_{DMT}) \).

Finally, the Gini coefficient was calculated for each curve. As discussed earlier, the Gini
coefficient can be calculated as 
\[
 G = 1 - \sum_{i=1}^{n} \left[ x_i' \times (Y_j + Y_{i-1}) \right] \]
where 
\[
 x_i' = \frac{x_i}{x_1 + x_2 + ... + x_n} \]
Using the specific nomenclature for the neurologist/DMT Lorenz curves, 
\( x_i' = f_{MD} \) and
\( Y_i = F_{DMT_i} \) the formula for the Gini coefficient can be rewritten as
\[
 G = 1 - \sum_{i=1}^{n} \left[ f_{MD} \times \left( F_{DMT_i} + F_{DMT_{i-1}} \right) \right] \]
Defining each individual component of the
summation involved in this equation as \( g_i \), where 
\( g_i = f_{MD} \times \left( F_{DMT_i} + F_{DMT_{i-1}} \right) \), each value
of \( g_i \) was calculated and entered into the last column of the spreadsheet. Finally the Gini was calculated by subtracting the summation of this final column from 1: \[ G = 1 - \sum_{i=1}^{n} g_i. \]

To allow the Lorenz curves to be compared more formally than by visual inspection alone, standard errors of the Gini curves were first calculated using the jackknifing technique of Ogwang.\(^{179}\) First, \( n \) pseudo-Gini coefficients were constructed for each curve to obtain the variance of the true Gini using the formula

\[ \text{var}(G) = \left( \frac{n-1}{n} \right) \sum_{i=1}^{n} \left( G(n,i) - \bar{G}(n) \right)^2 \]

as previously described. From this, the 95% confidence intervals were calculated as

\[ 95\% \text{CIs} = G \pm Z_{\frac{\alpha}{2}} \times SE(G) \]

where \( \alpha = 0.05 \),

\[ Z_{\frac{\alpha}{2}} = 1.96 \] and \( SE(G) = \sqrt{\text{var}(G)} \).

As an example, Table 6 reproduces the Excel spreadsheet for all the non-Avonex prescriptions made by Ontario physicians who prescribed any DMT and had a primary practice address corresponding to one of the MS clinic FSAs. This spreadsheet was used to create the corresponding Lorenz curve in Figure 5. Of note, all of the above calculations had been performed on site at ICES for privacy reasons before the spreadsheets were stripped of any identifying information, including the actual number of scripts made by each neurologist, so the sample table does not include the DMT columns.
Using the methods described above, seven separate graphs of Lorenz curves were constructed. In the first, the cumulative percentage of all Ontario neurologists was plotted against the cumulative percentage of total DMTs prescribed (ie: all four DMTs were pooled).
In the remaining six graphs, only Ontario neurologists who prescribed a DMT in 2009 were examined in keeping with the study hypotheses. In second graph, the cumulative percentage of prescribing neurologists was plotted against the cumulative percentage of scripts with each separate DMT examined (four curves on graph).

For the other graphs, demographic and practice-characteristics (ie: academic, urban, high volume-prescriber) were examined. For each graph, a total of eight Lorenz curves and corresponding Gini coefficients could theoretically be plotted on each graph if each of the four DMTs was plotted separately for each of the two dichotomous neurologist characteristics being examined. Such an approach was felt to be both unwieldy and liable to potentially generate spurious “statistically significant” findings purely by chance. Therefore, in keeping with the original hypotheses which focussed on the difference between Avonex and the other three DMTs, the DMTs were dichotomized in two groups. The first group comprised only the Avonex prescriptions alone and the second consisted of all the scripts of the other three DMTs combined together in one aggregate number.

Using this approach of plotting four curves on one graph, the third, fourth and fifth graphs were constructed to examine practice characteristics and the sixth and seventh graphs to examine neurologist demographic characteristics.

The third graph plotted the cumulative percentage of prescribing neurologists against DMT script percentage splitting into MS clinic and non-MS-clinic based practice locations. Four curves were therefore plotted on this graph: MSCLINIC/Avonex, MSCLINIC/nonAvonex, non-MSCLINIC/Avonex, non-MSCLINIC/nonAvonex. For the
fourth graph, high and low-volume prescribers were dichotomized creating four curves for 
≤100 scripts/Avonex, ≤100 scripts/nonAvonex, >100 scripts/Avonex and >100 scripts/nonAvonex. Similarly, to examine rural and urban prescribing, the fifth graph plotted rural/Avonex, rural/nonAvonex, urban/Avonex and urban/nonAvonex.

In the sixth graph, length of time in neurological practice was studied by plotting the four Lorenz curves ≤20 years post graduation/Avonex, ≤20 years post graduation/nonAvonex, >20 years post graduation/Avonex and >20 years post graduation/nonAvonex. Finally gender effect was examined in the seventh graph which plotted female/Avonex, female/nonAvonex, male/Avonex and male/nonAvonex.
Results

Table 7 shows that a total of 16,790 DMT prescriptions were filled with partial EAP copayments in the province of Ontario in 2009. Of these, 75.2% were prescribed by a neurologist. A total of 2268 scripts were not associated with a valid IKN in the ICES databases and therefore could not be linked to a specific Ontario physician. This presumably partially reflects the coding errors which are inherent in any administrative database. It is also due to DMT prescribing by non-Ontario neurologists; for example for patients in the extreme North-Eastern parts of the province who are treated in Manitoba.

Table 7: Disease-modifying prescriptions filled through Trillium

<table>
<thead>
<tr>
<th>Prescribing Physician</th>
<th>DMT number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurologists</td>
<td>12628 (75.2)</td>
</tr>
<tr>
<td>Non-Neurologists</td>
<td>1894 (11.3)</td>
</tr>
<tr>
<td>Invalid IKN */Prescriber Information</td>
<td>2268 (13.5)</td>
</tr>
<tr>
<td>Total</td>
<td>16790 (100)</td>
</tr>
</tbody>
</table>

IKN, ICES Key Number
*Not usable for construction of Lorenz curves

Table 8: All private and publicly funded DMT prescriptions recorded in the Brogan commercial database for 2009

<table>
<thead>
<tr>
<th>Database</th>
<th>Trade Name</th>
<th>2009 Claims</th>
</tr>
</thead>
<tbody>
<tr>
<td>Private</td>
<td>Avonex</td>
<td>7666</td>
</tr>
<tr>
<td></td>
<td>Betaseron</td>
<td>4492</td>
</tr>
<tr>
<td></td>
<td>Rebif</td>
<td>7567</td>
</tr>
<tr>
<td></td>
<td>Copaxone</td>
<td>9147</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>28872</td>
</tr>
<tr>
<td>Public</td>
<td>Avonex</td>
<td>4319</td>
</tr>
<tr>
<td></td>
<td>Betaseron</td>
<td>3090</td>
</tr>
<tr>
<td></td>
<td>Rebif</td>
<td>4792</td>
</tr>
<tr>
<td></td>
<td>Copaxone</td>
<td>4592</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>16793</td>
</tr>
</tbody>
</table>

*All variants of each of marked product combined into category

Of note, the total number of scripts (16,790) found through the Trillium database abstraction was approximately the same as the total number of publicly-insured scripts...
(16793) found through the commercial Brogan database (Table 8). The private and public-funded DMT scripts in Table 8 cannot be combined to give a “total” number of DMT scripts filled in the province. This is because there is overlap from the scripts of patients with partial private coverage and partial EAP/Trillium funding which will be coded twice in the Brogan database. The number of scripts with such joint coverage cannot be abstracted separately from the database.

