COMORBIDITY AND PERSISTENCE OF DISEASE-MODIFYING THERAPY USE FOR RELAPSING REMITTING MULTIPLE SCLEROSIS

by

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ABSTRACT

Comorbidity, the burden of diseases other than the index disease of interest, may impact the use of disease-modifying therapies (DMTs) among individuals with relapsing remitting multiple sclerosis (RRMS). Our objectives were to characterize the relationship between comorbidity and (1) persistence to initial DMT, (2) choice of initial DMT, and (3) reasons for initial DMT discontinuation. We identified individuals with RRMS or clinically isolated syndrome (CIS) starting a platform DMT (glatiramer acetate, interferon-β, dimethyl fumarate, teriflunomide) as initial therapy from 2001 to 2016 using the Dalhousie Multiple Sclerosis Research Unit database. Comorbidity was determined by linkage to administrative data from Health Data Nova Scotia. Among 1464 individuals with RRMS/CIS beginning platform therapy as initial DMT, median duration of DMT persistence was 4 years. There was no effect of comorbidity count on DMT persistence. Among specific comorbidities, there was an increased risk of discontinuing DMT in the presence of mental health comorbidity. Prior to 2013 when platform therapy consisted of only injectable DMT options, there was increased selection of glatiramer acetate compared to interferon-β among those with ≥2 comorbidities. From 2013 onward, there was no effect of comorbidity on selection of injectable versus oral DMT. There was increased risk of discontinuing initial DMT for lack of tolerability with ≥2 comorbidities. There was no effect of comorbidity on discontinuing initial DMT for lack of efficacy. Understanding the relationship between comorbidity and initial DMT patterns has implications on counselling patients with a new diagnosis of RRMS.

LIST OF ABBREVIATIONS USED

CI	Confidence Interval
CIS	Clinically Isolated Syndrome
DMSRU	Dalhousie Multiple Sclerosis Research Unit
DMT	Disease-Modifying Therapy
EDSS	Expanded Disability Status Scale
HCN	Health Card Number
HDNS	Health Data Nova Scotia
HLA	Human Leukocyte Antigen
HR	Hazard Ratio
IBD	Inflammatory Bowel Disease
ICD	International Classification of Diseases
ID	Identification Number
IHD	Ischemic Heart Disease
IQR	Interquartile Range
ITP	Immune Thrombocytopenic Purpura
MRI	Magnetic Resonance Imaging
MS	Multiple Sclerosis
NEDA	No Evident Disease Activity
NS	Nova Scotia
OR	Odds Ratio
PCCF	Postal Code Conversion Files
PDC	Proportion of Days Covered
PML	Progressive Multifocal Leukoencephalopathy
PPMS	Primary Progressive Multiple Sclerosis
QALY	Quality-Adjusted Life Year
RCT	Randomized Controlled Trial
RRMS	Relapsing Remitting Multiple Sclerosis
SE	Standard Error
SPMS	Secondary Progressive Multiple Sclerosis

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CHAPTER 1 INTRODUCTION

Multiple sclerosis (MS) is a demyelinating disease of the central nervous system that often results in functional impairment and reduced quality of life[1,2]. Among individuals with newly diagnosed MS, 85% of cases are classified as relapsing remitting multiple sclerosis (RRMS) which is characterized by subacute deterioration due to inflammatory attacks interspersed with periods of remission[1]. Although there is no cure for MS, there are more than ten disease-modifying therapies (DMTs) approved by Health Canada for RRMS[3].

Comorbidity is the total burden of illness other than the index disease of interest[4]. The most prevalent comorbidities among individuals with MS are depression (23.7%), anxiety (21.9%), hypertension (18.6%), hyperlipidemia (10.9%), and chronic lung disease (10.0%)[5]. Comorbidity is associated with delayed diagnosis of MS[6], increased risk of relapse[7], and increased risk of disability progression[8,9]. Although evidence is limited in RRMS, comorbidity may affect the efficacy, safety, and tolerability of DMT[10]. Comorbidity has been associated with a lower likelihood of initiating DMT[11]. There is emerging evidence that comorbidity results in an increased risk of discontinuing initial DMT due to lack of tolerability but not lack of efficacy[12].

Our aim was to characterize the relationship between comorbidity and DMT persistence. In addition, we described how comorbidity influences DMT selection along with reasons for DMT discontinuation. Comorbidity was expressed as a comorbidity count or the presence of an individual comorbidity (mental health disorder, hypertension, hyperlipidemia, diabetes, ischemic heart disease, lung disease, epilepsy, inflammatory bowel disease). Greater understanding of the effect of comorbidity on DMT use and persistence may facilitate more appropriate DMT

selection for patients with comorbidity. Ultimately, this may contribute to clinical decision-making by informing the discussion related to recommending DMT for individuals with MS and comorbidity.

CHAPTER 2 LITERATURE REVIEW AND RATIONALE

2.1 Overview of Multiple Sclerosis

MS causes demyelination of the brain, optic nerves, and spinal cord[1]. Although this process is believed to be immune-mediated, the etiology of MS remains unknown[13]. Across the MS spectrum, there are co-existing pathological findings of inflammation with demyelination and gliosis with neurodegeneration[14]. The immune system is closely linked with MS as classic inflammatory demyelinating lesions are mainly composed of T lymphocytes and macrophages while B lymphocytes activate T lymphocytes[15,16]. In addition, B lymphocyte aggregation within meninges is associated with cortical demyelination[14,17]. Microglial activation and astrocytosis are associated with axonal degeneration[14,17]. These pathological features coexist along the MS continuum despite inflammation traditionally associated with relapses and neurodegeneration traditionally associated with progression[14,17].

There is an approximately ten-fold increased risk of MS among first-degree relatives due to a combination of genetic and environmental factors[18]. Although there is no single gene implicated in the development of MS, genome wide association studies suggest that >230 genes, many influencing immune system function, contribute to greater risk of developing MS[19]. Human leukocyte antigen (HLA) genes including HLA-DRB1*15:01 have the strongest association with MS[19,20]. Well established risk factors associated with MS include reduced sun exposure/low vitamin D, smoking, Epstein Barr virus infection, and adolescent obesity[21]. Prior Epstein Barr virus exposure, adolescent obesity, and smoking may interact with HLA genes to increase susceptibility to MS[21].

Canada has among the highest prevalence of MS in the world with prevalence estimates as high as 279/100,000[22,23]. Based on analyses of Nova Scotia (NS) provincial health administrative data in 2010, the age-standardized prevalence of MS was 266.9 (95% confidence interval (CI) 257.1-277.1) per 100,000 and incidence 5.17 (95% CI 3.78-6.56) per 100,000/year[24]. In this population, incidence of MS was three-fold greater among women compared to men with peak incidence at age 40-44 years for women and 50-54 years for men[24]. MS has a significant impact on function which is supported by the finding that individuals with MS have three-fold higher odds of being unemployed[2]. In addition, there is an average loss of ten quality-adjusted life years (QALYs) among individuals with MS[2].

2.2 Clinical Evaluation of Multiple Sclerosis

Diagnosis of MS is based on evolving diagnostic criteria[25-31]. In 2001, the diagnostic criteria for RRMS were significantly revised with the McDonald criteria placing greater emphasis on magnetic resonance imaging (MRI) findings[28-31]. Currently, diagnosis of RRMS according to McDonald criteria requires evidence of demyelination with dissemination in space and time provided by a combination of clinical history, physical examination, MRI, and cerebrospinal fluid analysis demonstrating oligoclonal banding[31]. A single demyelinating attack not fulfilling McDonald criteria for diagnosis of RRMS is referred to as clinically isolated syndrome (CIS)[28-31]. Those identified with CIS are at high risk of conversion to RRMS if there are ≥1 clinically silent lesions consistent with demyelination on MRI brain at baseline[32]. As the McDonald criteria evolve, RRMS is diagnosed earlier in the clinical course including individuals that would have been diagnosed with CIS according to older criteria[33].

MS activity is typically described in terms of evidence of inflammatory disease activity (relapses and new inflammatory lesions on MRI) and progression (accumulation of disability)[34]. A relapse is a monophasic episode of symptoms or objective findings due to demyelination which evolves over ≥24 hours in the absence of fever or infection[31]. Typical attacks of demyelination called relapses include optic neuritis, partial myelitis, or brainstem/cerebellar symptoms. Disability is described using a validated assessment tool with the most widely accepted disability measure for MS being the Expanded Disability Status Scale (EDSS)[35]. The EDSS ranges from 0 (no MS-related symptoms) to 10 (death related to MS). The EDSS is heavily based on motor disability with scores of 4.0 to 7.5 based on ambulatory distance and use of a gait aid. MRI demonstrates characteristic demyelinating lesions in ≥2 locations among periventricular, cortical/juxtacortical, infratentorial, and spinal cord regions[31]. Absence of relapses, progression, and new inflammatory lesions on imaging is referred to as NEDA or 'no evident disease activity'[36].

At initial MS diagnosis, 85% of MS cases are due to RRMS which is characterized by subacute deterioration due to inflammatory attacks interspersed with periods of remission[1]. Over time, RRMS may transition into secondary progressive multiple sclerosis (SPMS) which is characterized by progressive accumulation of disability that is independent of relapses. Approximately 15% of MS patients experience primary progressive multiple sclerosis (PPMS) with gradual accumulation of disability, independent of relapses, from disease onset. Despite these clinical classifications, there are co-existing pathological findings of inflammation with demyelination and gliosis with neurodegeneration across the MS spectrum[14].

2.3 Treatment of Relapsing Remitting Multiple Sclerosis/Clinically Isolated Syndrome

Although there is no cure for MS, there are more than ten DMTs approved by Health Canada for RRMS while a limited subset also have Health Canada approval for CIS[3]. All DMTs modulate or suppress the immune system to reduce inflammatory disease activity with improvement in risk of relapses[37]. DMTs are grouped into platform and higher-efficacy treatments (Figure 1). Platform therapies are initial treatment for the majority of patients. Higher-efficacy therapies are reserved for individuals with breakthrough disease on a platform therapy or in a select group of patients with newly diagnosed rapidly evolving severe RRMS[37-39]. At the time of this study, funding from provincial or private insurance plans in Canada (including NS) was typically limited to platform therapy options as initial treatment for RRMS.

Platform therapies include injectable (glatiramer acetate, interferon-β) and oral (dimethyl fumarate, teriflunomide) therapies. Injectable platform therapies (glatiramer acetate, interferon-β) are the only DMTs with Health Canada approval for treatment of CIS[3]. Higher-efficacy therapies consist primarily of biologic agents administered by infusion (natalizumab, alemtuzumab, ocrelizumab) although some oral therapies (fingolimod, cladribine) may be considered in this category[37,40,41]. Each DMT has at least one randomized controlled trial (RCT) demonstrating reduction in inflammatory disease activity compared to placebo or another DMT. Among platform therapies, clinical trials have demonstrated relapse reduction compared to placebo for glatiramer acetate[42], interferon-β[43,44], teriflunomide[45,46], and dimethyl fumarate[47,48]. In addition, clinical trials of platform therapies have demonstrated reduction in new demyelinating lesions on MRI compared to placebo for interferon-β[49,50], teriflunomide[45], and dimethyl fumarate[47,48]. Clinical trials of platform therapies do not provide consistent evidence of improvement in disability progression[42-48]. DMTs slow short-term disability progression measured using EDSS following treatment initiation compared to pre-treatment[51]. Overall,

observational studies indicate DMTs probably alter long-term disability progression including extending the interval to developing SPMS[52,53].

Treatment options for RRMS have been evolving over the past approximately 20 years with a greater variety of DMT options as medications are approved by Health Canada (Table 1)[54]. For many years, injectable therapies (glatiramer acetate, interferon-β) were the only DMTs available. In the past approximately 7 years, there has been access to oral platform therapies. In the era prior to availability of oral platform therapy (before 2013), initial choice of therapy would have focused on selection of glatiramer acetate versus interferon-β. In the era following availability of oral platform therapy (from 2013 onward), initial decision-making for choosing MS therapy often begins by deliberating on the merits of injectable (glatiramer acetate, interferon-β) versus oral (dimethyl fumarate, teriflunomide) DMT. Higher-efficacy therapy is generally reserved for failure of a platform therapy although higher-efficacy therapy may be used as initial therapy for a select group of patients with aggressive RRMS onset[37-39].

Deriving a clinical benefit from DMT for RRMS relies on medication persistence and adherence as it is unlikely for a medication to be effective if it is not taken as prescribed. Persistence is the time period spanning the date of initiation to the date of discontinuation provided there is no interval exceeding a specified treatment gap[55]. Adherence is the extent to which doses are taken as prescribed which is typically reported as a percentage[55]. In MS literature, adherence is expressed as proportion of days covered (PDC) defined as the number of days DMT supplied divided by the number of days in the treatment period[56,57]. A PDC ≥80% is often defined as adequate adherence although this threshold is arbitrary. In general, poor adherence to medications is associated with increased morbidity, mortality, and cost to the healthcare system[58].

Among individuals with RRMS starting on an injectable DMT in the Canadian province of Manitoba, the median time to therapy discontinuation was 4.2 years[57]. Among those who remained on therapy for ≥1 year, 80% of participants exhibited adequate adherence defined as PDC ≥80% during the first year of treatment. In a Canadian cohort from three provinces, the median time to discontinuation of injectable DMT ranged from 4.1 to 5.9 years[56]. If only initial DMT was considered, the median time to discontinuation of injectable DMT ranged from 1.9 to 4.0 years. In this Canadian cohort, 76.4% of participants exhibited adequate adherence defined as PDC ≥80% during the first year following DMT initiation. Among individuals with RRMS starting on an oral DMT (dimethyl fumarate, fingolimod, teriflunomide) in the Canadian province of British Columbia, approximately 20% had discontinued therapy at 1 year[59]. In this cohort, 81.7% exhibited PDC ≥80% at 1 year.

Age, sex, and socioeconomic status were not associated with persistence or adherence in a Canadian cohort examining injectable DMT[56]. In that Canadian cohort, there was improved adherence among those with four or more physician visits in the year before injectable therapy was initiated. As well, there was reduced DMT persistence with increasing number of non-MS medications as a proxy for comorbidity[56]. Age, sex, and comorbidity were not associated with persistence or adherence in a cohort from British Columbia examining oral DMT[59]. In this oral therapy cohort, there was greater adherence among those who had previously received DMT[59].

2.4 Comorbidity and Multiple Sclerosis

Comorbidity, multimorbidity, and frailty are concepts of increasing interest in healthcare[60]. Comorbidity refers to medical conditions other than the index disease of interest that are present at the time of diagnosis or following diagnosis of the index disease but are not a consequence of

the index disease[4,60]. Multimorbidity is proposed to be the co-occurrence of two or more chronic diseases, without specific reference to an index disease, although there is substantial variability in the application of this term[60]. Frailty is the presence of increased vulnerability to adverse health outcomes[61]. Frailty may be quantified using a frailty index. Health deficits included in a frailty index may include symptoms, signs, diseases, disabilities, or abnormal test results. The frailty index is expressed as a ratio of the count of health deficits present in an individual relative to the total count of health deficits considered. Among different studies using a frailty index, there is a strong association between the frailty index and adverse outcomes including risk of death and institutionalization[61].

The most prevalent comorbidities among individuals with MS are depression (23.7%), anxiety (21.9%), hypertension (18.6%), hyperlipidemia (10.9%), and chronic lung disease (10.0%) according to a meta-analysis[5]. Comparison of individuals with MS to age-, sex-, and geographically-matched controls from a population-based Canadian cohort including NS demonstrated that all examined conditions (hypertension, diabetes, hyperlipidemia, ischemic heart disease [IHD], chronic lung disease, epilepsy, fibromyalgia, inflammatory bowel disease [IBD], depression, anxiety, bipolar disorder, schizophrenia) with the exception of hyperlipidemia were more common among individuals with MS compared to controls at the time of MS diagnosis[62]. In this study, men with MS had a disproportionately higher relative risk than women with MS as compared to matched persons without MS of the same sex for a number of comorbidities including hypertension, diabetes, epilepsy, depression, and anxiety.

