

**Impact of Generic Competition on Prices of Branded Self-administered Disease-Modifying
Therapies for Multiple Sclerosis**

by

Álvaro San Juan Rodríguez

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This thesis was presented

by

Álvaro San Juan Rodríguez

It was defended on

November 24, 2020

and approved by

Inmaculada Hernandez, PharmD, PhD, Assistant Professor, Department of Pharmacy and
Therapeutics, School of Pharmacy, University of Pittsburgh

Julie M. Donohue, PhD, Professor, Department of Health Policy and Management, Graduate
School of Public Health, University of Pittsburgh

Thesis Advisor: Eric T. Roberts, PhD, Assistant Professor, Department of Health Policy and
Management, Graduate School of Public Health, University of Pittsburgh

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Álvaro San Juan Rodríguez, MS

University of Pittsburgh, 2020

ABSTRACT

Prices of disease-modifying therapies (DMTs) for multiple sclerosis (MS) in the US increased drastically over the last decade, continuing to grow even after the introduction of generic competition. Prior research on DMT prices mostly employed measures of list prices, which do not account for discounts. Thus, the extent to which discounts offset list price increases of individual agents and the impact of generic competition on net prices of DMTs remains unclear.

In this retrospective descriptive study, we used 2010-2019 pricing data for branded self-administered DMTs from SSR Health, which provides estimates of net prices and discounts for most branded prescription drugs. For each drug and year, we estimated annual costs of treatment based on list and net prices, and discounts for Medicaid and other payers. We constructed interrupted time series analysis models to test whether the introduction of generic competition was associated with a change in price trajectories of incumbent agents.

List prices of DMTs experienced a drastic growth in 2010-2019, increasing at an annual rate of 10.4%. Discounts varied widely within the category, and for most agents, only offset list price increases partially. After accounting for discounts, net prices still increased substantially at an annual rate of 8.9%. After the introduction of the first generic glatiramer in 2015, net price growth of original glatiramer, subcutaneous interferon beta-1a and fingolimod slowed down

significantly. The second wave of generic entries in 2017 was associated with a significant change in net price trajectories of original glatiramer, leading to a considerable decrease in net price.

Public health significance: MS affects almost one million individuals in the US, and treatment with DMTs is crucial for reducing clinical exacerbations' frequency and severity. However, high and rising prices of DMTs can limit affordability, reducing patient access and adherence. Understanding pricing patterns, the role of manufacturer discounts, and the impact of generic competition in the DMT category will be paramount to inform policymakers in developing policies aiming to facilitate the entry of generics and biosimilars into the US prescription drug market. Such policies will likely reduce affordability barriers, improving patients' quality of life, and clinical outcomes.

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1.0 BACKGROUND

1.1 Overview of Multiple Sclerosis

1.1.1 Pathology, Pathogenesis, and Clinical Course

Multiple sclerosis (MS) is an inflammatory, neurodegenerative disorder of the central nervous system (CNS).^{1,2} The characteristic neuropathologic hallmark of MS is the presence of focal demyelinating plaques within the CNS.³ Damage to the myelin sheath—the insulating layer that facilitates the transmission of nerve impulses—leads to the neurological manifestations of the disease.⁴ MS is a heterogeneous disease whose clinical features vary depending on the number, location, and extension of these lesions. Common neurological symptoms of MS include weakness of limbs, vision problems, numbness or tingling, impaired cognitive functions, clumsiness and poor balance, or incontinence, among others.^{4,5}

Early in the course of disease, patients usually experience transient episodes of neurologic disability—referred to as relapses or exacerbations—which last from days to weeks, followed by periods of relief.³ Relapses are the clinical manifestations of acute focal lesions to the myelin sheath.⁶ Nevertheless, during this initial course of MS, known as relapsing-remitting MS, remyelination leads to a partial or full recovery of the neurologic functions.⁴ Axons are relatively preserved in the early stage of the disease;³ however, as the disease progresses, patients experience an extensive and chronic axonal degeneration that leads to the non-relapsing progression of the disease.⁴ This phase is characterized by an accumulation of motor and cognitive disability.²