Table 9: Number of Scripts from Non-Neurologists in 2009

<table>
<thead>
<tr>
<th>Main Specialty</th>
<th>Avonex</th>
<th>Betaseron</th>
<th>Rebif</th>
<th>Copaxone</th>
<th>Total DMTs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unknown</td>
<td>26</td>
<td>58</td>
<td>75</td>
<td>20</td>
<td>179</td>
</tr>
<tr>
<td>Anaesthesia</td>
<td>&lt;5</td>
<td>7</td>
<td>&lt;5</td>
<td>&lt;5</td>
<td>9</td>
</tr>
<tr>
<td>Cardio/thoracic surgery</td>
<td>&lt;5</td>
<td>&lt;5</td>
<td>&lt;5</td>
<td>&lt;5</td>
<td>&lt;5</td>
</tr>
<tr>
<td>Emergency medicine</td>
<td>&lt;5</td>
<td>&lt;5</td>
<td>11</td>
<td>&lt;5</td>
<td>15</td>
</tr>
<tr>
<td>FP/emergency medicine</td>
<td>24</td>
<td>32</td>
<td>13</td>
<td>&lt;5</td>
<td>70</td>
</tr>
<tr>
<td>General surgery</td>
<td>&lt;5</td>
<td>14</td>
<td>14</td>
<td>5</td>
<td>33</td>
</tr>
<tr>
<td>GP/FP</td>
<td>327</td>
<td>317</td>
<td>451</td>
<td>312</td>
<td>1407</td>
</tr>
<tr>
<td>Internal medicine</td>
<td>&lt;5</td>
<td>&lt;5</td>
<td>&lt;5</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Medical oncology</td>
<td>&lt;5</td>
<td>12</td>
<td>&lt;5</td>
<td>&lt;5</td>
<td>16</td>
</tr>
<tr>
<td>Nephrology</td>
<td>&lt;5</td>
<td>&lt;5</td>
<td>&lt;5</td>
<td>&lt;5</td>
<td>&lt;5</td>
</tr>
<tr>
<td>Ophthalmology</td>
<td>&lt;5</td>
<td>7</td>
<td>19</td>
<td>&lt;5</td>
<td>26</td>
</tr>
<tr>
<td>Orthopedic surgery</td>
<td>&lt;5</td>
<td>&lt;5</td>
<td>8</td>
<td>8</td>
<td>16</td>
</tr>
<tr>
<td>Pediatrics</td>
<td>20</td>
<td>&lt;5</td>
<td>8</td>
<td>5</td>
<td>33</td>
</tr>
<tr>
<td>Physical medicine and rehabilitation</td>
<td>&lt;5</td>
<td>&lt;5</td>
<td>&lt;5</td>
<td>&lt;5</td>
<td>&lt;5</td>
</tr>
<tr>
<td>Plastic surgery</td>
<td>&lt;5</td>
<td>&lt;5</td>
<td>&lt;5</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>Psychiatry</td>
<td>&lt;5</td>
<td>&lt;5</td>
<td>&lt;5</td>
<td>&lt;5</td>
<td>6</td>
</tr>
<tr>
<td>Respirology</td>
<td>&lt;5</td>
<td>&lt;5</td>
<td>35</td>
<td>&lt;5</td>
<td>35</td>
</tr>
<tr>
<td><strong>Totals</strong></td>
<td><strong>406</strong></td>
<td><strong>451</strong></td>
<td><strong>644</strong></td>
<td><strong>368</strong></td>
<td><strong>1869</strong></td>
</tr>
</tbody>
</table>

FP, family practitioner; GP, general practitioner

*NB:* All cell counts <5 have to be reported as such for privacy reasons as mandated by ICES
The breakdown of scripts prescribed by non-neurologists is presented in Table 9. These scripts were not used in the calculation of the Lorenz curves as the hypotheses centred on neurologist-prescribing patterns. Presumably these reflect refill prescriptions as the initial EAP/Trillium application process is dependent on neurologist input given the specificity of the data required which would generally require a neurologist to complete the initial application.

Tables 10 and 11 show the number of DMT scripts generated in 2009 by neurologists with specific demographic and professional practice characteristics. This information is presented both as the number of scripts generated by neurologists in each category (Table 10) and as the percentage of prescribing neurologists in each category who prescribed a specific DMT (Table 11). As shown in Table 10, a total of 12826 DMT scripts with partial EAP copayment were prescribed by the 286 neurologists practicing in Ontario represented in the IPDB.

Less than five Ontario neurologists practicing in a rural environment (as defined by the 2004 version of Rurality Index of Ontario) in 2009 prescribed any DMTs. (The actual number of rural neurologists cannot be stated due to ICES’ privacy policies). This meant that the planned comparison between urban and rural neurologist prescribing patterns was unnecessary. A partial Lorenz curve was still constructed for the sake of completeness in an attempt to fulfill the stated hypotheses as much as possible; however the rural neurologists data was not plotted on the Lorenz curve shown in Figure 7.
Table 11 also demonstrates the key finding that within the community of Ontario neurologists, DMT prescribing is markedly skewed with only ~41% (116/286) prescribing any DMT in 2009.

**Table 10: DMT Prescriptions Stratified by Characteristics of Prescribing Neurologist**

<table>
<thead>
<tr>
<th>Neurologists</th>
<th>Avonex</th>
<th>Betaseron</th>
<th>Rebif</th>
<th>Copaxone</th>
<th>All Non-Avonex</th>
<th>Any DMTs</th>
</tr>
</thead>
<tbody>
<tr>
<td>MS Clinic</td>
<td>1480 (21.93)</td>
<td>1345 (19.93)</td>
<td>2039 (30.21)</td>
<td>1885 (27.93)</td>
<td>5269 (78.07)</td>
<td>6749 (100)</td>
</tr>
<tr>
<td>Non-MS Clinic</td>
<td>1824 (31.03)</td>
<td>973 (16.55)</td>
<td>1350 (22.96)</td>
<td>1732 (29.46)</td>
<td>4055 (68.97)</td>
<td>5879 (100)</td>
</tr>
<tr>
<td>≤100 scripts</td>
<td>954 (39.8)</td>
<td>386 (16.1)</td>
<td>609 (25.4)</td>
<td>447 (18.7)</td>
<td>1442 (60.2)</td>
<td>2396 (100)</td>
</tr>
<tr>
<td>&gt;100 scripts</td>
<td>2350 (23.0)</td>
<td>1932 (18.9)</td>
<td>2780 (27.2)</td>
<td>3170 (31.0)</td>
<td>7882 (77.0)</td>
<td>10232 (100)</td>
</tr>
<tr>
<td>Rural</td>
<td>190 (54.44)</td>
<td>51 (14.61)</td>
<td>16 (4.58)</td>
<td>92 (26.36)</td>
<td>159 (45.56)</td>
<td>349 (100)</td>
</tr>
<tr>
<td>Urban</td>
<td>3114 (25.36)</td>
<td>2267 (18.46)</td>
<td>3373 (27.47)</td>
<td>3525 (28.71)</td>
<td>9165 (74.64)</td>
<td>12279 (100)</td>
</tr>
<tr>
<td>Grad ≤20 years</td>
<td>1026 (27.89)</td>
<td>545 (14.81)</td>
<td>832 (22.61)</td>
<td>1276 (34.68)</td>
<td>2653 (72.11)</td>
<td>3679 (100)</td>
</tr>
<tr>
<td>Grad &gt;20 years</td>
<td>2278 (25.46)</td>
<td>1773 (19.81)</td>
<td>2557 (28.57)</td>
<td>2341 (26.16)</td>
<td>6671 (74.54)</td>
<td>8949 (100)</td>
</tr>
<tr>
<td>Female</td>
<td>606 (23.06)</td>
<td>478 (18.19)</td>
<td>512 (19.48)</td>
<td>1032 (39.27)</td>
<td>2022 (76.94)</td>
<td>2628 (100)</td>
</tr>
<tr>
<td>Male</td>
<td>2698 (26.98)</td>
<td>1840 (18.4)</td>
<td>2877 (28.77)</td>
<td>2585 (25.85)</td>
<td>7302 (73.02)</td>
<td>10000 (100)</td>
</tr>
<tr>
<td>All</td>
<td>3304 (26.16)</td>
<td>2318 (18.36)</td>
<td>3389 (26.84)</td>
<td>3617 (28.64)</td>
<td>9324 (73.84)</td>
<td>12628 (100)</td>
</tr>
</tbody>
</table>