Comorbidity has implications for MS diagnosis and prognosis. Diagnosis of MS is delayed in the presence of comorbidity[6,63]. In a North American registry study, diagnostic delay was reliably increased when vascular, autoimmune, musculoskeletal, gastrointestinal, visual, or

mental comorbidity was present[6]. In a Danish cohort, diagnostic delay was increased in the presence of cerebrovascular, cardiovascular, lung, diabetes, and cancer comorbidity[63]. In addition, comorbidity confers 1.66 increased odds of moderate versus mild disability at diagnosis with evidence of a dose-response effect whereby each additional comorbidity confers increased odds of moderate or severe rather than mild disability at diagnosis[6].

Higher burden of comorbidity is likely associated with increased risk of relapse and may be associated with increased risk of disability progression. Among a cohort of 885 individuals with relapsing disease at diagnosis from four Canadian provinces, high comorbidity burden, defined as ≥3 comorbid conditions at baseline, was associated with a 1.45 increased risk of relapse over the next 2 years[7]. Secondary analysis of data from a clinical trial of injectable therapies resulted in a similar finding that individuals with ≥2 comorbidities are at greater risk of relapse than individuals with no comorbidity[64]. Comorbidity may impact long-term prognosis in MS with burden of comorbidity correlated with long-term EDSS disability progression[8,9]. In a large Canadian cohort, each additional physical comorbidity was associated with a 0.18 increase in EDSS[9]. Specific conditions associated with increased EDSS included IHD and epilepsy[9]. Among individuals with a vascular comorbidity at the time of MS diagnosis, the median time to use a cane was 13 years compared to 19 years among those without a vascular comorbidity at the time of MS diagnosis[8]. Conversely, secondary analysis of data from a clinical trial of injectable therapy did not demonstrate an effect of comorbidity on disability progression[64].

Among individuals with MS, comorbidity is associated with an increased risk of all-cause hospitalization excluding admissions due to childbirth[65,66]. Comorbidity, particularly a mental health comorbidity, among individuals with MS was associated with increased risk of collecting a disability pension in a Swedish cohort[67]. Although comorbidity increases mortality risk among

individuals with MS, the effect of comorbidity on mortality is similar to age-, sex-, and geographically-matched controls in a population-based Canadian cohort[68].

2.5 Comorbidity Measurement

Comorbidity may be considered individually or quantified using a comorbidity count or a comorbidity index[4]. A comorbidity count is the simple sum of conditions[4]. While a count is easy for a clinician to use, it considers all comorbidities to be equal. High comorbidity burden has previously been described in MS as ≥2 or ≥3 conditions[7,64,69]. High comorbidity burden is associated with increased risk of relapse and disability progression[7,64,69]. Each additional physical comorbidity confers an added risk of accelerated EDSS progression[9]. EDSS scores were not censored based on specific comorbidity as it remains unknown which comorbidities might or might not contribute to disability progression in MS[9].

A comorbidity index is a weighted measure applying different weights to different conditions which may also account for disease severity[4]. There is no validated comorbidity index specifically for individuals with MS. An example of a comorbidity index is the Charlson Comorbidity Index which is a validated measure to predict 1-year mortality among hospitalized patients[70]. The original index assigned a weight of 1 to 6 for each of 19 comorbid conditions based on risk of mortality at 1 year. Subsequently, the Charlson Comorbidity Index was modified to retain 17 comorbid conditions defined by international classification of diseases (ICD) codes including ICD-9 and ICD-10 codes for application of administrative data[71,72]. The Charlson Comorbidity Index is primarily employed when mortality is the outcome of interest[4]. A modified version of the Charlson Comorbidity Index excluding potential MS-related

complications including hemiplegia, paraplegia, and dementia has previously been used to quantify disability in studies examining burden of comorbidity in MS[59,73].

Comorbidity may be assessed using patient self-report, clinician diagnoses, and administrative data. Administrative case definitions for specific health conditions among individuals with MS in NS have previously been validated[74]. In NS, validation was performed by exploring agreement between self-report and administrative data for 1923 individuals with MS in NS. Administrative data was searched using ICD-9 and ICD-10 codes based on lists of ICD 9/10 codes compared to clinical terms for specific health conditions. Several case definitions were developed for each health condition varying the number of hospital and physician claims required and number of years of data used to determine whether the individual was affected. Administrative case definitions were originally developed in the province of Manitoba with subsequent use in Nova Scotia. Positive predictive value of validated administrative case definitions for specific health conditions among individuals with MS in NS are: hypertension 74%, hyperlipidemia 68%, diabetes 67%, IHD 36%, IBD 90%, epilepsy 51%, depression 53%, and anxiety 34%[74].

In addition, validated case definitions for chronic lung disease, migraine, any mental health disorder, and psoriasis have been developed for individuals with MS in Manitoba[75-77]. In Manitoba, administrative health data can be searched for physician, hospital, and prescription claims while administrative health data did not include prescription claims in NS during the study period. Comorbidity case definitions developed in Manitoba explored physician and hospital claims with and without prescription claims. Administrative case definitions for conditions such as chronic lung disease performed better with inclusion of prescription claims[75]. Using definitions with only hospital and physician claims, the positive predictive value was 33%

for chronic lung disease and 66% for any mental health disorder[75,76]. Health conditions of interest were selected based on prevalence of comorbidity among individuals with MS and/or the literature suggested an association of the comorbidity with MS clinical outcomes[5,9,62].

2.6 Comorbidity and Multiple Sclerosis Treatment

Although evidence is limited in RRMS, comorbidity may affect the efficacy, safety, and tolerability of DMT[10,12]. In addition, there may be increased risk of drug-drug and drug-disease interactions. Many RCTs showing benefit of DMT in RRMS exclude individuals with comorbidity[10]. Although exclusion of individuals with comorbidity is intended to maximize participant safety in RCTs, there is a resulting paucity of information regarding the efficacy, safety, and tolerability of DMTs among MS patients with comorbidity.

There are many potential adverse effects of DMT (Table 2). A number of DMTs are associated with an elevated risk for abnormal liver enzymes including interferon-β, teriflunomide, dimethyl fumarate, and fingolimod; this may lead to avoidance of these medications among individuals with comorbid liver disease. There is an increased risk of macular edema among individuals with MS and comorbid diabetes or uveitis after starting fingolimod[78]. Fingolimod is contraindicated in individuals with recent myocardial infarction or history of heart block due to risk of cardiac arrhythmia. Dimethyl fumarate is associated with gastrointestinal symptoms which may limit use among individuals with IBD or irritable bowel syndrome. In contrast, there are potential beneficial effects of DMTs on comorbidities; such as dimethyl fumarate improving psoriatic skin lesions[79].

A greater number of comorbidities is associated with a lower likelihood of initiating DMT[11]. Although combined data from three Canadian provinces did not demonstrate a

preference of injectable DMT by comorbidity count, there was greater likelihood of selecting glatiramer acetate in NS with ≥3 comorbidities[11]. Canadian administrative data by province for Manitoba, Saskatchewan, and British Columbia showed that median persistence of any DMT ranged from 4.1 to 5.9 years while median persistence to initial DMT ranged from 1.9 to 4.0 years[56]. Persistence is the interval spanning from initiation to discontinuation provided there is no interval exceeding a specified treatment gap[55]. In MS literature, DMT persistence is typically defined as a switch to another DMT or lapse in treatment exceeding a specified time interval[56]. There is emerging evidence that comorbidity effects DMT persistence with increased risk of switching from initial DMT due to intolerance but not lack of efficacy[12]. Among 1877 participants with MS starting DMT within 1 year of diagnosis in Italy, approximately half discontinued DMT by 3 years with comorbidity associated with an increased risk of stopping for lack of tolerability (hazard ratio [HR] 1.42, 95% confidence interval [CI] 1.07-1.87) but not lack of efficacy (HR 1.19, 95% CI 0.92-1.55).

Overall, there is a lack of information on the relationship between comorbidity and DMT use. Comorbidity has been shown to influence MS including delaying MS diagnosis[6], increasing risk of disability progression[9], and decreasing likelihood of starting DMT[11]. Clinical trials evaluating DMT have excluded individuals with comorbidity leading to a poor understanding of DMT persistence, efficacy, and safety in this population[10]. In this study, we described the relationship between comorbidity and persistence to initial platform DMT for individuals with CIS and RRMS. As well, we characterized the effect of comorbidity on selection of initial platform DMT and reasons for discontinuation. This study examined platform DMT (glatiramer acetate, interferon-β, dimethyl fumarate, teriflunomide) as the majority of newly diagnosed

individuals, without features of aggressive onset RRMS, were started on one of these therapies during the study period.

Table 1. Disease-Modifying Therapy Availability in Canada (as of January 1, 2020)

Drug: Generic (Brand)	Original Market Date in Canada[a]	DMT Category	DMT Route of Administration
Interferon-β 1b (Betaseron, Extavia)	December 1995, May 2010	Platform	Injectable
Interferon-β 1a (Rebif, Avonex)	February 1998, June 1998	Platform	Injectable
Peginterferon-β 1a (Plegridy)	September 2015	Platform	Injectable
Glatiramer acetate 20 mg daily, 40 mg thrice weekly (Copaxone)	October 1997, August 2016	Platform	Injectable
Natalizumab (Tysabri)	November 2006	Higher-Efficacy	Infusion
Fingolimod (Gilenya)	March 2011	Higher-Efficacy	Oral
Dimethyl Fumarate (Tecfidera)	April 2013	Platform	Oral
Teriflunomide (Aubagio)	November 2013	Platform	Oral
Alemtuzumab (Lemtrada)	January 2014	Higher-Efficacy	Infusion
Ocrelizumab (Ocrevus)[b]	September 2017	Higher-Efficacy	Infusion
Cladribine (Mavenclad)	November 2017	Higher-Efficacy	Oral

DMT disease-modifying therapy

[a]Original marketing dates obtained from Drug Product Database[54]

[b]Ocrelizumab may be used as first-line therapy but was not available during the study period

Daclizumab (Zinbryta) withdrawn without any patients in NS exposed

Table 2. Disease-Modifying Therapy Safety Profile

	Safety Profile	
Drug: Generic (Brand)	**Common (>5%)**	**Uncommon (<5%)**
Interferon-β 1b (Betaseron, Extavia)	Injection site reaction, malaise, elevated liver enzymes, abnormal blood counts, menstrual disorder, hypertension	Liver failure, depression
Interferon-β 1a (Rebif, Avonex)	As above	As above
Peginterferon-β 1a (Plegridy)	As above	As above
Glatiramer acetate 20 mg daily, 40 mg thrice weekly (Copaxone)	Injection site reaction, post-injection reaction	Nil significant
Natalizumab (Tysabri)	Nil significant	Anaphylaxis, increased risk infection, PML
Fingolimod (Gilenya)	Headache, increased risk infection, elevated liver enzymes	Disseminated herpes infection, cardiac arrhythmia, macular edema, PML
Dimethyl Fumarate (Tecfidera)	Flushing, diarrhea, lymphopenia	Increased risk infection, elevated liver enzymes, PML
Teriflunomide (Aubagio)	Alopecia, diarrhea, elevated liver enzymes	Hypertension, increased risk infection, neutropenia
Alemtuzumab (Lemtrada)	Autoimmune thyroid disorders, anaphylaxis	Increased risk infection, ITP, Goodpasture's disease, autoimmune hepatitis, pulmonary alveolar hemorrhage, stroke
Ocrelizumab (Ocrevus)	Anaphylaxis, increased risk infection	Increased risk cancer
Cladribine (Mavenclad)	Headache, lymphopenia	Increased risk infection

ITP immune thrombocytopenic purpura, PML progressive multifocal leukoencephalopathy

Adverse effect profile obtained from product monographs

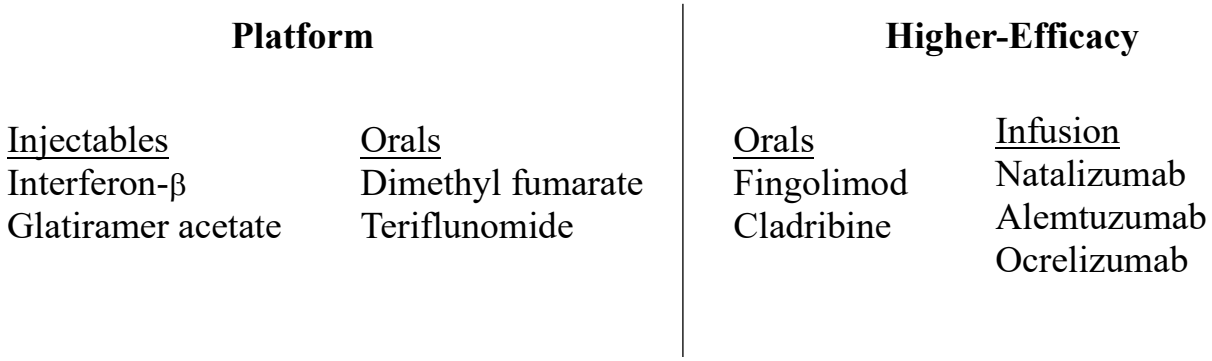


Figure 1. Disease-modifying therapy for relapsing remitting multiple sclerosis

CHAPTER 3 RESEARCH OBJECTIVES

Comorbidity influences MS-related outcomes with higher comorbidity burden associated with increased risk of relapse and increased risk of disability progression[7,9]. However, there is limited information concerning the effect of comorbidity on DMT persistence, efficacy, and safety[10]. We wanted to understand the relationship between comorbidity and initial platform DMT use to inform the discussion around starting platform DMT among RRMS patients with comorbidity.

3.1 Objectives

3.1.1 Primary Objectives

1. Evaluate effect of comorbidity on initial DMT persistence
    a. Examine the effect of comorbidity count on initial DMT persistence
    b. Determine the effect of specific comorbidities on initial DMT persistence

3.1.2 Secondary Objectives

1. Evaluate effect of comorbidity on initial DMT selection
    a. Examine the effect of comorbidity count on initial DMT selection
    b. Determine the effect of specific comorbidities on initial DMT selection
2. Evaluate effect of comorbidity on initial DMT reasons for discontinuation
    a. Examine the effect of comorbidity count on initial DMT reasons for discontinuation
    b. Determine the effect of specific comorbidities on initial DMT reasons for discontinuation

3.2 Hypotheses

We hypothesized that increased burden of comorbidity is associated with shorter persistence to initial DMT. In addition, we hypothesized that increased burden of comorbidity is associated with selection of a DMT with fewer potential adverse effects. In the period prior to the availability of oral platform therapy (before 2013), higher comorbidity burden was hypothesized to be associated with increased selection of glatiramer acetate compared to interferon-β. In the period following introduction of oral platform therapy (from 2013 onward), higher comorbidity burden was hypothesized to be associated with increased selection of injectable therapy compared to oral therapy. Finally, we hypothesized that increased burden of comorbidity is associated with increased risk of discontinuing initial DMT for lack of tolerability but not lack of efficacy.

CHAPTER 4 METHODS

4.1 Research Design

Secondary data analyses were performed using data from the Dalhousie Multiple Sclerosis Research Unit (DMSRU) and Health Data Nova Scotia (HDNS). The study design was a retrospective cohort design whereby the exposure was comorbidity and the primary outcome was initial DMT persistence. We evaluated the relationship between comorbidity and initial DMT persistence among all individuals with CIS or RRMS in NS starting initial DMT between 2001 and 2016. Research ethics board approval was obtained from the Nova Scotia Health Authority Research Ethics Board (#1023555).