**Table 11: Number of Neurologists Prescribing Various DMTs, Stratified by Characteristics of Prescriber**

<table>
<thead>
<tr>
<th>Neurologists</th>
<th>Avonex</th>
<th>Betaseron</th>
<th>Rebif</th>
<th>Copaxone</th>
<th>Any DMT</th>
<th>No DMTs</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>MS Clinic</td>
<td>23 (23)</td>
<td>22 (22)</td>
<td>24 (24)</td>
<td>22 (22)</td>
<td>30 (30)</td>
<td>70 (70)</td>
<td>100 (100)</td>
</tr>
<tr>
<td>Non-MS Clinic</td>
<td>60 (32.26)</td>
<td>47 (25.27)</td>
<td>51 (27.42)</td>
<td>51 (27.42)</td>
<td>86 (46.24)</td>
<td>100 (53.76)</td>
<td>186 (100)</td>
</tr>
<tr>
<td>≤100 scripts</td>
<td>48 (19.3)</td>
<td>35 (14.1)</td>
<td>42 (16.9)</td>
<td>36 (14.5)</td>
<td>79 (31.7)</td>
<td>170 (68.3)</td>
<td>249 (100)</td>
</tr>
<tr>
<td>&gt;100 scripts</td>
<td>35 (94.6)</td>
<td>34 (91.9)</td>
<td>33 (89.2)</td>
<td>37 (100)</td>
<td>37 (100)</td>
<td>0 (0)</td>
<td>37 (100)</td>
</tr>
<tr>
<td>Rural</td>
<td>&lt;5</td>
<td>&lt;5</td>
<td>&lt;5</td>
<td>&lt;5</td>
<td>&lt;5</td>
<td>&lt;5</td>
<td>&lt;5</td>
</tr>
<tr>
<td>Urban</td>
<td>82 (28.98)</td>
<td>68 (24.03)</td>
<td>74 (26.15)</td>
<td>72 (25.44)</td>
<td>115 (40.64)</td>
<td>168 (59.36)</td>
<td>283 (100)</td>
</tr>
<tr>
<td>Grad ≤20 years</td>
<td>26 (22.22)</td>
<td>20 (17.09)</td>
<td>27 (23.08)</td>
<td>27 (23.08)</td>
<td>37 (31.62)</td>
<td>80 (68.38)</td>
<td>117 (100)</td>
</tr>
<tr>
<td>Grad &gt;20 years</td>
<td>57 (33.73)</td>
<td>49 (28.99)</td>
<td>48 (28.4)</td>
<td>46 (27.22)</td>
<td>79 (46.75)</td>
<td>90 (53.25)</td>
<td>169 (100)</td>
</tr>
<tr>
<td>Female</td>
<td>18 (23.68)</td>
<td>23 (30.26)</td>
<td>18 (23.68)</td>
<td>21 (27.63)</td>
<td>27 (35.53)</td>
<td>49 (64.47)</td>
<td>76 (100)</td>
</tr>
<tr>
<td>Male</td>
<td>65 (30.95)</td>
<td>46 (21.9)</td>
<td>57 (27.14)</td>
<td>52 (24.76)</td>
<td>89 (42.38)</td>
<td>121 (57.62)</td>
<td>210 (100)</td>
</tr>
<tr>
<td>All Prescribers</td>
<td>83 (29.02)</td>
<td>69 (24.13)</td>
<td>75 (26.22)</td>
<td>73 (25.52)</td>
<td>116 (40.56)</td>
<td>170 (59.44)</td>
<td>286 (100)</td>
</tr>
</tbody>
</table>

*NB: All cell counts <5 have to be reported as such for privacy reasons as mandated by ICES*
Figure 3: DMT Prescribing of All Ontario Neurologists

The Lorenz curve shown in Figure 3 depicts the proportion of the total number of DMT scripts dispensed in the province of Ontario in 2009 with an EAP Trillium co-payment as a function of the total number of neurologists practising in the province. The associated Gini coefficient of 0.86 reflects the significant skew away from the line of equality that is apparent on visual inspection of the figure. The majority of neurologists in the province did not prescribe any DMTs in 2009 with a relatively small proportion prescribing the vast majority of DMTs. The raw Excel spreadsheet data used to generate Figure 3 was
inspected to assess how many Ontario neurologists prescribed certain key percentages of DMTs, both separately and in total (Table 12). Figure 3 and table 12 show the significant specialization of MS-DMT prescribing in the province with 40% of neurologists responsible for all of the scripts. Perhaps more dramatically, 80% of DMT scripts were generated by only 12% of the neurologists in the province. The final column of table 12 is also of interest as it shows the focus of DMT prescribing to be even more concentrated when each DMT is examined individually. Given that ~40% of neurologists prescribe all the DMTs as a whole but only ~25% of neurologists generate all the scripts for an individual DMT, even with the subset of high-volume prescribers, certain physicians must prescribe differently.

<table>
<thead>
<tr>
<th>DMT</th>
<th>% of DMT scripts</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>50</td>
</tr>
<tr>
<td>Avonex</td>
<td>5</td>
</tr>
<tr>
<td>Betaseron</td>
<td>3.5</td>
</tr>
<tr>
<td>Rebif</td>
<td>3</td>
</tr>
<tr>
<td>Copaxone</td>
<td>4.5</td>
</tr>
<tr>
<td>Total</td>
<td>5</td>
</tr>
</tbody>
</table>
Figure 4: Individual DMTS Amongst All Prescribing Neurologists

Figure 4 depicts four separate Lorenz curves, one for each specific DMT. In this and all subsequent Lorenz curves, the neurologist population consists solely of those Ontario neurologists who prescribed at least one DMT in 2009. Visual inspection at first seems to suggest that the Avonex curve is closer to the line of equality than the other three DMTs, indicating a more even distribution of Avonex scripts amongst prescribing neurologists. However the Gini coefficient 95% confidence intervals (CIs) for all four of the curves overlap indicating that there is no statistically significant difference in the distribution of DMT prescribing amongst the cohort of 116 prescribing neurologists.
This is graphically reflected in the presence of overlap at the extreme right side of the graphs where the curves cross over each other.

The Gini coefficients shown in Figure 4 (range 0.65-0.76) are all less than the Gini for all DMTs / all Ontario neurologists (0.86) shown in Figure 3 which is not completely unsurprising given that Figure 4 is limited only to prescribing neurologists. However, it is worthwhile to note that even within this more select physician population, the Lorenz curves and corresponding Gini coefficients all indicate that marked prescribing inequalities continue to persist with most of the DMT scripts generated by a minority of individual prescribers. Table 13 depicts these numbers using the same benchmark script percentages as Table 12, omitting the 100% column as by definition, this cohort of neurologists was responsible was for the total aggregate number of DMT prescriptions.

<table>
<thead>
<tr>
<th>DMT</th>
<th>% of DMT scripts</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>50</td>
</tr>
<tr>
<td>Avonex</td>
<td>13</td>
</tr>
<tr>
<td>Betaseron</td>
<td>9</td>
</tr>
<tr>
<td>Rebif</td>
<td>6.5</td>
</tr>
<tr>
<td>Copaxone</td>
<td>10</td>
</tr>
</tbody>
</table>

Figures 5—9 all examine the hypotheses of differential Avonex prescribing versus the other three DMTs for specific neurologist practice locations, practice specialization and demographic characteristics. Each figure plots four Lorenz curves; splitting the population of prescribing neurologists by the particular characteristic of interest and splitting the DMTs into Avonex and non-Avonex (Betaseron, Rebif, Copaxone all combined).
Figure 5: Prescribing Patterns by Geography: MS Clinic vs. non-MS Clinic

Figure 5 shows the prescribing patterns for MS clinic and non-MS clinic neurologists. As is evident on visual inspection of the overlapping curves and confirmed by the overlapping Gini coefficients, no differences were identified between MS Clinic specialists and general neurologists.