4.2 Population

The study population consisted of individuals with CIS or RRMS in NS starting initial platform DMT between January 1, 2001 and December 31, 2016 identified using the DMSRU database. CIS was included as the diagnostic criteria for RRMS continued to evolve over the study period with individuals receiving a diagnosis of CIS according to earlier criteria having RRMS according to more recent diagnostic criteria[33]. As well, initial platform DMT specifically injectable therapies (glatiramer acetate, interferon-β) are approved for both CIS and RRMS[3]. Date of starting initial DMT was the index date. The DMSRU has maintained a prospective database since 1980 with information on demographics, RRMS diagnosis, RRMS treatment, and RRMS outcomes. All individuals included in this study from the DMSRU database provided consent for use of their health information for research purposes including linkage to administrative data for research purposes. In the DMSRU database, >95% of the relevant MS

population provided consent for participation in research including linkage to administrative data. Since 1998, all NS residents receiving provincial funding for DMT required annual evaluation at the DMSRU[80]. The DMSRU was the only provider of MS specialty care in NS until early 2017. As a result, there is expected to be near complete case ascertainment for individuals with CIS or RRMS in NS starting initial DMT during the study period[24]. Case ascertainment beginning in 2001 corresponds to the implementation of modern MS diagnostic criteria using MRI features to facilitate MS diagnosis[28].

All individuals with RRMS identified using the DMSRU database had records linked to data from HDNS. This was accomplished by sending study-specific identification number (ID), NS health card number (HCN), sex, and date of birth to Medavie Blue Cross for encryption of HCN according to established HDNS protocols. In addition, the DMSRU prepared a file containing demographic and clinical data which was sent directly from the DMSRU to HDNS with the study ID used for linkage.

Comorbidities were determined from provincial MSI Physician Billings and CIHI Discharge Abstract Database using ICD-9/10 codes. Administrative data was searched beginning 5 years prior to and continuing for 1 year after the index date. Administrative case definitions for comorbidity among individuals with MS in NS have previously been validated[74]. Validated case definitions for comorbidity among individuals with MS in NS have been developed for hypertension, hyperlipidemia, diabetes, IHD, IBD, and epilepsy. A validated case definition for chronic lung disease has been developed for individuals with MS in Manitoba and previously applied to administrative health data in NS[75]. A validated case definition for any mental health disorder has been developed for individuals with MS in Manitoba and previously applied to administrative health data in NS[76]. Administrative case definitions were validated by

evaluating performance against patient-reported comorbidities[74,75] or diagnoses extracted from the medical record[75,76].

Comorbidity definitions for individuals with MS were available for many of the most prevalent comorbidities among individuals with MS which include depression, anxiety, hypertension, and hyperlipidemia[5]. In addition to common comorbidities, we were interested in comorbidities that may be associated with MS clinical outcomes including the presence of co-existing central nervous system or inflammatory disorders. Vascular comorbidity including IHD is associated with an increased risk of disability progression[8,9]. There is a validated case definition for IHD among individuals with MS in NS[9,74,81]. A co-existing central nervous system disorder of interest was epilepsy. There is a three-fold greater prevalence of epilepsy among individuals with MS compared to the general population[75]. Epilepsy has a validated case definition in NS[74]. An inflammatory disorder of interest was IBD. In addition to being an inflammatory disorder, IBD may influence choice of platform therapy as dimethyl fumarate is associated with worsening of gastrointestinal symptoms. There is a validated case definition for IBD among individuals with MS in NS[74].

4.3 Measures of Interest

Measures extracted from the DMSRU database included demographic information along with details of RRMS diagnosis and treatment (Table 3). Measures in the DMSRU database were based on clinical data reported on a standardized data entry form completed by the treating neurologist. Demographic information included sex, age at RRMS diagnosis, and postal code. Sex was a variable of interest as RRMS affects females to males in a 3:1 ratio although DMT persistence has not been associated with sex[24,56]. Age at RRMS diagnosis was a variable of

interest as late onset RRMS demonstrates more rapid accumulation of disability although DMT persistence has not been associated with age[56,82]. Postal code was used to determine neighbourhood income quintile according to the Statistics Canada Postal Code Conversion Files (PCCF) created using data from the 2006 long form census presented as quintile within census region[83]. Neighbourhood income quintile was used as a measure of socioeconomic status although DMT persistence has not been associated with socioeconomic status[56]. Age, sex, and socioeconomic status were considered important variables to include given the importance of social determinants of health in chronic disease[84].

Details of RRMS diagnosis included year of RRMS diagnosis, diagnostic lag, and disability measured using EDSS at DMT initiation. Year of RRMS diagnosis determined DMT options available. Diagnostic lag or duration from symptom onset to RRMS diagnosis was a variable of interest as diagnosis of MS is delayed in the presence of comorbidity[6]. EDSS at DMT initiation was included as diagnosis of MS is delayed in the presence of comorbidity with increased disability at diagnosis[6]. EDSS is a validated MS disability scale, ranging from 0 (no MS-related symptoms) to 10 (death related to MS), and is the most widely accepted measure of MS disability[35]. EDSS at DMT initiation was defined as the most recent EDSS prior to starting initial DMT within ≤1 year.

Details of initial DMT included year of DMT initiation, DMT duration, DMT type, and reason for DMT discontinuation. Year of DMT initiation was a variable of interest as this determined therapy options available. Duration of initial DMT was the primary outcome of interest. DMT discontinuation was defined as a switch to another DMT or a lapse in DMT >30 days. Selection of first DMT type was a secondary outcome of interest. Type of DMT was categorized into injectable (glatiramer acetate, interferon-β) versus oral (dimethyl fumarate,

teriflunomide) DMT. Reason for discontinuation of first DMT was a secondary outcome of interest. Examined reasons for discontinuation included discontinuation due to lack of efficacy (treatment failure), discontinuation due to lack of tolerability, and other reason for discontinuation.

Comorbidity, the key exposure variable, was obtained from HDNS by searching MSI Physician Billings and CIHI Discharge Abstract Database for administrative case definitions of hypertension, hyperlipidemia, diabetes, chronic lung disease, ischemic heart disease (IHD), epilepsy, inflammatory bowel disease (IBD), and mental health disorder (anxiety, depression, bipolar disorder, schizophrenia) (Table 4, Table 5). First claim for the comorbidity was considered the date of diagnosis. Once a comorbidity occurred, it was considered present for the rest of follow-up. The approach of considering a comorbidity present for the rest of follow-up has previously been used in examining the association between comorbidity and initiation of DMT for RRMS[11]. It is acknowledged that the diagnostic threshold and/or severity of a comorbidity may change over time. Administrative data were searched beginning five years prior to date of DMT initiation and extending to one year after date of DMT initiation to maintain a consistent observation period.

4.4 Statistical Analysis

The primary exposure of interest was comorbidity count and the primary outcome of interest was initial DMT persistence. The main survival analysis was time to discontinuation of initial DMT according to comorbidity count (0, 1, ≥2) examined using Kaplan Meier survival analyses and Cox proportional hazards regression models. Comorbidity count was selected given prior use in MS literature with sample size resulting in count of 0, 1, or ≥2 comorbidities[7,64,69]. Subgroup

analyses were performed to examine the effect of DMT type on initial DMT persistence. DMT type was explored as a binary variable categorized into injectable versus oral DMT. The effect of specific validated comorbidities was examined by replacing comorbidity count in the Cox proportional hazards regression model with a single model including the specific comorbidities of interest. Any validated comorbidity with fewer than 10 affected individuals was included in the model in aggregate form as 'other comorbidity' provided 'other comorbidity' had a total of ≥10 individuals. This was done to avoid reporting blocks with small sample size and to improve the performance of the model.

Secondary outcomes of interest included initial DMT selection and reason for DMT discontinuation with comorbidity as the exposure of interest. Logistic regression models were developed to explore the relationship between comorbidity and DMT selection. As a result of the evolving availability of DMT over time, selection of DMT was analyzed differently in the period prior to the availability of oral platform therapy (before 2013) and following introduction of oral platform therapy (from 2013 onward). Logistic regression models for selection of therapy prior to availability of oral platform therapy used a binary outcome of interferon-β versus glatiramer acetate. Logistic regression models for selection of therapy following availability of oral platform therapy used a binary outcome of injectable (glatiramer acetate, interferon-β) versus oral (dimethyl fumarate, teriflunomide) DMT. Logistic regression models used comorbidity count as the primary exposure of interest. Subsequently, logistic regression analysis was performed replacing comorbidity count with a single model including the specific comorbidities of interest.

Logistic regression models were developed to explore the relationship between comorbidity and reason for DMT discontinuation. Only initial discontinuation of first DMT was

considered. Discontinuation was defined as switch to another DMT or interruption of DMT >30 days. Logistic regression models used a binary outcome of discontinuation due to lack of efficacy (treatment failure) or not while separate logistic regression models examined discontinuation for lack of tolerability or not. Two models were developed as discontinuing for lack of efficacy and/or lack of tolerability were not mutually exclusive events. Logistic regression models used comorbidity count as the primary exposure of interest. Subsequently, logistic regression analysis was performed replacing comorbidity count with a single model including the specific comorbidities of interest. Subgroup analyses were performed to examine the effect of DMT type on discontinuation due to lack of efficacy and discontinuation for lack of tolerability. DMT type was explored as a binary variable categorized into injectable versus oral DMT.

Although there is evidence that DMT persistence is not associated with age, sex, or socioeconomic status, we considered these variables as potential confounding variables due to the importance of social determinants of health in chronic disease[56,84]. Additional potential confounding variables were date of first DMT initiation, age at RRMS diagnosis, diagnostic lag and disability at first DMT initiation. Date of first DMT initiation may be a confounding variable due to DMT availability as not all current medications were available for the duration of the study period. Age at RRMS diagnosis, diagnostic lag and disability at first DMT initiation may act as confounding variables due to perceptions concerning requirement for DMT given age, duration of symptoms over a certain time period, or accumulation of significant disability defined as EDSS ≥3. Previously, non-adherence to DMT has been associated with mild disability and longer disease duration[85]. All models examined potential confounding variables as follows:

- Sex, male (reference)
- Age at RRMS diagnosis, years (continuous)
- Diagnostic lag, years (continuous)
- Disability at DMT initiation, EDSS (continuous)
- Neighbourhood income quintile, lowest (reference)

Key assumptions of the Cox proportional hazards model are non-informative censoring and proportionality of the hazard rates. Proportionality of hazard rates in Cox proportional hazards models were checked using a log-log plot of survival and Schoenfeld residuals. As well, Cox proportional hazards models were evaluated using Harrell's C-statistic. Logistic regression assumes that observations are independent. Logistic regression models were examined using Pearson goodness of fit test and C-statistic.

Statistical analyses were performed using STATA 15.1[86].

4.5 Power Calculation

The minimum detectable relative risk was determined for comorbidity count as the exposure of interest and the primary outcome of initial DMT persistence. Review of the literature indicates there is an increased risk of discontinuing DMT at 3 years in the presence of comorbidity due to tolerability[12]. The probability of discontinuing DMT by 3 years was estimated to be 41% among those without comorbidity and 50% among those with comorbidity. The number of individuals started on first DMT during the study period at the DMSRU was estimated at 1000 and was a fixed sample size. Stata statistical software was used to estimate power for two-sample proportions using Pearson's chi-squared test [code: power twoproportions .41 .50, effect(rrisk) n(1000)]. The estimated power was 0.82 with a minimum detectable relative risk of 1.22. A

prior study investigating comorbidity and switch from first DMT found that comorbidity had a significant effect on switch due to intolerance (hazard ratio 1.42, confidence interval 1.07-1.87, p=0.014)[12].

Table 3. Measures Extracted from the Dalhousie Multiple Sclerosis Research Unit Database

Variable	Unit of Measurement	Comments
Demographic Information		
Sex	Male/Female	
Age RRMS diagnosis	Years	
Postal Code	Income quintile	Calculated using PCCF[83]
RRMS Information		
Year RRMS diagnosis	Year	
Diagnostic lag	Years	
EDSS DMT initiation	EDSS (0-10)	Most recent prior to DMT initiation within ≤1 year
First DMT Information		
Year DMT initiation	Year	
DMT duration[a]	Years	DMT discontinuation defined as a switch to another DMT or a lapse in DMT >30 days
DMT type[b]	Specific DMT	Categorized into injectable versus oral therapy
DMT discontinuation[b]	Specific reasons for DMT discontinuation	Categorized as discontinuation for tolerability, efficacy, and/or other reason

DMT disease-modifying therapy; EDSS expanded disability status scale; PCCF postal code conversion files; RRMS relapsing remitting multiple sclerosis

[a]Primary outcome variable

[b]Secondary outcome variable

Table 4. Comorbidity Administrative Case Definitions

Comorbidity	ICD-9 codes	ICD-10 codes	Years of Data	Number and type of hospital (H) or physician (P) claims
Hypertension[74]	401, 402, 403, 404, 405	I10, I11, I12, I13, I15	2	≥1H or ≥2P
Hyperlipidemia[74]	272	E78.0, E78.2, E78.4, E78.5	5	≥1H or ≥2P
Diabetes[74]	250	E10, E11, E12, E13, E14	5	≥1H or ≥2P
Chronic lung disease[75]	491, 492, 493, 496	J40, J42, J43, J44, J45, J46	5	≥1H or ≥2P
Ischemic heart disease[74,81]	410, 411, 412, 413, 414	I20, I21, I22, I23, I24, I25	5	≥1H or ≥2P
Epilepsy[74]	345	G40, G41	3	≥1H or ≥2P
Inflammatory bowel disease[74]	555,556	K50, K51		≥5H or P; or if resident in province <2 years ≥3H or P
Mental health disorder (anxiety, depression, bipolar disorder, schizophrenia)[76]	300.0, 300.2, 296.2, 296.3, 298.0, 300.4, 311, 296.0, 296.1, 296.04, 296.14, 296.4, 296.44, 296.5, 296.54, 296.6, 296.7, 296.8, 295	F40, F41, F32, F33, F34, F31, F20, F25	5	≥1H or ≥5P

Table 5. Performance of Comorbidity Administrative Case Definitions in Nova Scotia

Comorbidity	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
Hypertension[74]	0.79	0.91	0.74	0.93
Hyperlipidemia[74]	0.53	0.95	0.68	0.91
Diabetes[74]	0.80	0.97	0.67	0.99
Chronic lung disease[75]	0.39[a]	0.95[a]	0.33[a]	0.96[a]
Ischemic heart disease[74]	0.58	0.96	0.36	0.99
Epilepsy[74]	0.47	0.99	0.51	0.98
Inflammatory bowel disease[74]	0.59	1.0	0.90	0.99
Mental health disorder[76]	0.57[a]	0.88[a]	0.66[a]	0.83[a]

[a]Performance of administrative case definition reported for Manitoba

CHAPTER 5 RESULTS

5.1 Population

There were 1615 individuals starting initial DMT between January 1, 2001 and December 31, 2016 identified using the DMSRU database (Figure 2). There were 1563 individuals remaining after removing those with a diagnosis other than RRMS or CIS at DMT initiation. Among those with RRMS or CIS, there were 1464 individuals started on a platform therapy as initial DMT (Table 6).

At the most recent clinic visit, 1280 (87.4%) had RRMS, 177 (12.1%) had SPMS, and 7 (0.5%) had CIS. Median age of symptom onset was 33.0 years (IQR 26.4-40.6). Median age at MS diagnosis was 36.6 years (IQR 29.3-44.6). There was a 3:1 female predominance. Median delay from MS diagnosis to DMT initiation was 0 years (IQR 0-2). Median EDSS at DMT initiation was 2.0 (IQR 1.5-3.0). Statistics Canada neighbourhood income quintiles were evenly represented in this population. There were 1292 (88.3%) individuals started on an injectable platform therapy while 172 (11.7%) were started on an oral platform therapy.

There were 904 (61.7%) individuals with no comorbidity, 422 (28.8%) with 1 comorbidity, and 138 (9.4%) with ≥2 comorbidities. Among those with comorbidity, there were 296 (20.2%) with a mental health diagnosis, 186 (12.7%) with hypertension, 90 (6.1%) with a lung diagnosis, 69 (4.7%) with dyslipidemia, 61 (4.2%) with diabetes, 18 (1.2%) with ischemic heart disease (IHD), 9 (0.6%) with epilepsy, and 6 (0.4%) with inflammatory bowel disease (IBD) (Figure 3).

5.2 Initial Disease-Modifying Therapy Persistence

Among 1464 individuals starting platform therapy as initial DMT, the median duration of DMT persistence was 4 years (95% CI 4 – 4) (Figure 4). Duration of DMT persistence did not significantly differ by comorbidity count (0, 1, ≥2) according to the Log-rank test (p=0.5) (Figure 5). Cox proportional hazards models for DMT persistence did not demonstrate a significant effect of comorbidity count after adjusting for age at MS diagnosis, diagnostic delay, EDSS at DMT initiation, sex, and income quintile (Table 7). Cox proportional hazards models evaluating specific comorbidities identified individuals with a mental health comorbidity as having increased risk of discontinuing DMT (HR 1.20, 95% CI 1.02-1.41) adjusting for covariates (Table 8). Median DMT persistence was 3 years (95% CI 3-4) among those with a mental health comorbidity and 4 years (95% CI 4-5) for those without a mental health comorbidity (Figure 6). In Cox proportional hazards models, there was a significant effect of age on DMT persistence with younger individuals at increased risk of discontinuing DMT (HR 0.98, 95% CI 0.97-0.99).

Median duration of DMT persistence was 4 years for both injectable (95% CI 4 – 4) and oral therapy (95% CI 3 – not reached). Distribution of comorbidities was similar between injectable and oral therapy groups (Table 9). Subgroup analysis for DMT type (injectable versus oral therapy) did not reveal a relationship between comorbidity count and duration of initial DMT (Table 10; Table 11). Subgroup analysis of DMT type showed that having a mental health comorbidity increased risk of discontinuing DMT among those on injectable therapy (HR 1.20, 95% CI 1.02-1.42) (Table 12) but not oral therapy (Table 13). Among those receiving injectable therapy, there was increased risk of DMT discontinuation with younger age (HR 0.98, 95% CI 0.97-0.99) and higher EDSS (HR 1.06, 95% CI 1.00-1.11).

A log-log plot of DMT persistence according to comorbidity count demonstrated parallel curves indicating the proportional hazards assumption was not violated (Figure 7). Schoenfeld residuals confirmed there was no evidence that the proportional hazards assumption was violated. Harrell's c-statistic was 0.6 for Cox proportional hazards models indicating relatively low ability of the model to predict the outcome of interest.

5.3 Initial Disease-Modifying Therapy Selection

Effect of comorbidity on initial DMT selection was evaluated differently in the period before 2013 versus from 2013 onward due to differences in DMT availability. In the period prior to the availability of oral platform therapy (before 2013), the effect of comorbidity on selection of interferon-β versus glatiramer acetate as injectable therapy was evaluated. In the period following introduction of oral platform therapy (from 2013 onward), the effect of comorbidity on selection of injectable (glatiramer acetate, interferon-β) versus oral (dimethyl fumarate, teriflunomide) therapy was evaluated.

In the period before 2013, there were 403 participants initially on glatiramer acetate and 717 participants initially on interferon-β. Logistic regression analysis examining the relationship between choice of injectable therapy and comorbidity count (0, 1, ≥2) controlling for age at MS diagnosis, diagnostic lag, EDSS at DMT initiation, sex, and income quintile revealed selection of glatiramer acetate was more common among those with ≥2 comorbidities (OR 1.68, 95% CI 1.06-2.68) (Table 14). No specific comorbidity examined influenced choice of injectable therapy (Table 15). Women had increased odds of being started on glatiramer acetate (OR 1.57, 95% CI 1.12-2.18).

In the period from 2013 onward, there were 172 participants initially on injectable therapy and 171 participants initially on oral therapy. Logistic regression analysis examining the relationship between choice of injectable versus oral therapy and comorbidity count (0, 1, ≥2) revealed no difference in therapy selection with increased burden of comorbidity (Table 16). No specific comorbidity examined influenced choice of injectable versus oral therapy (Table 17).

Plots of deviance residuals suggested these models adhere to the assumptions of constant variance and independence. Pearson goodness of fit tests did not reject the described models. C-statistic was 0.6 for logistic regression models indicating relatively low ability of the model to predict the outcome of interest.

5.4 Reason for Disease-Modifying Therapy Discontinuation

Effect of comorbidity on reason for DMT discontinuation was examined. Overall, there were 1139/1464 (77.8%) participants discontinuing initial DMT during the study period including 1053/1292 (81.5%) discontinuing injectable therapy and 86/172 (50.0%) discontinuing oral therapy (Table 18). There were 649 (57.0%) participants discontinuing for tolerability issues. Reasons recorded for discontinuing due to lack of tolerability included injection-related issues (n=225), flu-like symptoms (111), bloodwork abnormalities (43), depression (30), allergy (19), and comorbidity (15). There were 300 (26.3%) participants discontinuing for efficacy issues. Reasons for discontinuing due to lack of efficacy included relapse (n=155), progression (148), and MRI changes (43). In addition, there were 452 (39.7%) participants discontinuing for other reasons not related to lack of tolerability or lack of efficacy. Other reasons recorded for stopping included patient choice (190), lost to follow-up (107), pregnancy (72), non-adherence (42),

planned titration (15), positive neutralizing antibodies (12), death (7), change in diagnosis (5), and cost associated with acquiring DMT (5).

Logistic regression analysis examining the relationship between discontinuing for lack of tolerability and comorbidity count (0, 1, ≥2) controlling for age at MS diagnosis, diagnostic lag, EDSS at DMT initiation, sex, and income quintile showed ≥2 comorbidities were associated with an increased risk of discontinuing initial DMT due to lack of tolerability (OR 1.72, 95% CI 1.05-2.82) (Table 19). No specific comorbidity examined influenced discontinuing due to a tolerability issue (Table 20). Discontinuing due to lack of tolerability was more common among women (OR 1.54, 95% CI 1.14-2.09), individuals with lower EDSS at DMT initiation (OR 0.80, 95% CI 0.72-0.88), and younger age at MS diagnosis (OR 0.98, 95% CI 0.97-1.00).

Among 1053 participants who discontinued injectable therapy, there were 609 (57.8%) participants who discontinued for lack of tolerability. Among 86 participants who discontinued oral therapy, there were 40 (46.5%) participants who discontinued for lack of tolerability. Logistic regression analysis did not reveal an association between discontinuing an injectable therapy for lack of tolerability and comorbidity count (Table 21) or a specific comorbidity (Table 22). Discontinuing injectable therapy for lack of tolerability was more common among women (OR 1.62, 95% CI 1.18-2.23) and those with lower EDSS at DMT initiation (OR 0.79, 95% CI 0.71-0.87). Logistic regression analysis did not reveal an association between discontinuing an oral therapy for lack of tolerability and comorbidity count while analysis of specific comorbidities was limited by sample size.

Among 1139 participants discontinuing initial DMT, there were 300 (26.3%) participants discontinuing for lack of efficacy. Logistic regression analysis examining the relationship between discontinuing for lack of efficacy and comorbidity count (0, 1, ≥2) controlling for age at

MS diagnosis, diagnostic lag, EDSS at DMT initiation, sex, and income quintile revealed no difference in discontinuing for lack of efficacy with burden of comorbidity (Table 23). No specific comorbidity examined influenced discontinuing due to an efficacy issue (Table 24). Discontinuing due to lack of efficacy was more common among individuals with higher EDSS at DMT initiation (OR 1.37, 95% CI 1.23-1.53), less likely among women (OR 0.70, 95% CI 0.50-0.97), and more likely with older age at MS diagnosis (OR 1.02, 95% CI 1.00-1.04).

Among 1053 participants who discontinued injectable therapy, there were 287 (27.3%) participants who discontinued for lack of efficacy. Among 86 participants who discontinued oral therapy, there were 13 (15.1%) participants who discontinued for lack of efficacy. Logistic regression analysis did not reveal an association between discontinuing an injectable therapy for lack of efficacy and comorbidity count or a specific comorbidity. Discontinuing injectable therapy for lack of efficacy was more common among individuals with higher EDSS at DMT initiation (OR 1.35, 95% CI 1.21-1.51), less likely among women (OR 0.69, 95% CI 0.49-0.98), and more likely with older age at MS diagnosis (OR 1.02, 95% CI 1.00-1.04). Logistic regression analysis examining discontinuation of oral therapy for lack of efficacy and comorbidity count or specific comorbidities was limited by sample size.

Plots of deviance residuals suggested these models adhere to the assumptions of constant variance and independence. Pearson goodness of fit tests did not reject the described models. C-statistic was 0.6 for logistic regression models indicating relatively low ability of the model to predict the outcome of interest.

Table 6. Baseline Characteristics of Study Cohort Starting Initial Platform Disease-Modifying Therapy

Cohort Characteristics	n	
MS Subtype (most recent) (n,%)	1464	
RRMS		1280 (87.4%)
SPMS		177 (12.1%)
CIS		7 (0.5%)
Age symptom onset, years (median, IQR)	1459	33.0 (26.4-40.6)
Age MS diagnosis, years (median, IQR)	1445	36.6 (29.3-44.6)
Sex (n,%)	1463	
Male		341 (23.3%)
Female		1122 (76.7%)
Delay MS diagnosis to first DMT, years (median, IQR)	1445	0 (0-2)
EDSS at DMT initiation (median, IQR)	1343	2.0 (1.5-3.0)
Neighbourhood income quintile (n,%)	1408	
1 (lowest)		263 (18.7%)
2		280 (19.9%)
3		295 (21.0%)
4		294 (20.9%)
5 (highest)		276 (19.6%)
First DMT (n,%)	1464	
Interferon-β		814 (55.6%)
Glatiramer acetate		478 (32.7%)
Dimethyl fumarate (Tecfidera) 240 mg bid		117 (8.0%)
Teriflunomide (Aubagio) 14 mg daily		55 (3.8%)
Comorbidity count (n,%)	1464	
0		904 (61.7%)
1		422 (28.8%)
≥2		138 (9.4%)

CIS clinically isolated syndrome; DMT disease-modifying therapy; EDSS expanded disability status scale; IQR interquartile range; RRMS relapsing remitting multiple sclerosis; SPMS secondary progressive multiple sclerosis

Table 7. Persistence of Disease-Modifying Therapy According to Comorbidity Count, Cox Proportional Hazards Regression (n=1140)

	HR	95% CI	SE	Wald	p value
Comorbidity Count					
0	1	-	-	-	-
1	1.07	0.92-1.25	0.08	0.89	0.4
≥2	1.03	0.80-1.32	0.13	0.22	0.8
Age MS diagnosis	**0.98**	**0.97-0.99**	**0.004**	**-5.30**	**<0.01**
Diagnostic lag	1.00	0.98-1.01	0.01	-0.44	0.7
EDSS at DMT initiation	1.05	1.00-1.10	0.03	1.78	0.07
Sex					
Male	1	-	-	-	-
Female	0.96	0.82-1.12	0.08	-0.54	0.6
Income quintile					
1 (lowest)	1	-	-	-	-
2	0.92	0.74-1.15	0.10	-0.73	0.5
3	1.01	0.82-1.25	0.11	0.12	0.9
4	1.06	0.86-1.31	0.11	0.52	0.6
5 (highest)	1.08	0.87-1.34	0.12	0.69	0.5

CI confidence interval; DMT disease-modifying therapy; EDSS expanded disability status scale; HR hazard ratio; MS multiple sclerosis; SE standard error

Table 8. Persistence of Disease-Modifying Therapy According to Specific Comorbidity, Cox Proportional Hazards Regression (n=1140)

	HR	95% CI	SE	Wald	p value
Comorbidity					
Mental health disorder	**1.20**	**1.02-1.41**	**0.10**	**2.15**	**0.03**
Hypertension	0.97	0.78-1.19	0.10	-0.33	0.7
Hyperlipidemia	0.80	0.56-1.14	0.14	-1.24	0.2
Diabetes	0.82	0.57-1.17	0.15	-1.11	0.3
Ischemic heart disease	1.10	0.59-2.03	0.34	0.30	0.8
Lung disease	1.08	0.82-1.43	0.15	0.56	0.6
Other[a]	0.48	0.21-1.10	0.20	-1.74	0.1
Age MS diagnosis	**0.98**	**0.97-0.99**	**0.004**	**-4.75**	**<0.01**
Diagnostic lag	1.00	0.98-1.01	0.01	-0.38	0.7
EDSS at DMT initiation	1.05	1.00-1.11	0.03	2.00	0.05
Sex					
Male	1	-	-	-	-
Female	0.94	0.80-1.10	0.08	-0.75	0.5
Income quintile					
1 (lowest)	1	-	-	-	-
2	0.91	0.73-1.14	0.10	-0.82	0.4
3	1.01	0.82-1.25	0.11	0.12	0.9
4	1.04	0.84-1.28	0.11	0.35	0.7
5 (highest)	1.07	0.86-1.33	0.12	0.59	0.6

CI confidence interval; DMT disease-modifying therapy; EDSS expanded disability status scale; HR hazard ratio; MS multiple sclerosis; SE standard error

[a]Epilepsy and inflammatory bowel disease

Table 9. Baseline Characteristics of Study Cohort Starting Initial Platform Disease-Modifying Therapy (Injectable versus Oral Disease-Modifying Therapy)

Cohort Characteristics	Injectable n=1292	Oral n=172
MS Subtype (most recent) (n)	1292	172
RRMS (n,%)	1112 (86.1%)	168 (97.7%)
SPMS	173 (13.4%)	Suppressed for cell size <5
CIS	7 (0.5%)	Suppressed for cell size <5
Age symptom onset, years (n)	1289	170
(median, IQR)	32.9 (26.3-40.1)	34.1 (27.4-44.7)
Age MS diagnosis, years (n)	1274	171
(median, IQR)	36.3 (29.0-44.2)	39.4 (31.3-48.9)
Sex (n)	1291	172
Male (n,%)	295 (22.9%)	46 (26.7%)
Female	996 (77.1%)	126 (73.3%)
Delay MS diagnosis to first DMT, years (n)	1274	171
(median, IQR)	1 (0-2)	0 (0-1)
EDSS at DMT initiation (n)	1185	158
(median, IQR)	2.0 (1.5-3.0)	2.0 (1.0-3.0)
Neighbourhood income quintile (n)	1259	149
1 (lowest) (n,%)	234 (18.6%)	29 (19.5%)
2	246 (19.5%)	34 (22.8%)
3	267 (21.2%)	28 (18.8%)
4	264 (21.0%)	30 (20.1%)
5 (highest)	248 (19.7%)	28 (18.8%)
Comorbidity count (n,%)	1292	172
0	801 (62.0%)	103 (59.9%)
1	372 (28.8%)	50 (29.1%)
≥2	119 (9.2%)	19 (11.0%)

Table 10. Persistence of Disease-Modifying Therapy According to Comorbidity Count for Injectable Therapy, Cox Proportional Hazards Regression (n=1019)