Figure 6 in contrast shows significant differences in prescribing patterns between low- and high-volume prescribing neurologists. Both curves for the low-volume prescribing neurologists are more markedly skewed away from the line of equality. This demonstrates that these physicians focus on fewer specific DMTs overall when treating
MS patients. In contrast, both the Avonex and non-Avonex curves for the high-volume prescribers are closer to the line of equality than the two curves for the low-volume prescribing neurologists with correspondingly smaller Gini-coefficients. This indicates that these Ontario neurologists not only prescribe more scripts but also that they use a wider range of DMTs rather than just focusing on select ones from the four first-line ones that are available.

Figure 6: Prescribing Patterns by Volume: High vs. Low-volume DMT Prescribers

As visual inspection would suggest, the four curve-to-curve comparisons between the low- and high-volume prescribers are all significantly different as shown by non-overlap
of the Gini coefficient 95% CIs, with the exception of the ≤100 script/non-Avonex and >100 script/Avonex curves which do cross. Conversely, as evident on Figure 6, the two curve-to-curve comparisons within the low-volume and high-volume groups of prescribers are not significantly different.

Figure 7: Prescribing Patterns by Geography: Urban Neurologists

Figure 7 depicts the Lorenz curves dichotomizing urban neurologist scripts’ into Avonex/non-Avonex. This figure is included for completeness, although it is omits the two Lorenz curves representing rural neurologists due to the unexpectedly small number
(<5) practicing in Ontario in 2009 that were identified using the standard ICES definition of rural geographic status (see Table 10). No statistically significant differences were seen between the two Lorenz curves for urban neurologists as shown by the overlapping Gini coefficient 95% CIs, although Avonex curve is slightly closer to the line of equality.

Figure 8: Prescribing Practices by Length of Time in Practice

Figure 8 shows the four Lorenz curves dichotomizing Avonex and non-Avonex prescribers by the length of time in practice, determined by using the year of graduation from medical school as a surrogate. Visually, there does seem to be some spread of the
curves, albeit with overlapping at the extreme left and right tails. However, the Gini coefficient 95% CIs all overlap, including those for the ≤20 years post-graduation/non-Avonex and >20 years post-graduation/non-Avonex groups which visually appear the most divergent.

**Figure 9: Prescribing Patterns by Gender**

Figure 9, which examines prescribing patterns by gender, looks superficially similar to Figure 8. This is not unsurprising given the increasing number of female physicians in
medicine which would indicate that there is an interaction between the “female” and “≤20
years post-graduation” demographic cohorts. Of note, in Figure 9, the female/non-
Avonex and male/non-Avonex curves (the equivalent of the ≤20 years post-
graduation/non-Avonex and >20 years post-graduation/non-Avonex comparison in figure
7) are significantly different. This statistically significant finding is likely spurious, as
discussed later.
Discussion

The primary over-arching hypothesis guiding the majority of the data analysis plan laid out in the methods section stemmed from the anecdotal observations of those patients started on DMT in the community prior to their subsequent assessment in the St. Michael’s Hospital MS Clinic in Toronto, Ontario. In such patients, Avonex seemed to be by far the most common DMT prescribed by community neurologists. This observation generated the hypothesis that non-MS-specialist neurologists would focus on prescribing the DMT which has the fewest injections per week (one) as that would be perceived as resulting in fewer subsequent tolerability issues. In contrast, MS specialists working in dedicated MS clinics would feel more comfortable with prescribing all four first-line DMTs and perhaps more importantly, would have greater access to nursing and clerical support to aid in both the initial prescribing and subsequent monitoring of patients. Testing this hypothesis involved having access to a province-wide database linking prescription information to characteristics of prescribing neurologists. This was accomplished through the linked Ontario health care databases available through ICES.

This study has demonstrated that DMT prescribing is not uniform across the province with only 12% of Ontario neurologists responsible for 80% of the DMT prescriptions dispensed through the ODB in 2009, as demonstrated in Figure 3, in keeping with the first hypothesis (page 46). This percentage was approximately the same as those for the four DMTs when they were analyzed individually (range 9-13%). When only those neurologists who prescribed any DMTs were examined in isolation, Avonex did seem to be more uniformly prescribed (Figure 4) on cursory visual inspection of the Lorenz
curves. However, the tails of the curves did cross and the 95% CIs of the four Gini coefficients also overlapped. Nevertheless, Figure 4 would suggest that there was a non-significant trend in favour of the second hypothesis (page 46) that Avonex was the most evenly prescribed DMT. In contrast, Rebif was used by a small minority of neurologists. As shown in Table 13, while approximately 10% of neurologists prescribed 50% of Avonex, Betaseron and Copaxone, the same percentage prescribed fully 80% of Rebif. Figure 4 and Table 13 also show that even within the cohort of 116 neurologists (40% of the total number in the province) who treated MS patients with DMTs, the degree of prescribing was still markedly unequal. The Gini coefficients depicted in Figure 4 ranged from 0.65 to 0.76 and roughly 10% of this cohort of prescribing neurologists generated 50% of the DMT scripts. Of note, as shown in Table 3, all of DMTs were available in 2009 for the treatment of RRMS, however Copaxone was only added to the formulary in 2011 for the treatment of CIS. It possible that this could have acted to lower the number of Copaxone prescriptions, even though this was still the second most widely prescribed DMT as shown in Table 10. However, it is quite common for neurologists and/or patients to elect to adopt a “watchful waiting” approach in CIS rather than treat CIS patients who may have benign MS. For this reason, it is likely that most of the patients treated with DMT started treatment with a confirmed diagnosis of RRMS.

Confidentiality rules precluded MS specialist neurologists from being isolated from the rest of the Ontario neurologists listed in the ICES IPDB. To circumvent this issue, the neurologists with a primary practice address in the IPDB corresponding to the postal code of one of the MS clinics in the province were used as a proxy for “MS clinic” despite the
fact that this group would include other academic subspeciality or generalist neurologists working in the same hospital. It seems reasonable to assume, however, that most of the scripts coming from these postal codes would be coming from “true” MS-specialist neurologists at the MS clinic. For example, an epilepsy specialist at a teaching hospital with an MS clinic would likely transfer care to the MS clinic rather than start a patient on DMT her/himself. However, there is no guarantee that this happens exclusively. In that regard, the divergent results for the MSC/nonMSC and the high/low-volume prescribers bears comment and comparison.

Contrary to third overall hypothesis (page 46), no significant differences in the four Lorenz curves plotted for the MSC/nonMSC neurologists were seen as shown in Figure 5. The Gini coefficients (all ~0.6) indicate that moderate skewing was present for the prescribers of all four sets of DMTs here (ie: within each group, ~20% of neurologists generated ~60% of the scripts reading from the curves). The degree of skew was approximately equal between the curves as can be seen visually and confirmed mathematically by the essentially similar Gini coefficients with overlapping 95% CIs.

In contrast, Figure 6 shows that high- and low-volume prescribers used DMTs quite differently as anticipated with the fourth hypothesis (page 46). The degree of skew was markedly less with the high-volume prescribers for both groups of DMTs (Avonex being in one group and the other three in the second group) in comparison to the low-volume prescribing neurologists. If as above, most scripts coming from a postal code corresponding to an MS clinic can be assumed to emanate from an MS-neurologist, why
are Figure 5 and 6 not more alike? A re-examination of Tables 10 and 11 provides some insight. As shown in Table 11, 100 of the 286 (35%) neurologists in the province work at an address with an MSC while only 37 (13%) of Ontario neurologists were high-volume prescribers in 2009. Table 10 however shows that while high-volume prescribers produced the vast majority of DMT scripts, 10232/12628 or 81%, only 6749/12628 or 53% came from “MSC” neurologists.