	HR	95% CI	SE	Wald	p value
Comorbidity Count					
0	1	-	-	-	-
1	1.10	0.94-1.28	0.09	1.16	0.2
≥2	1.04	0.81-1.35	0.14	0.33	0.7
Age MS diagnosis	**0.98**	**0.97-0.99**	**0.004**	**-5.37**	**<0.01**
Diagnostic lag	1.00	0.98-1.01	0.01	-0.51	0.6
EDSS at DMT initiation	**1.06**	**1.00-1.11**	**0.03**	**2.02**	**0.04**
Sex					
Male	1	-	-	-	-
Female	0.97	0.83-1.15	0.08	-0.31	0.8
Income quintile					
1 (lowest)	1	-	-	-	-
2	0.94	0.75-1.18	0.11	-0.56	0.6
3	1.05	0.84-1.31	0.12	0.45	0.7
4	1.09	0.88-1.36	0.12	0.80	0.4
5 (highest)	1.14	0.91-1.43	0.13	1.14	0.3

CI confidence interval; DMT disease-modifying therapy; EDSS expanded disability status scale; HR hazard ratio; MS multiple sclerosis; SE standard error

Table 11. Persistence of Disease-Modifying Therapy According to Comorbidity Count for Oral Therapy, Cox Proportional Hazards Regression (n=121)

	HR	95% CI	SE	Wald	p value
Comorbidity Count					
0	1	-	-	-	-
1	0.70	0.35-1.37	0.24	-1.05	0.3
≥2	0.55	0.19-1.64	0.31	-1.07	0.3
Age MS diagnosis	1.00	0.97-1.02	0.01	-0.33	0.7
Diagnostic lag	1.00	0.96-1.05	0.02	0.00	1.0
EDSS at DMT initiation	0.95	0.78-1.16	0.10	-0.48	0.6
Sex					
Male	1	-	-	-	-
Female	0.73	0.39-1.37	0.23	-0.98	0.3
Income quintile					
1 (lowest)	1	-	-	-	-
2	0.90	0.40-2.00	0.37	-0.27	0.8
3	0.49	0.20-1.20	0.22	-1.56	0.1
4	0.61	0.25-1.52	0.28	-1.05	0.3
5 (highest)	0.42	0.16-1.09	0.20	-1.79	0.1

CI confidence interval; DMT disease-modifying therapy; EDSS expanded disability status scale; HR hazard ratio; MS multiple sclerosis; SE standard error

Table 12. Persistence of Disease-Modifying Therapy According to Specific Comorbidity for Injectable Therapy, Cox Proportional Hazards Regression (n=1019)

	HR	95% CI	SE	Wald	p value
Comorbidity					
Mental health disorder	**1.20**	**1.02-1.42**	**0.10**	**2.15**	**0.03**
Hypertension	0.96	0.77-1.19	0.11	-0.38	0.7
Hyperlipidemia	0.81	0.56-1.17	0.15	-1.14	0.3
Diabetes	0.78	0.53-1.15	0.15	-1.25	0.2
Ischemic heart disease	1.11	0.60-2.05	0.35	0.33	0.7
Lung disease	1.18	0.88-1.56	0.17	1.11	0.3
Other[a]	0.48	0.21-1.09	0.20	-1.76	0.08
Age MS diagnosis	**0.98**	**0.97-0.99**	**0.004**	**-4.80**	**<0.01**
Diagnostic lag	1.00	0.98-1.01	0.01	-0.48	0.6
EDSS at DMT initiation	**1.06**	**1.01-1.12**	**0.03**	**2.23**	**0.03**
Sex					
Male	1	-	-	-	-
Female	0.96	0.81-1.13	0.08	-0.54	0.6
Income quintile					
1 (lowest)	1	-	-	-	-
2	0.93	0.74-1.17	0.11	-0.63	0.5
3	1.05	0.85-1.31	0.12	0.48	0.6
4	1.07	0.86-1.34	0.12	0.62	0.5
5 (highest)	1.13	0.90-1.41	0.13	1.05	0.3

CI confidence interval; DMT disease-modifying therapy; EDSS expanded disability status scale; HR hazard ratio; MS multiple sclerosis; SE standard error

[a]Epilepsy and inflammatory bowel disease

Table 13. Persistence of Disease-Modifying Therapy According to Specific Comorbidity for Oral Therapy, Cox Proportional Hazards Regression (n=121)

	HR	95% CI	SE	Wald	p value
Comorbidity[a]					
Mental health disorder	1.01	0.40-2.55	0.48	0.02	1.0
Hypertension	0.73	0.28-1.89	0.35	-0.65	0.5
Hyperlipidemia	0.52	0.14-1.94	0.35	-0.97	0.3
Diabetes	0.88	0.29-2.68	0.50	-0.23	0.8
Lung disease	0.43	0.13-1.44	0.26	-1.37	0.2
Age MS diagnosis	1.00	0.97-1.03	0.02	-0.19	0.8
Diagnostic lag	1.00	0.95-1.05	0.02	-0.10	0.9
EDSS at DMT initiation	0.95	0.78-1.16	0.10	-0.48	0.6
Sex					
Male	1	-	-	-	-
Female	0.70	0.37-1.32	0.23	-1.10	0.3
Income quintile					
1 (lowest)	1	-	-	-	-
2	0.94	0.42-2.09	0.38	-0.15	0.9
3	0.53	0.21-1.32	0.25	-1.37	0.2
4	0.66	0.26-1.65	0.31	-0.89	0.4
5 (highest)	0.46	0.17-1.21	0.23	-1.58	0.1

CI confidence interval; DMT disease-modifying therapy; EDSS expanded disability status scale; HR hazard ratio; MS multiple sclerosis; SE standard error

[a]Epilepsy, ischemic heart disease, and inflammatory bowel disease not included as combined number of affected individuals <10

Table 14. Selection of Disease-Modifying Therapy Before 2013 (Interferon-β versus Glatiramer Acetate) According to Comorbidity Count, Logistic Regression (n=1011)

	OR	95% CI	SE	Wald	P value
Comorbidity Count					
0	1	-	-	-	-
1	1.02	0.76-1.37	0.15	0.13	0.9
≥2	**1.68**	**1.06-2.68**	**0.40**	**2.19**	**0.03**
Age MS diagnosis	1.01	0.99-1.02	0.01	0.84	0.4
Diagnostic lag	1.02	0.99-1.05	0.01	1.39	0.2
EDSS at DMT initiation	0.96	0.87-1.06	0.05	-0.85	0.4
Sex					
Male	1	-	-	-	-
Female	**1.57**	**1.12-2.18**	**0.26**	**2.65**	**0.01**
Income quintile					
1 (lowest)	1	-	-	-	-
2	0.92	0.61-1.39	0.19	-0.39	0.7
3	0.70	0.47-1.05	0.15	-1.70	0.1
4	0.89	0.59-1.33	0.18	-0.59	0.6
5 (highest)	0.70	0.46-1.07	0.15	-1.64	0.1

CI confidence interval; DMT disease-modifying therapy; EDSS expanded disability status scale; MS multiple sclerosis; OR odds ratio; SE standard error

Table 15. Selection of Disease-Modifying Therapy Before 2013 (Interferon-β versus Glatiramer Acetate) According to Specific Comorbidity, Logistic Regression (n=1011)

	OR	95% CI	SE	Wald	P value
Comorbidity					
Mental health disorder	1.15	0.84-1.58	0.19	0.89	0.4
Hypertension	1.11	0.75-1.65	0.22	0.52	0.6
Hyperlipidemia	1.16	0.60-2.25	0.39	0.44	0.7
Diabetes	1.30	0.65-2.58	0.45	0.75	0.5
Ischemic heart disease	1.94	0.62-6.11	1.14	1.13	0.3
Lung disease	1.17	0.67-2.02	0.33	0.55	0.6
Other[a]	1.50	0.39-5.75	1.03	0.59	0.6
Age MS diagnosis	1.01	0.99-1.02	0.01	0.72	0.5
Diagnostic lag	1.02	0.99-1.05	0.01	1.45	0.1
EDSS at DMT initiation	0.95	0.86-1.06	0.05	-0.90	0.4
Sex					
Male	1	-	-	-	-
Female	**1.57**	**1.13-2.20**	**0.27**	**2.67**	**0.01**
Income quintile					
1 (lowest)	1	-	-	-	-
2	0.93	0.61-1.40	0.19	-0.37	0.7
3	0.69	0.46-1.04	0.14	-1.76	0.1
4	0.89	0.59-1.33	0.18	-0.58	0.6
5 (highest)	0.70	0.46-1.07	0.15	-1.66	0.1

CI confidence interval; DMT disease-modifying therapy; EDSS expanded disability status scale; MS multiple sclerosis; OR odds ratio; SE standard error

[a]Epilepsy and inflammatory bowel disease

Table 16. Selection of Disease-Modifying Therapy From 2013 Onward (Injectable versus Oral) According to Comorbidity Count, Logistic Regression (n=275)

	OR	95% CI	SE	Wald	P value
Comorbidity Count					
0	1	-	-	-	-
1	0.93	0.53-1.63	0.27	-0.27	0.8
≥2	0.95	0.43-2.11	0.39	-0.13	0.9
Age MS diagnosis	0.99	0.96-1.01	0.01	-0.97	0.3
Diagnostic lag	1.03	0.99-1.07	0.02	1.34	0.2
EDSS at DMT initiation	0.91	0.76-1.08	0.08	-1.08	0.3
Sex					
Male	1	-	-	-	-
Female	0.87	0.50-1.52	0.25	-0.50	0.6
Income quintile					
1 (lowest)	1	-	-	-	-
2	0.71	0.33-1.53	0.28	-0.88	0.4
3	0.81	0.36-1.83	0.34	-0.50	0.6
4	0.61	0.28-1.33	0.24	-1.24	0.2
5 (highest)	0.56	0.26-1.21	0.22	-1.48	0.1

CI confidence interval; DMT disease-modifying therapy; EDSS expanded disability status scale; MS multiple sclerosis; OR odds ratio; SE standard error

Table 17. Selection of Disease-Modifying Therapy From 2013 Onward (Injectable versus Oral) According to Specific Comorbidity, Logistic Regression (n=275)

	OR	95% CI	SE	Wald	P value
Comorbidity[a]					
Mental health disorder	0.72	0.38-1.37	0.23	-1.00	0.3
Hypertension	0.75	0.36-1.58	0.29	-0.75	0.5
Hyperlipidemia	0.92	0.34-2.48	0.47	-0.16	0.9
Diabetes	1.41	0.51-3.89	0.73	0.67	0.5
Lung disease	1.79	0.74-4.35	0.81	1.29	0.2
Age MS diagnosis	0.99	0.97-1.02	0.01	-0.72	0.5
Diagnostic lag	1.03	0.99-1.07	0.02	1.40	0.2
EDSS at DMT initiation	0.90	0.76-1.08	0.08	-1.11	0.3
Sex					
Male	1	-	-	-	-
Female	0.89	0.51-1.56	0.26	-0.41	0.7
Income quintile					
1 (lowest)	1	-	-	-	-
2	0.68	0.31-1.47	0.27	-0.98	0.3
3	0.79	0.34-1.80	0.33	-0.57	0.6
4	0.60	0.27-1.33	0.24	-1.25	0.2
5 (highest)	0.52	0.24-1.15	0.21	-1.61	0.1

CI confidence interval; DMT disease-modifying therapy; EDSS expanded disability status scale; MS multiple sclerosis; OR odds ratio; SE standard error

[a]Epilepsy, ischemic heart disease, and inflammatory bowel disease not included as combined number of affected individuals <10

Table 18. Reasons for Stopping Disease-Modifying Therapy

Reasons for Stopping DMT[a]	All (n=1139)	DMT Discontinued Injectable (n=1053)	Oral (n=86)
Tolerability	649	609	40
Injection-related issues	225	225	0
Flu-like symptoms	111	111	0
Bloodwork abnormalities	43	33	10
Depression	30	Suppressed for cell size <5	
Allergy	19	Suppressed for cell size <5	
Comorbidity	15	Suppressed for cell size <5	
Efficacy	300	287	13
Relapse	155	147	8
Progression	148	Suppressed for cell size <5	
MRI changes	43	Suppressed for cell size <5	
Other	452	412	40
Patient choice	190	Suppressed for cell size <5	
Lost to follow-up	107	78	29
Pregnancy	72	Suppressed for cell size <5	
Lack of compliance	42	Suppressed for cell size <5	
Planned titration	15	15	0
Neutralizing antibodies	12	12	0
Death	7	7	0
Change in diagnosis	5	5	0
Cost	5	5	0

DMT Disease-Modifying Therapy

[a]Reasons for stopping disease-modifying therapy are presented as specified and are not mutually exclusive

Table 19. Stopping Disease-Modifying Therapy Due to Tolerability According to Comorbidity Count, Logistic Regression (n=1012)

	OR	95% CI	SE	Wald	P value
Comorbidity Count					
0	1	-	-	-	-
1	1.10	0.82-1.47	0.16	0.63	0.5
≥2	**1.72**	**1.05-2.82**	**0.43**	**2.14**	**0.03**
Age MS diagnosis	**0.98**	**0.97-1.00**	**0.01**	**-2.19**	**0.03**
Diagnostic lag	1.00	0.98-1.03	0.01	0.28	0.8
EDSS at DMT initiation	**0.80**	**0.72-0.88**	**0.04**	**-4.52**	**<0.001**
Sex					
Male	1	-	-	-	-
Female	**1.54**	**1.14-2.09**	**0.24**	**2.79**	**0.01**
Income quintile					
1 (lowest)	1	-	-	-	-
2	0.87	0.58-1.32	0.19	-0.64	0.5
3	0.92	0.62-1.37	0.19	-0.41	0.7
4	1.04	0.70-1.56	0.21	0.21	0.8
5 (highest)	0.93	0.61-1.40	0.19	-0.36	0.7

CI confidence interval; DMT disease-modifying therapy; EDSS expanded disability status scale; MS multiple sclerosis; OR odds ratio; SE standard error

Table 20. Stopping Disease-Modifying Therapy Due to Tolerability According to Specific Comorbidity, Logistic Regression (n=1012)

	OR	95% CI	SE	Wald	P value
Comorbidity					
Mental health disorder	1.22	0.89-1.67	0.20	1.22	0.2
Hypertension	1.23	0.81-1.85	0.26	0.96	0.3
Hyperlipidemia	1.13	0.56-2.25	0.40	0.33	0.7
Diabetes	1.01	0.50-2.04	0.36	0.02	1.0
Ischemic heart disease	2.11	0.60-7.48	1.36	1.16	0.2
Lung disease	1.21	0.70-2.08	0.34	0.67	0.5
Other[a]	1.52	0.34-6.81	1.16	0.55	0.6
Age MS diagnosis	**0.98**	**0.97-1.00**	**0.01**	**-2.16**	**0.03**
Diagnostic lag	1.00	0.98-1.03	0.01	0.27	0.8
EDSS at DMT initiation	**0.80**	**0.72-0.88**	**0.04**	**-4.50**	**<0.001**
Sex					
Male	1	-	-	-	-
Female	**1.55**	**1.14-2.10**	**0.24**	**2.80**	**0.01**
Income quintile					
1 (lowest)	1	-	-	-	-
2	0.88	0.58-1.33	0.19	-0.61	0.5
3	0.91	0.61-1.36	0.19	-0.47	0.6
4	1.04	0.70-1.56	0.21	0.19	0.8
5 (highest)	0.92	0.61-1.39	0.19	-0.39	0.7

CI confidence interval; DMT disease-modifying therapy; EDSS expanded disability status scale; MS multiple sclerosis; OR odds ratio; SE standard error

[a]Epilepsy and inflammatory bowel disease

Table 21. Stopping Disease-Modifying Therapy Due to Tolerability According to Comorbidity Count for Injectable Therapy, Logistic Regression (n=945)

	OR	95% CI	SE	Wald	P value
Comorbidity Count					
0	1	-	-	-	-
1	1.04	0.77-1.41	0.16	0.28	0.8
≥2	1.63	0.97-2.73	0.43	1.85	0.1
Age MS diagnosis	0.99	0.97-1.00	0.01	-1.86	0.1
Diagnostic lag	1.00	0.97-1.03	0.02	-0.30	0.8
EDSS at DMT initiation	**0.79**	**0.71-0.87**	**0.04**	**-4.58**	**<0.001**
Sex					
Male	1	-	-	-	-
Female	**1.62**	**1.18-2.23**	**0.26**	**3.01**	**0.003**
Income quintile					
1 (lowest)	1	-	-	-	-
2	0.86	0.55-1.33	0.19	-0.68	0.5
3	0.91	0.60-1.39	0.19	-0.42	0.7
4	1.05	0.69-1.60	0.23	0.21	0.8
5 (highest)	0.92	0.60-1.42	0.20	-0.37	0.7

CI confidence interval; DMT disease-modifying therapy; EDSS expanded disability status scale; MS multiple sclerosis; OR odds ratio; SE standard error

Table 22. Stopping Disease-Modifying Therapy Due to Tolerability According to Specific Comorbidity for Injectable Therapy, Logistic Regression (n=945)

	OR	95% CI	SE	Wald	P value
Comorbidity					
Mental health disorder	1.14	0.83-1.59	0.19	0.81	0.4
Hypertension	1.23	0.81-1.91	0.27	1.02	0.3
Hyperlipidemia	1.27	0.61-2.62	0.47	0.64	0.5
Diabetes	0.84	0.39-1.78	0.32	-0.46	0.6
Ischemic heart disease	2.12	0.59-7.62	1.38	1.15	0.2
Lung disease	1.19	0.67-2.09	0.34	0.59	0.6
Other[a]	1.54	0.34-7.03	1.19	0.56	0.6
Age MS diagnosis	0.98	0.97-1.00	0.01	-1.98	0.05
Diagnostic lag	1.00	0.97-1.03	0.02	-0.27	0.8
EDSS at DMT initiation	**0.79**	**0.71-0.87**	**0.04**	**-4.53**	**<0.001**
Sex					
Male	1	-	-	-	-
Female	**1.65**	**1.20-2.27**	**0.27**	**3.07**	**<0.01**
Income quintile					
1 (lowest)	1	-	-	-	-
2	0.86	0.55-1.33	0.19	-0.67	0.5
3	0.90	0.59-1.37	0.19	-0.48	0.6
4	1.04	0.68-1.59	0.22	0.19	0.8
5 (highest)	0.92	0.60-1.41	0.20	-0.40	0.7

CI confidence interval; DMT disease-modifying therapy; EDSS expanded disability status scale; MS multiple sclerosis; OR odds ratio; SE standard error

[a]Epilepsy and inflammatory bowel disease

Table 23. Stopping Disease-Modifying Therapy Due to Efficacy According to Comorbidity Count, Logistic Regression (n=1012)

	OR	95% CI	SE	Wald	P value
Comorbidity Count					
0	1	-	-	-	-
1	1.11	0.80-1.54	0.18	0.62	0.5
≥2	0.67	0.38-1.18	0.19	-1.38	0.2
Age MS diagnosis	**1.02**	**1.00-1.04**	**0.01**	**2.30**	**0.02**
Diagnostic lag	1.00	0.97-1.03	0.02	0.12	0.9
EDSS at DMT initiation	**1.37**	**1.23-1.53**	**0.07**	**5.86**	**<0.001**
Sex					
Male	1	-	-	-	-
Female	**0.70**	**0.50-0.97**	**0.12**	**-2.12**	**0.03**
Income quintile					
1 (lowest)	1	-	-	-	-
2	0.96	0.59-1.57	0.24	-0.17	0.9
3	1.03	0.64-1.63	0.24	0.10	0.9
4	1.43	0.91-2.24	0.33	1.55	0.1
5 (highest)	1.31	0.82-2.10	0.31	1.15	0.3

CI confidence interval; DMT disease-modifying therapy; EDSS expanded disability status scale; MS multiple sclerosis; OR odds ratio; SE standard error

Table 24. Stopping Disease-Modifying Therapy Due to Efficacy According to Specific Comorbidity, Logistic Regression (n=1012)

	OR	95% CI	SE	Wald	P value
Comorbidity					
Mental health disorder	0.97	0.68-1.39	0.18	-0.16	0.9
Hypertension	1.15	0.74-1.80	0.26	0.62	0.5
Hyperlipidemia	0.69	0.32-1.52	0.28	-0.92	0.4
Diabetes	0.96	0.44-2.09	0.38	-0.10	0.9
Ischemic heart disease	0.91	0.25-3.33	0.60	-0.14	0.9
Lung disease	0.79	0.42-1.51	0.26	-0.71	0.5
Other[a]	0.79	0.14-4.36	0.69	-0.27	0.8
Age MS diagnosis	**1.02**	**1.00-1.04**	**0.01**	**2.09**	**0.04**
Diagnostic lag	1.00	0.97-1.03	0.02	0.12	0.9
EDSS at DMT initiation	**1.37**	**1.23-1.52**	**0.07**	**5.79**	**<0.001**
Sex					
Male	1	-	-	-	-
Female	**0.69**	**0.50-0.97**	**0.12**	**-2.15**	**0.03**
Income quintile					
1 (lowest)	1	-	-	-	-
2	0.96	0.59-1.58	0.24	-0.14	0.9
3	1.03	0.65-1.65	0.25	0.14	0.9
4	1.44	0.91-2.25	0.33	1.57	0.1
5 (highest)	1.33	0.83-2.12	0.32	1.20	0.2

CI confidence interval; DMT disease-modifying therapy; EDSS expanded disability status scale; MS multiple sclerosis; OR odds ratio; SE standard error

[a]Epilepsy and inflammatory bowel disease

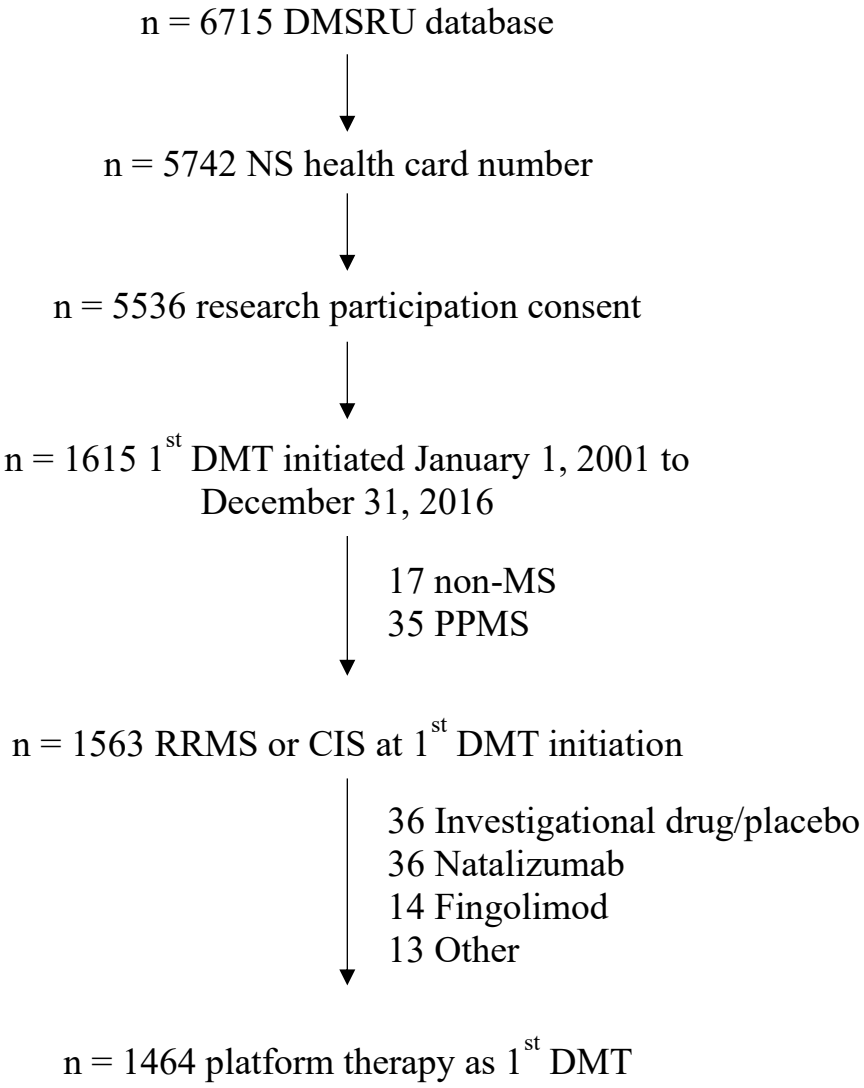


Figure 2. Flow diagram of study population

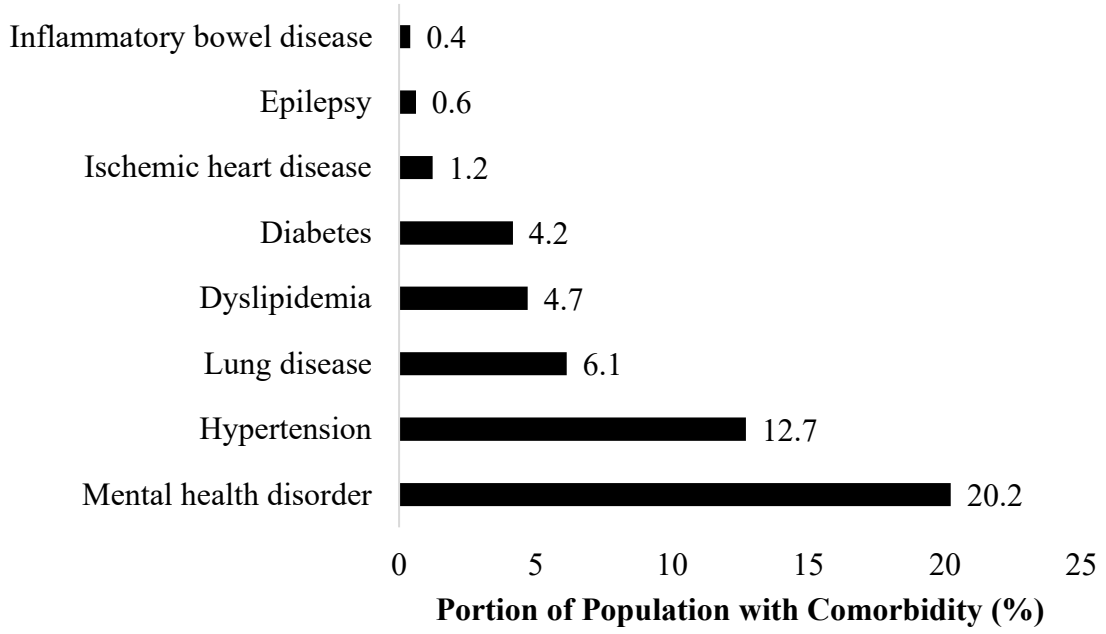
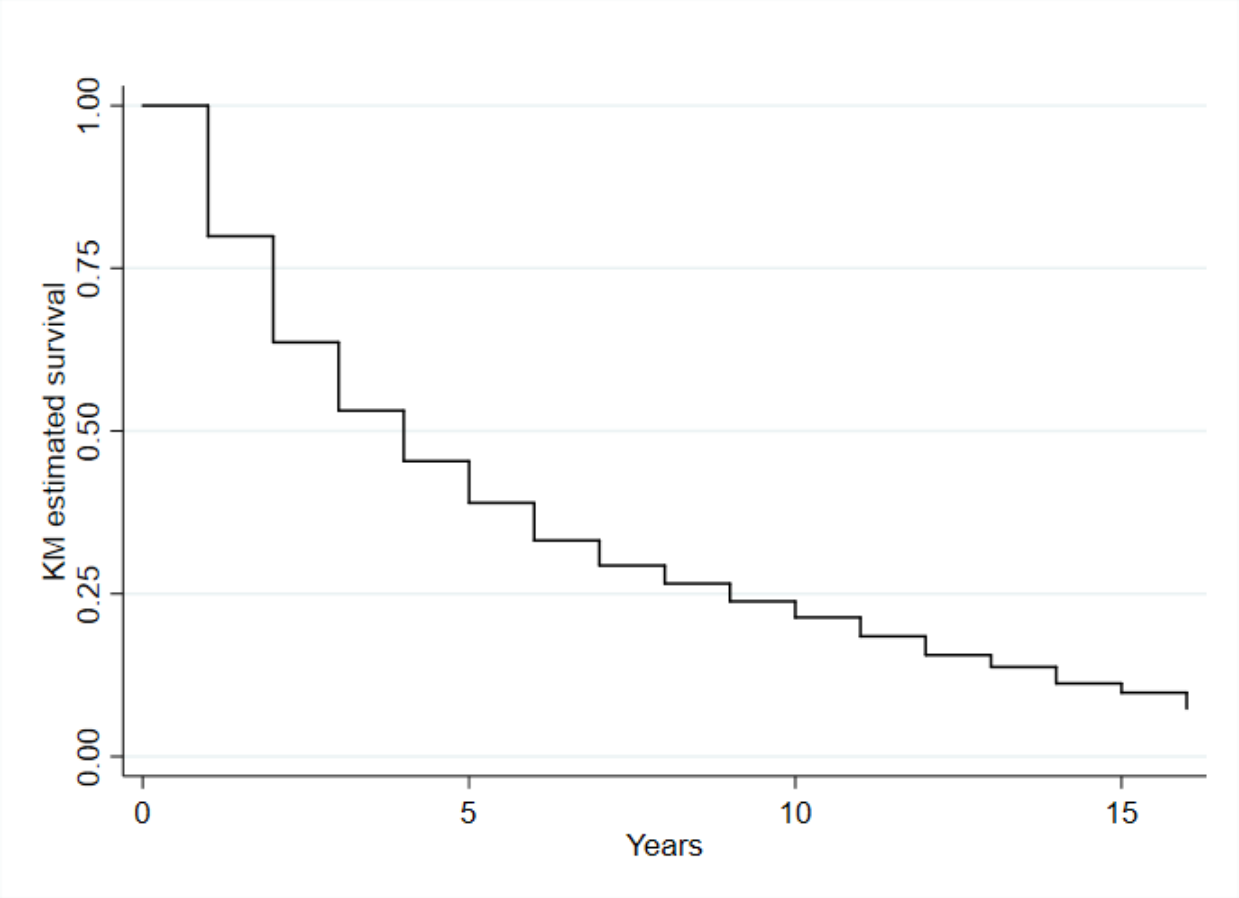