This is likely the result of two factors. Firstly, community neurologists with a subspecialty interest in MS who devote a lot of their time to MS patient care, either solely in their private community office or part-time in a MS clinic, will be inappropriately coded as “nonMSC”, thereby inflating the number of scripts seemingly made by non-specialists in Table 10. Related to this is the fact that in Ontario, unlike most provinces, there are no restrictions on DMT prescribing by community neurologists, so any neurologist without an MS clinic affiliation could become a “high-volume” prescriber if she/he wished. As previously discussed, “MS clinic” neurologists could not be specifically queried in the IPDB because of privacy regulations; however the author and thesis supervisor can both attest to the fact that there are fewer then 37 MS clinic-based neurologists in the province. The 37 high-volume neurologists in the province must therefore by necessity include some purely community-based neurologists do not see patients in one of the provincial MS clinics. This raises the issue of whether high-volume prescribers are a better marker of “expert/specialist” in future analysis of either MS or other fields of medical practice that the methodological techniques used here could be adapted to study.
Figure 6 indicates that high-volume prescribers are comfortable with all DMTs and use the two groups of DMTs relatively equally. It is important to note that because of the specific nature of the hypothesis-driven questions asked, this analysis cannot examine the degree to which a single “nonAvonex” medication was distributed amongst either the high- or low-volume prescribers. It is likely that individual prescribers do not each prescribe all three nonAvonex DMTs equally, as Figure 4 and Table 13 discussed above would suggest. For example, one physician may favour Copaxone and another Betaseron. As these scripts are being combined in aggregate however, only the cumulative proportion of aggregate “nonAvonex” scripts were plotted in these Lorenz curves.

It needs to be acknowledged that the distinction made between MS specialists and general neurologists is somewhat artificial. The group of low-prescribing non-MS-specialists would also include other sub-specialists in addition to general neurologists. Such specialists might be expected to prescribe the least amount of DMTs given the nature of their practice. While a subset of these specialist neurologists would practice in the same tertiary hospitals that contain MS clinics—and therefore be coded as MS-clinic neurologists when analyzing practices based on postal codes—they also would work in other hospitals in the province in addition to outpatient clinics or private offices. As discussed above, it is unlikely that such subspecialist neurologists practising in a hospital that contains an MS clinic prescribe a significant amount of DMTs to significantly bias the findings in Figure 5. Additionally, a neurologist whose practice includes few MS
patients is going to have fewer opportunities to prescribe DMTs (even if s/he was willing
to do so). Such a “low-volume” neurologist would be less likely to demonstrate
variability in prescribing purely as a function of having a smaller MS practice.

No evidence was found to support any of the three secondary hypotheses. Figure 7 is
included for completeness. This graph was constructed to test the hypothesis that urban
and rural neurologists would have different prescribing patterns. Less than five
neurologists in total practiced in “rural” areas as defined using the <45/≥45 point
RIO2004 cutoff. This low number prevented meaningful rural/urban comparisons from
being made and the hypothesis that urban and rural neurologists have differential
prescribing patterns (page 47) was not testable.

“Rural” was defined using the standard index of rurality, the RIO2004, used in previous
ICES analyses. This scale takes into account a region’s population, distance from a
referral centre and local health services to create a composite one hundred point index.
An area of the province that has a score of greater or equal to 45 is considered to
represent a rural region and is treated as such in the standard ICES data extraction
algorithms. This standard measure however was not useful in exploring the hypothesis
that rural neurologists (who are more likely to be generalists) would focus more on
Avonex prescriptions over the other three DMTs.

It is possible that a less rigorous dichotomization of communities would have resulted in
different results. For example, if major metropolitan areas were isolated and contrasted
with regions consisting not only of rural communities but also smaller urban towns and cities, more support for this hypothesis might have been found. Nevertheless, it is still possible that even with this geographical classification, no differences would have been seen. As has been discussed in detail previously; one of the key findings of this study was that high-volume DMT prescribers were not limited only to academic, MS Clinic based neurologists but also included community based neurologists. If some of these high-volume prescribing community neurologists worked in smaller cities, the Lorenz curves generated from these physicians would likely have overlapped with those of the neurologists in major metropolitan areas (including MS clinic-based neurologists). In that case, no geographical differences would likely have been found even if this hypothesis was re-examined using a less stringent RIO2004 cut-off point.

Figures 8 and 9 are very similar, which is perhaps not unexpected as they classify prescribing neurologists by two inter-related demographic characteristics; age (Figure 8) and gender (Figure 9) with the former being formally defined by the length of time in practice. This variable was used rather than biological age to account for the age at which a neurologist completed his or her medical training. Given the changing demographics of the medical profession, it is not unsurprising that gender and time in practice are linked together. Neither graph shows compelling evidence of differential prescribing; with approximately equal degrees of skew found and only one statistically significant result, the comparison of the “female/nonAvonex” and “male/nonAvonex” curves in Figure 9. Given that this is an isolated event, it is of dubious practical significance and likely reflects the chance of getting statistically significant false-positive
result with multiple comparisons. Therefore, contrary to the final two secondary hypotheses (page 47), no other gender or age disparities in prescribing patterns were found. It is intriguing to note however that in both Figure 8 and 9, the two outer Lorenz curves are the inter-related female/≤20 years—non-Avonex and the male/>20 years—non-Avonex ones, hinting towards a non-significant trend towards differential prescribing.

In summary, this study has demonstrated marked inequalities in the DMT prescribing practices of Ontario neurologists. Only a minority of neurologists prescribed any DMTs in 2009 and even within this cohort of physicians, marked inequality existed with 80% of DMT scripts generated by 12% of the neurologists. No particular demographic or practice location characteristic could be correlated with prescribing patterns with the exception of prescription volume. High volume DMT prescribers as a group showed more uniform prescribing of Avonex and the other three DMTs combined.

Besides the specific questions about DMT prescribing, this study was also designed to assess the inter-related methodological issues of how best the ICES databases could be used for such a study and whether Lorenz curve analysis is an appropriate technique to employ. Lorenz curves provide an excellent visual depiction of how equitably a given characteristic is within a population. This diagrammatic representation is further enhanced by the use of Gini coefficients to mathematically express the degree of equality. The higher the Gini coefficient, the more skewed the Lorenz curve is towards the hypothetical line of inequality and the more concentrated the characteristic of interest is...
within that population. Gini coefficients are also useful as they allow researchers to
directly compare and contrast different Lorenz curves and determine if statistically
significant differences are present between the curves.

Despite the myriad of other applications that Lorenz curves have been adapted to explore
outside of the initial conceptualization as a measure of wealth distribution, including
those outlined in the “Background” to this paper, there have been few studies reported in
the literature where Lorenz curves have been used to examine prescribing practices.
Despite the paucity of peer-reviewed publications using Lorenz curves to assess
medication dispensation, they are widely used for this purpose by governments or health
policy agencies. For example, a comprehensive report from the Manitoba Centre for
Health Policy documenting potential sources of health inequality in that province
included Lorenz curves to assess whether any geographical disparity existed in the
prescribing of beta-blockers to myocardial infarction patients. The authors did not find
that any significant disparity existed in any of the four time epochs analyzed between
1996 and 2008, with the percentages of beta-blocker prescriptions graphed by percentage
of the population all overlapping with the line of equality.

This project has successfully demonstrated that the Lorenz/Gini techniques can be easily
applied to address focused questions related to the concentration of drug prescribing
within a population of physicians. It is nevertheless important to acknowledge that while
Lorenz curves can address specific questions at the population level, they are not well
suited to multivariate analysis or examining multiple different medications simultaneously.

These limitations did not hamper our ability to address the specific hypotheses addressed herein which all sought to compare Avonex alone to the other three first-line interferon DMTs as an aggregate group. However, if the research questions had required an analysis of each DMT individually, the number of Lorenz curves per graph would have been doubled. This would have made the curves harder to differentiate visually and likely would have resulted in some of the curves overlapping at the tails causing the Gini 95% confidence intervals to overlap. Additionally, all of our hypotheses had to be analyzed separately as no published, standardized mechanisms exist to perform multivariate analyses on Lorenz curves. For example, if this research had sought to examine for any interactions between neurologist and patient demographic characteristics which influenced DMT prescribing patterns, such an analysis would not have been possible with Lorenz curve statistical techniques.