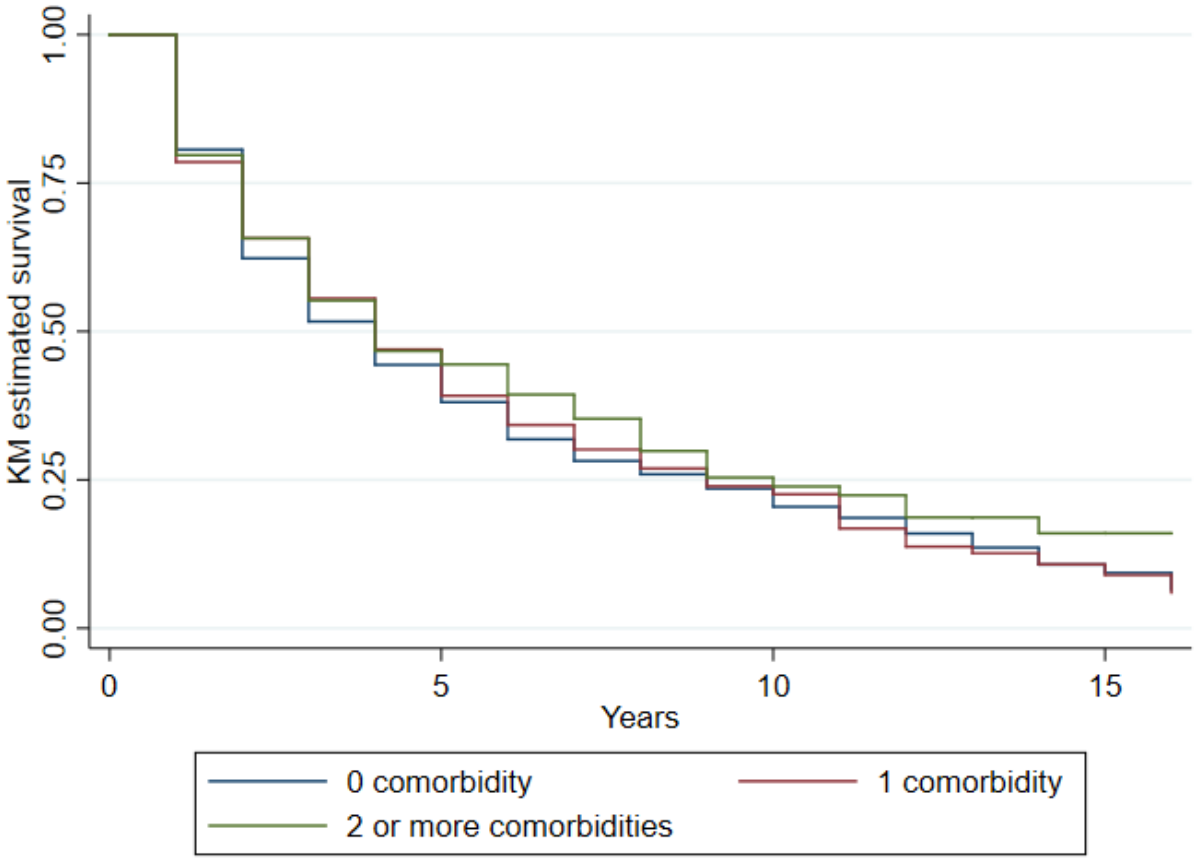
Figure 3. Portion of population with comorbidity (n=1464)



Number at risk

1295	474	193	40

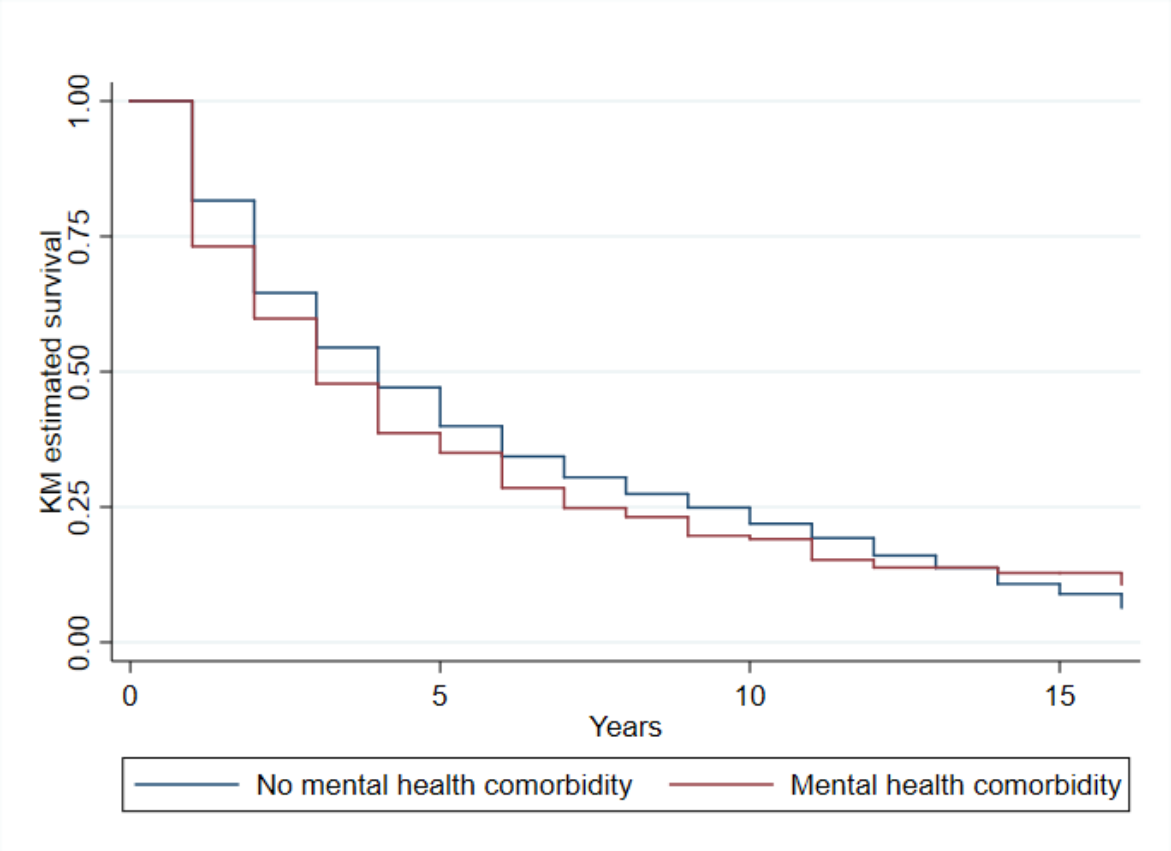
Figure 4. Kaplan Meier survival analysis of disease-modifying therapy persistence



Number at risk by comorbidity count

0	790	288	123	23
1	382	145	53	12
≥2	123	41	17	5

Figure 5. Kaplan Meier survival analysis of disease-modifying therapy persistence according to comorbidity count



Number at risk by mental health comorbidity

No	1038	389	161	29
Yes	257	85	32	11

Figure 6. Kaplan Meier survival analysis of disease-modifying therapy persistence according to mental health comorbidity

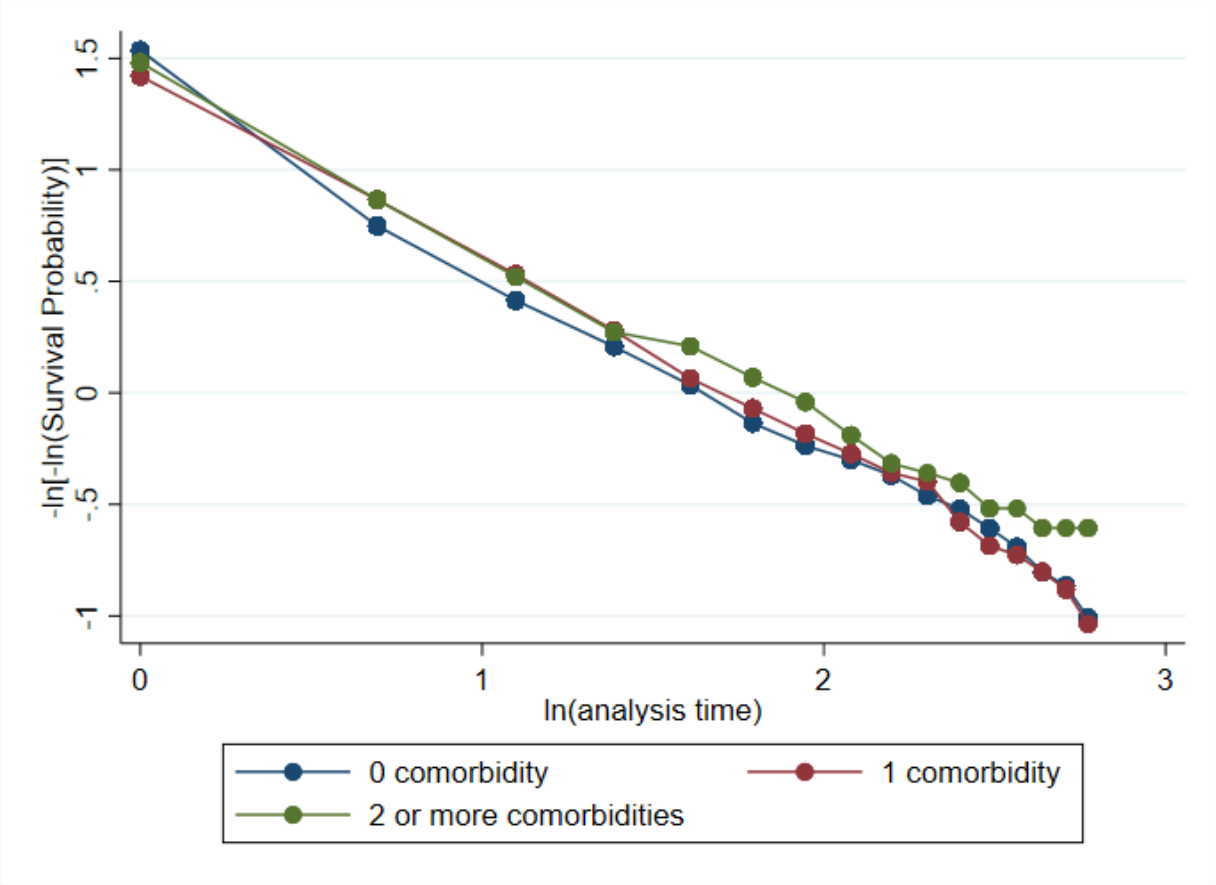


Figure 7. Log-log survival curve for disease-modifying therapy persistence according to comorbidity count

CHAPTER 6 DISCUSSION

6.1 Summary of Findings

In this cohort of individuals with CIS or RRMS starting platform DMT as initial therapy between 2001 and 2016, the median persistence of DMT was 4 years. There was no difference in duration of initial DMT by comorbidity count. Among examined comorbidities, the only comorbidity associated with an increased risk of discontinuing initial DMT was a mental health comorbidity. Those with a mental health comorbidity discontinued initial DMT after a median of 3 years versus 4 years for those without a mental health comorbidity. Increased risk of discontinuing initial DMT with a mental health comorbidity was demonstrated in subgroup analysis for injectable but not oral therapy. The results of subgroup analysis for oral therapy need to be interpreted with caution given limited sample size.

Prior to 2013 when platform therapy consisted of only injectable DMT options, there was increased selection of glatiramer acetate compared to interferon-β among those with ≥2 comorbidities. From 2013 onward, there was no effect of comorbidity count on selection of injectable versus oral DMT although this analysis may have been underpowered. There was increased risk of discontinuing initial DMT for lack of tolerability with ≥2 comorbidities. There was no effect of comorbidity count on discontinuing initial DMT for lack of efficacy. There was no effect of a specific comorbidity on choice of therapy or reason for therapy discontinuation.

6.2 Comorbidity and Multiple Sclerosis Treatment

Individuals with comorbidity have a reduced likelihood of starting DMT but there are conflicting findings concerning whether comorbidity influences persistence of DMT. In a cohort of >10,000 individuals with MS in three Canadian provinces (including NS) starting an injectable DMT,

increased burden of comorbidity was associated with reduced likelihood of initiating DMT[11]. Among examined comorbidities in that study (hypertension, hyperlipidemia, diabetes, IHD, chronic lung disease, epilepsy, anxiety, depression, bipolar disorder), IHD or anxiety at MS diagnosis was associated with a reduced likelihood of DMT initiation.

In our study, median persistence of DMT was 4 years with 38% of individuals having ≥1 comorbidity at DMT initiation. There was no effect of comorbidity count on duration of initial DMT. In a cohort of approximately 1800 individuals with MS from Italy among whom 24% had ≥1 comorbidity at MS diagnosis, approximately 50% of individuals switched DMT (among glatiramer acetate, interferon-β, dimethyl fumarate, teriflunomide, fingolimod, natalizumab) by 3 years[12]. Duration of therapy in the presence versus absence of comorbidity was not reported.

Similar to our study, the median duration of injectable DMT among 721 individuals with MS starting initial therapy in Manitoba was 4 years with no effect of comorbidity on persistence of DMT examined using number of non-MS medications or non-MS hospitalizations as a proxy of comorbidity[57]. Among 879 individuals with MS starting oral DMT (dimethyl fumarate, fingolimod, teriflunomide) in British Columbia, there was no effect of comorbidity, measured using the Charlson Comorbidity Index, on persistence of DMT at 6 months and 1 year[59]. In that cohort, 11% discontinued oral DMT at 6 months and 20% discontinued oral DMT at 1 year. In contrast to our study, a cohort of 4830 individuals with MS from three Canadian provinces showed an association between discontinuing injectable DMT and number of non-MS medications as a proxy of comorbidity with evidence of a dose-response relationship[56]. Although we hypothesized that higher comorbidity count would be associated with shorter duration on initial DMT, this was not supported by our findings. Differences between our study and Evans et al.[56], demonstrating increased risk of discontinuing DMT with increased

comorbidity burden, included identification of MS participants by administrative data, burden of non-MS medications used as a proxy of comorbidity, and larger sample size in the other study.

In our study, there was an increased risk of discontinuing initial DMT, particularly injectable therapy, in the presence of a mental health comorbidity. Individuals with a mental health condition remained on initial platform DMT for 3 years compared to 4 years for those without a mental health condition. In a Canadian cohort examining injectable DMT, the presence of anxiety reduced the likelihood of starting DMT (HR 0.78, 95% CI 0.69-0.87) including in the province of NS[11]. Conversely, the presence of depression at the time of DMT initiation showed a weak association with increased likelihood of starting treatment (HR 1.13, 95% CI 1.00-1.27) although this was not apparent on restricting analysis to data from NS[11]. In an Italian cohort, there was no association between discontinuing DMT, specifically interferon-β for lack of tolerability, and any specific comorbidity including mental health conditions[12]. In contrast, discontinuation of interferon-β at 6 months was associated with new or worsening depression among 99 individuals with MS receiving interferon-β[87]. Overall, there is likely increased risk of not starting or not persisting with DMT in the presence of a mental health comorbidity.

In terms of initial DMT selection, glatiramer acetate was preferred among individuals with ≥2 comorbidities during a period of time when only injectable DMT was available as platform therapy (before 2013). There was no effect of comorbidity on choice of injectable versus oral therapy (from 2013 onward) although this analysis may have been limited by sample size. In contrast to our study, there was no effect of comorbidity count on selection of glatiramer acetate versus interferon-β as initial DMT in a cohort of >10,000 individuals with MS in three Canadian provinces[11]. Although combined data from three Canadian provinces did not

demonstrate a preference of injectable DMT by comorbidity count, there was greater likelihood of selecting glatiramer acetate in NS with ≥3 comorbidities. Among approximately 1800 individuals with MS from Italy starting any DMT, there was no effect of comorbidity on choice of initial DMT[12]. Differences between our study and the Italian cohort included differences in case ascertainment and comorbidity measurement.

We hypothesized that the DMT with a more favourable side effect profile would be preferred among individuals with higher comorbidity burden with glatiramer acetate preferable to interferon-β and injectable therapy preferable to oral therapy. Our results supported this impression as higher burden of comorbidity was associated with use of glatiramer acetate instead of interferon-β. Our results did not support a difference in selection of injectable versus oral therapy although this analysis was likely underpowered.

In terms of initial DMT discontinuation, there was increased risk of discontinuing initial DMT for lack of tolerability with ≥2 comorbidities (OR 1.72, 95% CI 1.05-2.82). There was no effect of comorbidity count on discontinuing initial DMT for lack of efficacy. Similar to our study, an Italian cohort of approximately 1800 individuals with MS showed an increased risk of discontinuing DMT for intolerance in the presence of comorbidity (HR 1.42; 95% CI 1.07-1.87)[12]. The Italian study also showed no difference in risk of DMT discontinuation for lack of efficacy according to presence of comorbidity.