One limitation of the ICES drug prescription database is that only publicly funded scripts are captured. This is in contrast to other provincial databases such as British Columbia, Saskatchewan, and Manitoba where all scripts and refills are recorded regardless of the whether it is the patient, government or private insurance that pays for the medication at the time of dispensation to the patient. As mentioned previously, this limitation is why most drug utilization studies performed to date using the ICES databases have only studied the Ontario population older than 65 years as all of the
scripts for these individuals are stored in the ODB. Prescriptions for those patients less than 65 years old who self-pay or have full private insurance plans are not captured by the ODB and invisible within the ICES database structure. Given that RRMS is almost exclusively seen in patients younger than 65 years old, we could not take the same approach as previous ICES researchers. Province-wide information is available from commercial sources (Brogan, IMS Health). However, these datasets do not capture individual level data in a way that could be used to assess the links between prescribing patterns and neurologist characteristics. Privacy concerns also prevent commercial databases from being linked to the ICES data holdings which would allow for such province-wide comparisons.

A total of 2268 scripts (13.5% of the total) were not analyzed as they had invalid IKNs (preventing them from being linked to the prescribing physician [neurologist or non-neurologist]) or invalid associated prescriber information. No particular pattern was observed with these scripts to skew our data; as discussed elsewhere the ratios of the four DMT prescriptions obtained from ICES was similar to the ratios in the Brogan commercial database of publicly- and privately-funded prescriptions. These scripts reflect coding and database entry/linkage errors in addition to prescriptions made by non-Ontario physicians including Manitoba physicians caring for MS patients in western Ontario.

It is important to highlight that despite the limitation that this study was only able to assess prescribing patterns for DMTs funded wholly or partially through the ODB, our
goal of examining province-wide neurologist prescribing would not have been feasible in other Canadian provinces. Other provinces such as Manitoba, Saskatchewan and British Columbia have more comprehensive provincial prescription databases that track all prescriptions regardless of payment scheme as mentioned above. In these other provinces however, DMT scripts can only originate from a dedicated MS clinic. The Ontario government in contrast does not place restrictions on which neurologists can prescribe DMTs. In a province such as Manitoba for example, even though all scripts would be captured in the provincial drug prescription database, it is impossible to study variations in DMT prescribing when all the scripts have to come from the province’s only MS clinic in Winnipeg.

The other provinces have various DMT prescribing rules and drug databases with different degrees of both data comprehensiveness and research access. In Nova Scotia, for example, the prescription information available is generally similar to that of Ontario in that only scripts for seniors are automatically collected in the linked databases in the Research Data Depository kept by the Population Health Research Unit at Dalhousie University. The interesting exception to this is the MS DMTs which, unlike in Ontario, are all recorded in a separate province-wide database. However, as with other provinces, only MS specialists can prescribe DMTs in Nova Scotia, so it would not be possible to replicate this study in that province. Access to provincial drug databases for research in other Canadian provinces is limited, irrespective of the specifics of who can prescribe DMTs in those provinces. Thus, despite the limitations imposed on this work
by the incomplete data available in the ODB, the same type of analysis undertaken in this project could not have been performed elsewhere in Canada.

One issue we could not explore which could affect neurologist prescribing is the degree of interaction with the pharmaceutical industry. As is evident from the medication prices listed in Table 2, there is a lot of revenue to be generated from MS DMT prescriptions. It is possible that prescribing at the individual physician level is influenced by the degree of interactions with industry (eg: visits from pharmaceutical representatives, attendance at sponsored meeting). Such influence could effect the prescribing patterns of neurologists; regardless of specialization or prescription volume. It is impossible to quantify this however without access to corporate records or the means to link such information to the ICES data holdings.

In addition, it is important to acknowledge that comparing the data in the ODB to that obtained from Brogan (available at the aggregate level), the ratios of the different DMTs being prescribed on a province-wide basis are comparable. This suggests that despite the limitations of the ICES database with respect to prescriptions in those less than 65 years of age, our results are externally valid. Furthermore, for our results to not extrapolate to all DMT scripts in the province there would have to exist some mechanism by which neurologists prescribed differently to those with Trillium coverage versus those with private coverage. Individual patients could be concerned with high co-payments or deductibles and opt for a “cheaper” DMT (ie: opt against high-dose Rebif specifically for example), however this is unlikely to cause differential prescribing as this would be a
factor with both private insurance plans and with the Trillium deductible. Therefore, while it is impossible to completely exclude the possibility of differential prescribing to MS patients based on their insurance status, this is not likely to be a significant issue impacting on the generalizability of this analysis.

This analysis was also confined to approximately 75% of the DMT scripts recorded in the ODB for the 2009 calendar year. Of the total 16,790 scripts found, 1894 (11.3%) were prescribed by non-neurologists and therefore outside the scope of this project. Of the remaining 14,896 scripts, a further 2268 (13.5%) were not associated with valid IKNs preventing them from being linked to a prescribing physician (either neurologist or non-neurologist). For this 13.5% of scripts to have influenced the data presented here, there would have to be a bias in which scripts for specific neurologists were systematically miscoded which would be unlikely if random data entry errors were to blame. The 11.3% of non-neurologist scripts presumably mostly reflect refill prescriptions as the EAP criteria for initial DMT approval require a specialized knowledge of MS. Neurologists would be initiating the EAP application for a particular patient and the choice of DMT would therefore reflect the preference of the prescribing neurologist even if refills were done by another practitioner such as the patient’s family physician.

This hypothesis-driven research has also focused exclusively on the neurologist’s role in DMT prescribing. This is not meant to be a negation of how a patient’s own preferences are a key factor in determining which DMT is prescribed. Regardless of physician input, it is the patient who ultimately decides whether or not to pick up a prescription from the
pharmacy. For example, if all four first-line DMTs were presented by a neurologist as equally valid choices, then the final decision which drug to use may be more reflective of an individual patient’s perception of the relative risk/benefit ratios, side-effect profiles, impact on lifestyle and other factors. This is in addition to the issue of whether an individual patient elects to take DMT at all after it has been recommended by her/his neurologist.

Despite this important caveat, the results described above do indeed demonstrate differential patterns of prescribing at the physician level. This would suggest that the opinion of the physician and/or the way in which the DMT choice is framed in a discussion with patients does affect which DMTs are ultimately chosen by patients and dispensed at the pharmacy. The interaction between neurologist preference and patient preference was beyond the scope of this current research. Nevertheless, the issue of how patient preference impacts on DMT prescribing patterns would be an important aspect of future research as discussed further in the “Future Directions” section.

One other point that bears comment is the issue of whether DMT scripts could have been written for different lengths of time in different patients. For example, a patient who received three months worth of drug at a time would have only four scripts entered into the ODB while another patient with monthly refills would have twelve. For this to have skewed our data, different neurologists would have had to uniformly prescribed in a different way (eg: male neurologists giving three months worth of drug at a time and female neurologists one month) which is hard to imagine. Nevertheless, the individual
level prescription data was examined to assess this issue and it was determined ~85% of each of the four first-line DMTs were prescribed for standard one month/30 day periods.

As this research was focused on neurologist prescribing, the 1894 prescriptions (11.3% of the total) made by non-neurologists were excluded from the analyses. The majority (1477) of these scripts were from general/family practitioners (Table 9). As discussed elsewhere, the presumably reflects refill prescriptions as the initial application process to Trillium would require a neurologist. It could be hypothesized that most Ontario GPs will have only a small number of patients with MS, so it is unlikely that “high-volume” prescribers exist amongst this group of physicians. Nevertheless, a similar analysis could be performed on these scripts to assess prescribing variability.

It must be acknowledged that a lot of the specific decisions made in the construction of the data-analysis plan were arbitrarily made and could be challenged. It was explicitly decided from the outset when designing this research project that a “fishing expedition” type of data-mining approach would not be performed. As one of the main goals was to determine the validity and utility of the Lorenz/Gini approach, the decision was made to focus in a hypothesis driven fashion on a small number of the potential analyses which could have been performed. For this reason, the data analysis plan was constructed around the inter-related hypotheses of differential Avonex prescribing discussed in detail above. This lead to the decision to split the DMTs into the two groups of “Avonex alone” and “Betaseron, Rebif, Copaxone combined” to create the Lorenz curves. Other dichotomization of the DMTs could have been performed however. For example, high-
dose Rebif costs approximately ~$8000/year more than Copaxone and ~$4000/year more than Betaseron but the head-to-head trials would suggest that these drugs are all equally efficacious (allowing for the sake of argument a cross-trial comparison of Betaseron and Rebif).\textsuperscript{87,88} An exploration of differential Rebif prescribing could therefore have been undertaken, in which case Rebif could have been compared to the other three DMTs. Alternately, the hypothesis could have been that low-volume prescribers or community neurologists preferentially use Copaxone given that this drug does not require monitoring bloodwork unlike IFN\textbeta. In this case, Copaxone could have been compared with the three interferons in aggregate. Alternatively, rather than examine the characteristics of the prescribing neurologists, an attempt could have been made to link patient demographics to specific scripts to assess whether socioeconomic status or patient geography was associated with differential utilization of DMTs.

This research focused on the potential issue of Avonex being overrepresented in the prescriptions of community neurologists despite the clinical trial evidence suggesting that on the whole it is the least effective of the four first-line DMTs. While this was not found to be the case, the methods used here can be adapted to examine other aspects of DMT prescribing patterns.

Lorenz curves have been applied to a wide variety of research questions outside of the initial application to economic disparities. Furthermore, the more recent development of techniques to derive confidence intervals for Gini coefficients means that Lorenz curves can be analyzed and compared in a more statistically rigorous fashion. To date, however,
only a handful of drug utilization studies based on Lorenz methodology have appeared in peer-reviewed publications. Lorenz curves are very helpful in assessing distributions and the degree of equality (or inequality) in a population; a point made very well in Figure 3 where the skew in cumulative DMT prescriptions versus cumulative Ontario neurologists shows dramatically how unequally neurologists use these medications. Lorenz curves, however, cannot be used to compare multiple variables at once. This is reflected in the data analysis plan created for this study where the three “non-Avonex” DMTs were grouped together so that only four curves would appear on a single graph. Unlike regression-based statistical techniques, the individual contributions of multiple different covariates (eg: practice location, age, gender) cannot be assessed simultaneously. Nevertheless, for our purposes, this methodology was able to adequately explore prescribing practices across Ontario and present the results in an easily understood visual format.

One extremely important finding from this study was how a small number of neurologists prescribed the overwhelming majority of DMTs in Ontario in 2009. This is perhaps not surprising given the increasing sub-specialization of neurological practice and medicine in general. The skew demonstrating that a small number of high-volume prescribers generate the majority of DMT scripts has both positive and negative policy implications. On the one hand, this skew indicates that Ontario MS patients currently do have access to MS clinic and community-based neurologists who have an active interest in MS. Such MS-specialists would be expected to deliver more expert care. Additionally, the high-volume prescribers who are affiliated with the MS Society of Canada-funded Ontario MS
Clinics would also have readier access to multidisciplinary teams to maximize patient care irrespective of DMT utilization.

Conversely, this finding is of significance with respect to future patient care since this means that MS patients who could benefit from DMT will need to have continued access to the relatively small subset of Ontario neurologists who prescribe such drugs. The prevalence of MS as a whole is increasing, so more and more patients will be eligible candidates for DMT. Our study only focused on the four first-line, well established DMTs which were developed in the 1990s. We did not examine natalizumab (Tysabri) which was only added to the Trillium formulary in the autumn of 2009. The risk of PML with Tysabri can reasonably be assumed to limit its use by non-MS-specialists. General neurologists understandably would typically want the opinion of a specialist before prescribing Tysabri and also would be reluctant to prescribe it on their own without ready access to the nursing support available in a MS clinic and the MRI and inpatient beds available in the tertiary hospitals affiliated with all of the Ontario MS clinics (except the satellite clinic in Thunder Bay).

While this thesis was being written, fingolimod (Gilenya®) became the sixth DMT, and the first oral DMT, to be approved for use by Health Canada. This drug has been shown to be effective in RRMS in two trials; one of which showed superiority to the first-line DMT Avonex. However, despite the enthusiasm with an oral agent, this treatment, like Tysabri, has rare but potentially serious side-effects. In addition, it also requires a degree of cardiorespiratory and ophthalmological baseline testing (although
subsequent monitoring of patients is not onerous). It is unlikely that such a medication will be widely embraced by the cohort of neurologists who currently do not prescribe the conventional DMTs which are markedly easier to monitor. Future planning for the care of MS patients must therefore ensure that adequate resources are in place for potential DMT-treatment candidates to receive timely access to MS specialists.

Unlike other provinces, the Ontario government made the decision to not restrict DMT prescribing to MS Clinic-based neurologists. It is somewhat ironic that nevertheless, the vast bulk of scripts are still generated by a fraction of the total number of neurologists in the province. Since the high-volume prescribing subset of Ontario neurologists includes both MS Clinic-based and community neurologists, any restriction on DMT prescribing in the province would only serve to increase the burden on the MS Clinic system and create a potential bottleneck delaying patient care.

Our results are also of significance from a more broad societal perspective given the significant cost of DMT prescriptions. As noted before, a comprehensive pan-Canadian study demonstrated a marked increase in the number of DMT prescriptions and associated costs from $187 million in 2002 to $287 million in 2007. This cost can be assumed to have continued to rise since 2007, especially with the addition of Tysabri which is priced ~$10,000—15,000 more than the standard therapies, and will doubtless increase in the future with the introduction of Gilenya and other agents in the future. Given that most provinces restrict DMT prescribing to MS clinics and this study has found that in Ontario most scripts are generated by the small number of high-volume
prescribers (either MS Clinic or community based), it would appear that a minority of neurologists are generating the vast majority of DMT costs. It is important to make sure that these medications are being used in a fashion that is both consistent with the clinical trial data; both within each province and across the country as a whole.
Conclusions

This analysis demonstrates the feasibility of using Lorenz Curve/Gini Coefficient statistical techniques in assessing the degree of variability in physician prescribing practices. The methodology used in this study could be adapted to address prescription patterns or health-care resource utilization in other medical contexts using pre-existing linked databases. Furthermore, the feasibility of using the ODB Database has also been demonstrated, despite the inherent limitations of a drug database which includes only scripts obtained through public drug insurance.

This study demonstrates that DMT prescribing is not uniform across the province with 12% of Ontario neurologists responsible for 80% of the MS DMT prescriptions filled through the ODB, in keeping with the first hypothesis. These percentages were also similar when each DMT was analyzed separately. When all prescribing neurologists were considered, regardless of other characteristics, only a trend was seen in support of the hypothesis that Avonex was more commonly prescribed. While these results were not statistically significant there was nevertheless a spread seen in the Lorenz curves with Avonex being the most uniformly prescribed (Gini 0.65), Rebif the most concentrated (Gini 0.76) with both Betaseron and Copaxone (Gini 0.73 for both) in between these two extremes.

The results also supported the hypothesis that the degree of neurological specialization was associated with different prescribing patterns. However, this was only shown when specialization was defined using prescription-volume. Neurologists who were high-
volume DMT prescribers (defined here using a 100 script cut-point) showed more variability in their prescribing practices versus low-volume prescribers who were more likely to use on a narrower range of DMTs. When specialization was defined by geographical co-localization with a MS clinic, differential prescribing patterns were not observed. As argued above, this suggests that within the ICES databases, prescription volume is reasonable proxy for medical specialization.

In contrast, the findings were not in keeping any of the three secondary hypotheses. Neither the length of time in practice nor gender were significantly correlated with DMT prescribing patterns and the urban/rural distinction was not testable. The only exception to this was significant difference between the non-Avonex prescription Lorenz curves of female and male neurologists which in isolation was presumably a spurious statistically significant result.