In our study, there was a trend toward increased risk of discontinuing DMT for lack of tolerability, that was not statistically significant, in subgroup analyses of injectable but not oral DMT. In an Italian cohort, increased risk of discontinuing DMT for lack of tolerability in the presence of comorbidity was apparent for those treated with interferon-β among a cohort of individuals treated with glatiramer acetate, interferon-β, natalizumab, and fingolimod[12]. The

detection of increased risk of discontinuing interferon-β for lack of tolerability may have been due to the higher number of participants taking interferon-β than any other DMT in this study leading to the other groups being underpowered. In our study, we examined the relationship between comorbidity and reason for discontinuation in subgroup analyses by categorizing DMT into injectable and oral therapy not by individual DMT due to small sample size. It is possible that combining glatiramer acetate and interferon-β into the same category of injectable therapy obscured the effect of discontinuing interferon-β for lack of tolerability with higher comorbidity burden if glatiramer acetate was well tolerated.

In analyses controlling for comorbidity, we found sex differences in choice of initial platform DMT and reasons for DMT discontinuation. In the period before 2013, women were more likely to start glatiramer acetate compared to interferon-β. In the period from 2013 onward, there was no sex difference in choice injectable versus oral therapy. A Canadian cohort of >10,000 individuals with MS from three Canadian provinces showed that women were more likely than men to start an injectable DMT[11]. The effect of sex while controlling for comorbidity on selection of glatiramer acetate versus interferon-β has not previously been reported. As well, we found that women had increased odds of discontinuing DMT for lack of tolerability while men had increased odds of discontinuing DMT for lack of efficacy. In general, women are known to report a higher rate of adverse drug reactions[88]. Similar to our findings, two Canadian cohorts found no sex difference in persistence of DMT while controlling for comorbidity[56,57]. The effect of sex while controlling for comorbidity on reasons for DMT discontinuation has not previously been reported.

Comorbidity is increasingly recognized as a factor which may influence patterns of DMT use. Recent American Academy of Neurology practice guidelines for disease-modifying

therapies for adults with MS suggest that patients should receive counselling about comorbid disease[89]. At the current time, there is limited information concerning the efficacy, safety, and tolerability of DMT among individuals with MS and comorbidity[10]. Our study has provided insight into the association between comorbidity and platform DMT persistence, selection, and discontinuation which will inform the discussion concerning comorbidity and use of initial platform DMT.

6.3 Mental Health Comorbidity and Multiple Sclerosis Treatment

Our finding that presence of a mental health condition is associated with increased risk of discontinuing initial DMT, particularly an injectable therapy, suggests that individuals with a mental health comorbidity may require increased support to maintain MS treatment. Psychiatric comorbidity is common among individuals with MS particularly depression affecting 23.7% and anxiety affecting 21.9%[5,90]. Psychiatric comorbidity is more common among individuals with MS compared to the general population with 71% increased incidence of depression and 42% increased incidence of anxiety among those with MS compared to age-, sex-, and geographically-matched controls[91]. The reasons for this are not fully known but are likely multifactorial with contributors including pathophysiology of MS, psychosocial issues associated with MS, and potentially the effects of MS treatments.

Among individuals with MS, increased burden of physical comorbidity is associated with increased risk of developing a psychiatric comorbidity including depression and anxiety in a dose-dependent manner[92]. The presence of a psychiatric comorbidity among individuals with MS is associated with reduced quality of life and increased risk of mortality[93,94]. In a Canadian cohort of individuals with MS starting injectable DMT, mental health comorbidity particularly

anxiety reduced the likelihood of starting DMT (HR 0.78, 95% CI 0.69-0.87) including in the province of NS[11].

In our study, there was increased risk of discontinuing DMT in the presence of a mental health diagnosis particularly for injectable therapy. Additionally, individuals with ≥2 comorbidities had increased risk of discontinuing DMT due to lack of tolerability. Although there was a trend toward increased risk of discontinuing DMT due to lack of tolerability among those with increased comorbidity burden in subgroup analysis of injectable therapy, this did not reach statistical significance. We did not find that any specific comorbidity was associated with DMT discontinuation for lack of tolerability or lack of efficacy.

There is limited information on the association between comorbidity and reasons for DMT discontinuation. Similar to our study, an Italian cohort demonstrating higher discontinuation of interferon-β for lack of tolerability in the presence of comorbidity did not show an association with any specific comorbidity including mental health conditions[12]. In a small study of 99 individuals treated with interferon-β, the presence of new or worsening depression was associated with increased risk of DMT discontinuation[87]. Among patients experiencing depression on interferon-β, treatment of depression with psychotherapy and/or antidepressant medication was associated with increased DMT persistence[95]. Despite early safety concerns regarding interferon-β as a risk factor for developing depression, this relationship is now controversial[96]. In our study, only 30 individuals discontinued injectable or oral DMT for depressive symptoms among 649 individuals discontinuing DMT for lack of tolerability. Injectable DMT may trigger needle phobia manifesting as anxiety which can contribute to DMT discontinuation[97]. In our study, only 18 individuals discontinued injectable therapy for needle phobia among 225 individuals discontinuing DMT for an injection-related

issue captured within discontinuations for lack of tolerability. There is no increased risk of diagnosis of a psychiatric comorbidity after exposure to oral therapies including teriflunomide and dimethyl fumarate[98].

Mental health disorders have previously been identified as a barrier to accessing prescription medication in a number of other health conditions including diabetes[99], hypertension[100], and cancer[101]. Depression has been shown to delay escalation of diabetes treatment[99]. Depression and anxiety have been implicated as strongly negative predictors for escalation of antihypertensive treatment[100]. In addition, depression has been shown to decrease the likelihood of receiving chemotherapy among individuals with pancreatic adenocarcinoma[101]. In a Canadian MS cohort, the presence of anxiety was strongly associated with not starting DMT[11].

There is limited information on the effect of mental health on DMT persistence. In an Italian cohort, there was no effect of specific comorbidity including mental health comorbidity on discontinuation of interferon-β due to lack of tolerability[12]. Among other health conditions, there is limited information on the effect of a mental health condition on persistence of treatment for comorbid disease. The presence of mental health comorbidity has been associated with decreased persistence to insulin among individuals with diabetes although this finding disappeared in multivariate analysis[102]. Among individuals with hypertension, the presence of mental health comorbidity was not associated with decreased persistence to antihypertensive medication[103].

The reasons why mental health comorbidity reduces persistence to initial DMT, particularly injectable therapy, for RRMS remains unclear. Potential contributing factors include difficulty communicating with healthcare providers due to symptoms of a mental health disorder,

increased burden of psychosocial issues limiting ability to follow treatment recommendations, and medication interactions with pharmacologic treatments for a mental health condition. Overall, the reason for increased risk of DMT discontinuation among individuals with mental health comorbidity requires further study.

6.4 Comorbidity, Multiple Sclerosis Treatment and Health Outcomes

Comorbidity and DMT have implications on the course of MS. Higher comorbidity burden is associated with increased risk of relapse although this effect is attenuated by adjustment for DMT use[7]. In addition, higher comorbidity burden is associated with increased risk of disability progression with each additional physical comorbidity contributing a 0.18 increase in EDSS which remains after considering use of a DMT[9]. Presence of a mood or anxiety disorder is associated with increased disability after adjusting for DMT use although this has been demonstrated among women but not men[104]. Increasing burden of comorbidity is associated with increased risk of hospitalization for any reason excluding childbirth in a dose-dependent manner although the role of DMT was not evaluated[66,105]. In a separate analysis, DMT utilization slightly reduced risk of hospitalization for any reason excluding childbirth although the role of comorbidity was not evaluated[106]. Comorbidity increases mortality among individuals with MS similar to age-, sex-, and geographically-matched controls although the role of DMT was not evaluated[68].

There are many adverse effects attributed to DMT (Table 2) which may be relevant to MS patients with comorbidity[107]. Prior to starting DMT, it is important to consider whether existing comorbidity presents a contraindication to initiating a specific DMT. Occasionally, a comorbid health condition may benefit from DMT prescribed for RRMS. Elevated liver

enzymes are a contraindication to starting several platform DMTs including interferon-β, teriflunomide, and dimethyl fumarate. Although DMT should not be started during a serious infection, platform injectable therapies and oral therapies (fingolimod, dimethyl fumarate) are not associated with increased risk of subsequent health encounters for infection after controlling for comorbidity[108]. The most common comorbid autoimmune conditions among individuals with MS are psoriasis and thyroid disease[109]. Among platform DMT, interferon-β has been associated with treatment-emergent autoimmune thyroid dysfunction which is more common among individuals with baseline and emergent thyroid autoimmunity[110]. Treatment-emergent thyroid dysfunction often does not require discontinuation of interferon-β. Psoriasis may actually benefit from selection of dimethyl fumarate for RRMS as it is also a treatment for psoriasis[79,111]. Overall, the interaction between comorbidity and MS treatment requires careful consideration of the individual patient for a customized approach to DMT selection.

Earlier initiation of DMT is associated with improved long-term outcome including when controlling for comorbidity[112,113]. Injectable DMT is believed to reduce disability progression in observational studies[52,53]. In addition, there is increasing evidence that early higher-efficacy therapy compared to platform therapy is associated with reduced disability progression and conversion to SPMS[114,115]. There is limited information available on DMT efficacy in the presence of comorbidity. Our study did not demonstrate an effect of comorbidity on discontinuing DMT for lack of efficacy. In a cohort of approximately 1800 RRMS patients with approximately 50% discontinuing therapy after 3 years, there was no effect of comorbidity on discontinuing therapy for lack of efficacy[12]. In this Italian cohort, there was increased risk of disability progression among those with comorbidity after controlling for DMT.

6.5 Strengths and Limitations

Strengths of this study include that it was population based. We expect there was near complete case ascertainment during the study period as the DMSRU was the only provider of specialized care for RRMS patients in NS during this time period. As well, >95% of the relevant MS population at the DMSRU provided consent for participation in research including linkage to administrative data. New diagnoses of RRMS were determined from the DMSRU database which records the date of clinical diagnosis and is more accurate than relying on administrative data for case ascertainment. Although administrative data has limitations, comorbidity was determined using administrative case definitions that have previously been validated among individuals with MS in NS or another Canadian province. Real-world data provides an opportunity to address concepts such as the relationship between comorbidity and patterns of initial DMT use which are not amenable to a randomized controlled trial design[116].

Limitations of this study included use of administrative case definitions to determine comorbidity. Only a limited number of comorbid conditions were included as we restricted comorbidities to conditions with a validated administrative case definition among an MS population in Canada. As a result, not all comorbid conditions were captured. Although all administrative case definitions used in this study have been validated in a Canadian population, positive predictive value of case definitions in NS ranged from 36% for IHD to 90% for IBD based on comparison of administrative case definitions to patient self-report. As a result, there was a risk of failing to capture some comorbidities of interest more than others through administrative data. Administrative case definitions indicated diagnosis of a medical condition but did not indicate disease severity. In addition, administrative health data in NS did not capture prescription medication during the study period. Administrative health definitions

perform better with the inclusion of prescription claims[75,76]. As well, there was incomplete information concerning onset of comorbidity as the date of first administrative claim was considered the date of diagnosis with the diagnosis considered present for the rest of follow-up. As a result of this definition, it was not possible to capture the date of symptom onset for a comorbidity or account for a comorbidity that was previously present but had since resolved.

There was missing data for potential confounding variables including EDSS at DMT initiation and neighbourhood income quintile in a small number of cases. Missing data was treated as missing completely at random. Cases with missing data were omitted from the relevant statistical model. We did not capture health behaviours including smoking, alcohol consumption, recreational use of drugs, diet, exercise, or body mass index. Although we attempted to account for socioeconomic status by using postal code to estimate median household income according to census region, this is ecological data and does not apply directly to the individual resulting in risk of ecological fallacy. We did not capture education which may be a confounding variable for DMT use.

The sample size for this study was fixed as the study population consisted of individuals with CIS or RRMS started on initial platform DMT from 2001 to 2016 in the DMSRU database. There was limited data regarding platform oral therapy as dimethyl fumarate and teriflunomide were introduced to the Canadian market in 2013 which limited the duration of observation on these therapies compared to platform injectable therapies which have been available since the 1990's. Subgroup analysis of specific DMT was limited by block size. As a result, subgroup analysis was performed with DMT as a binary variable. DMT was dichotomized as injectable or oral therapy except for analysis of treatment selection prior to 2013 which was dichotomized into glatiramer acetate or interferon-β. Although there are within group differences in the mechanism

of action and side effect profile of injectable (glatiramer acetate, interferon-β) and oral (dimethyl fumarate, teriflunomide) therapies, limited sample size prevented analysis of specific DMT.

CHAPTER 7 CONCLUSION

In this study, we investigated the relationship between comorbidity and patterns of initial platform DMT use. Overall, median persistence of initial platform DMT was 4 years. The presence of a mental health comorbidity was associated with increased risk of discontinuing DMT particularly injectable therapy. The amount of time on initial platform DMT was 3 years for those with a mental health comorbidity compared to 4 years for those without a mental health comorbidity.

Mental health comorbidity is a risk factor for reduced access to prescription medications for the treatment of chronic health conditions while an effect of mental health comorbidity on persistence to treatment for the same chronic health conditions has not been established[99,100,102,103]. Increased risk of discontinuing initial platform DMT in the presence of a mental health comorbidity suggests that individuals with a mental health comorbidity require increased support following diagnosis of MS to maintain therapy. Depression has previously been associated with increased risk of discontinuing interferon-β although treatment of depression has been associated with increased persistence to this medication[87,95]. There is reason to believe that individuals with MS and a comorbid mental health disorder are willing to access available resources for treatment as these individuals perceive a need for mental health care in the presence of anxiety or depression symptoms[117]. Treatment of depression, both psychological and pharmacologic, is effective in reducing depressive symptoms among individuals with MS[118]. Identifying and treating mental health comorbidity has the potential to improve health outcomes among individuals with MS including by increasing persistence of initial platform DMT.

In the period prior to availability of oral therapy (before 2013), high comorbidity count was associated with selection of glatiramer acetate over interferon-β. In the period following availability of oral therapy (2013 onward), there was no preference of injectable versus oral DMT with comorbidity count. We hypothesized that the DMT with a more favourable side effect profile would be preferred among individuals with high comorbidity burden. Our hypothesis was correct concerning the preferred selection of glatiramer acetate versus interferon-β among individuals with ≥2 comorbidities. Greater use of glatiramer acetate compared to interferon-β with high comorbidity burden has previously been demonstrated in NS[11]. Glatiramer acetate is likely an appealing option for individuals with multiple comorbidities given the low risk of serious adverse events compared to other DMT and lack of medication interactions. Although there was no difference in selection of injectable versus oral therapy according to comorbidity count, it is likely that this analysis was underpowered as fewer individuals have been exposed to oral DMT given the much shorter time period of availability.

There was increased risk of discontinuing DMT for lack of tolerability among individuals with high comorbidity count. Although there was a trend toward increased risk of discontinuation for lack of tolerability with increased comorbidity count in subgroup analysis of injectable therapy, this did not reach statistical significance. There was no effect of comorbidity count on risk of DMT discontinuation due to lack of efficacy. Increased risk of DMT discontinuation for lack of tolerability but not lack of efficacy in the presence of comorbidity has previously been demonstrated in an Italian cohort[12]. It is possible that higher burden of comorbidity results in higher risk of DMT adversely interacting with comorbid disease or resulting in medication interactions which lead to DMT discontinuation due to intolerance. The

reasons for higher risk of DMT intolerance in the presence of higher burden of comorbidity requires further investigation.

Understanding the relationship between comorbidity and initial DMT patterns of use has implications on counselling patients with a new diagnosis of RRMS. Overall, it seems reasonable that individuals with RRMS and comorbidity should be considered for all platform DMT options unless there is a specific contraindication to a specific DMT. Individuals with higher comorbidity burden and those with mental health comorbidity may have unique challenges that impact ability to continue DMT after treatment initiation. The nature of these barriers requires further study.

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