Since the introduction of the four first-line DMTs examined in this analysis, natalizumab and fingolimod have also been approved by Health Canada for use in RRMS. Relative to the interferons and glatiramer, both of these medications have rare but life-threatening side-effects and require much more frequent clinical and radiological monitoring. Fingolimod also requires an ophthalmoligcal assessment prior to and prolonged cardiac monitoring during administration of the first dose. Other medications under development such as alemtuzumab and ocrelizumab also have serious rare adverse events. It can be anticipated that the majority of Ontario neurologists who do not currently prescribe any of the first-line DMTs are unlikely to feel comfortable with the newer agents. As the
incidence of MS is increasing, it is imperative that processes are put in place to ensure that patients have access to MS specialist neurologists or high-volume prescribers.
Future Directions

From a methodological perspective, this research project has demonstrated that the ICES ODB prescription database can be utilized to examine populations other than the elderly, despite the limitations in assessing only a portion of the prescriptions written in the province. This will expand the range of issues that can be explored by ICES-affiliated researchers. Questions addressing drug prescribing or health-care resource utilization in other chronic diseases affecting non-elderly populations can be answered using these anonymized, linked databases. Such future research could expand on the analysis of DMT prescribing in Ontario undertaken so far. Additionally, this research could serve as a template to further assess prescribing practices for other neurological and non-neurological conditions in the province.

Of direct interest to the research presented here, the Lorenz curve techniques could address other aspects of DMT prescribing in Ontario. The specific DMTs could be examined individually or dichotomized differently as mentioned previously. For example, it could be hypothesized that Copaxone may be preferentially selected by prescribers and/or patients because of the perception that it has a more manageable side-effect profile than the interferons. This could be tested in a similar fashion to the data analysis plan utilized in the current study with Copaxone prescribing compared to the other three DMTs (either individually or in aggregate). From a health-care economics perspective, the prescribing patterns of high-dose Rebif could be compared and contrasted to the other DMTs as this medication seems comparable in efficacy to Copaxone but costs ~$8,000 more per patient per year.
This hypothesis-guided research data extraction and analysis plan focused solely on neurologist prescribing patterns. Patient preferences are also extremely important in clinical decision-making and could be examined in a similar fashion. Lorenz curves could be used to explore if geographical, socioeconomic or other MS patient characteristics were associated with differential prescribing by Ontario neurologists. For example, rural patients with less easy access to laboratories may preferentially choose Copaxone over the three interferon options as no monitoring blood-work is required with that particular DMT.

This project only explored the prescribing of the four first-line DMTs. It did not examine the prescribing of natalizumab (Tysabri®) or fingolimod (Gilenya®). Tysabri was added to the Exceptional Access Program in September 2009, although it had been available to Ontario patients with private insurance prior to that date. Gilenya is not yet available through the Trillium/EAP.

Although natalizumab is considered a more potent DMT (despite the lack of direct head-to-head comparator studies as detailed in the Background), it is generally considered to be a second-line DMT due to the risk of PML. This is reflected in the EAP criteria for natalizumab funding which require that a patient have shown either clinical or radiological deterioration despite the use of a first-line DMT or have documented intolerance to at least two of the four first-line DMTs. Furthermore, unlike the four first-line DMTs studied here, the EAP criteria explicitly state that a “MS specialist” must
request natalizumab. This latter requirement would automatically limit the number of Ontario neurologists prescribing this medication. Nevertheless it would be interesting to adapt the methodology used in this project to examine natalizumab prescribing, for example using the 2010 or 2011 calendar year.

As discussed previously, this study demonstrated that using “high-volume prescribers” as a surrogate for MS specialization revealed that a number of non-MS-clinic based neurologists were comfortable with the four first-line DMTs. However, as such neurologists are not able to prescribe natalizumab (at least through the EAP), it could be hypothesized that the MS clinic based geographical definition of MS specialist (as used in the third hypothesis) would correlate best with the majority of natalizumab prescriptions. The exception would be those neurologists with a primary practice address outside of a MS clinic recorded in the ICES physician database who work part-time in a MS clinic.

If fingolimod (Gilenya®) were to be added to the EAP in the future, it would also be of interest to explore how broadly Ontario neurologists prescribe the first available oral DMT. As with natalizumab however, the precise questions which could be asked would be dependant on how restrictive the reimbursement criteria would be with respect to which physicians could apply for EAP funding.

It would also be interesting to compare how specialized MS DMT use is in comparison to medications used in other neurological conditions. This could be approached in several different ways using Lorenz curves and the ICES databases. For example, the degree of
skew in prescribing within one patient population, such as Parkinson’s disease, could be examined as has been done in this research within the MS patient population. It could be hypothesized that the majority of Ontario neurologists, regardless of specialization or practice environment, would be comfortable with initiating levodopa/carbidopa therapy which is the most established therapy for Parkinson’s disease. In contrast, movement disorder specialists would be more likely to use other antiparkinsonian therapies such as dopamine agonists and catechol-O-methyl transferase inhibitors more liberally. If all Ontario neurologists were examined, with each class of antiparkinsonian treatment plotted individually, one would expect to see a series of nested Lorenz curves with levodopa/carbidopa closest to the line of equality. The neurologists prescribing the antiparkinsonian therapies demonstrating the greatest degree of skew away from the line of equality would represent the movement disorder specialists.

Another approach that could be taken would be to compare and contrast how “specialized” the management of different neurological disease complexes are. This could be done by creating aggregate groups of different prescriptions; including for example all MS DMTs, all antiepileptics, all antiparkinsonian agents and all triptans for migraine therapy. Each group of therapies could be used to create a Lorenz curve plotted for all Ontario neurologists. It could be assumed that all of the curves would show at least a moderate degree of skew as subspecializations exist for all classes or types of neurological conditions. Nevertheless, it could be hypothesized that conditions like MS would show a more marked skewing away from the line of inequality in comparison to
the curve for anti-migraine triptan therapies as these are much more standard medications which are commonly prescribed by both neurologists and non-neurologists.

It would also be of interest to assess the degree to which certain neurological conditions are treated by other physicians apart from neurologists. As mentioned above, conditions like migraine are commonly treated by non-neurologists so prescribing practices could be assessed amongst all Ontario physicians, or amongst general practitioners. The Lorenz curves for triptan prescribing of neurologists and non-neurologists could also be compared.

The examples of future research outlined above all relate to MS or neurology in general. The Lorenz methodology used here though could be adapted to study prescribing in other medical specialities. Regardless of the focus of such potential future research directions, it would be necessary to create testable hypotheses and to ensure that the Lorenz/Gini techniques are appropriate to address the specific clinical or health policy questions as outline previously. This research has demonstrated that important information on the distribution of MS DMT prescriptions by Ontario neurologists can be obtained using Lorenz curves. The combined simplicity and statistical utility of Lorenz curves makes them well suited to address medication utilization patterns to inform health policy decisions.
References


75 Kappos L, Polman CH, Freedman MS. Treatment with interferon beta-1b delays conversion to clinically definite and McDonald MS in patients with clinically isolated syndromes. Neurology 2006; 67:1242-1249.


97 Biogen Idec Canada, personal communication.


122 Ebers GC, Traboulsee A, Li D et al. Analysis of clinical outcomes according to original treatment groups 16 years after the pivotal IFNB-1b trial. JNNP 2010; 81:907-912.


214 Green CG, Krause DO, Wylie JL. Spatial analysis of campylobacter infection in the Canadian province of Manitoba. International Journal of Health Geographics 2006; 5:2


230 Health inequities in Manitoba: is the socioeconomic gap in health widening or narrowing over time? [Internet]. Winnipeg: Manitoba Centre for Health Policy; c2010. [cited 08/08/2011]. Available from http://mchp-appserv.cpe.umanitoba.ca/reference/Health_Ineq_final_WEB.pdf