1.1.2 Epidemiology

MS is one of the most common neurologic disorders worldwide,⁷ and in many countries, it constitutes the leading cause of disability among young adults aside from trauma.^{3,7} After 15 years of disease, 48% of MS patients require ambulatory aid (i.e., cane), and 33% bilateral support (i.e., two canes/walker) or worse (wheelchair/scooter, bedridden).⁸ Conditional on survival, these proportions increase up to 76% and 52%, respectively, after 45 years of disease.⁸ According to recent estimates, MS affects almost one million individuals in the US alone.⁹ For unknown reasons, MS is more prevalent among women,² with an estimated female to male ratio of 2.8:1.⁹ MS can emerge at any age, but onset usually occurs between ages 20 and 40.¹⁰ Relapsing-remitting MS accounts for approximately 85-90% of the cases at disease onset, while primary progressive MS accounts for the remaining 5-15% of cases.¹¹ After typically 10-20 years of relapsing-remitting MS,² around 65% of patients transition into the secondary progressive form of the disease.⁴ Both in primary and secondary forms of progressive MS, progression starts at around 40 years of age.¹² The median time to death is approximately 30 years from disease onset, which represents a 5-10 years reduction in life expectancy.¹³

1.1.3 Etiology

It remains unknown whether MS has a single or multiple causes, and no specific etiologic trigger has been identified.² Nonetheless, a series of genetic and environmental risk factors have been associated with the development of MS.²⁻⁴ More than 200 genetic polymorphisms have been associated with an increased risk of disease development,¹⁴ of which the most significant are those affecting the HLA-DRB1 locus.¹⁵⁻¹⁷ Major environmental risk factors include vitamin D, geographic latitude, infectious mononucleosis, smoking, and childhood obesity.² Higher

levels of vitamin D have been associated with a reduced risk of developing MS, and with a decreased clinical activity once the disease has been established.¹⁸ Additionally, there is a north-south gradient in the geographic distribution of MS, with a higher incidence in northern latitudes.⁹ This may reflect seasonal changes in sunlight exposure—in particular to ultraviolet B radiation—responsible for the cutaneous production of vitamin D; but also differences across regions in the genetic pool and other environmental factors.² Similarly, infectious mononucleosis,^{19,20} cigarette smoking,²¹ and childhood obesity²² have all been associated with increased development of MS. The mechanisms by which these factors increase the risk of MS are still under active investigation.²

1.2 Disease-Modifying Therapies Available for the Treatment of Multiple Sclerosis

There is no curative treatment for MS.⁵ Despite this, prompt initiation and adherence to disease-modifying therapies (DMTs)—the standard of care for most courses of MS—has shown beneficial effects for patients, reducing the frequency and severity of relapses and slowing the accumulation of lesions in the CNS.^{2,3} Additionally, accumulating data from recent observational studies suggest that the use of DMTs may also be associated with a lower risk of MS progression.²³⁻²⁵ Most DMTs are continued indefinitely in clinically stable patients unless adverse effects are unbearable or safety concerns emerge.^{26,27}

As of April 2020, there were 15 therapies approved by the US Food and Drug Administration (FDA) for modifying the course of MS.² These include 4 injectable therapies (interferon beta-1a, interferon beta-1b, peginterferon beta-1a, glatiramer acetate), 3 infusion therapies (natalizumab, alemtuzumab, and ocrelizumab), and 8 newer, oral therapies (fingolimod

hydrochloride, teriflunomide, dimethyl fumarate, cladribine, siponimod fumaric acid, diroximel fumarate, ozanimod hydrochloride, and monomethyl fumarate).²⁸ Injectable and oral therapies are typically self-administered, while infusion therapies are provider-administered. All agents approved for the treatment of MS, their manufacturer, route of administration, synthesis mechanism, and approval date are listed in **Table 1**.

Table 1. List of Disease-Modifying Therapies Available for the Treatment of Multiple Sclerosis

| Generic Name | Brand Name | Manufacturer | Route | Synthesis | Approval |
|--------------------------|--------------------------|----------------------|-------|------------|----------------|
| Interferon beta-1b | Betaseron | Bayer | SC | Biological | July 1993 |
| Interferon beta-1a | Avonex | Biogen | IM | Biological | May 1996 |
| Glatiramer acetate 20 mg | Copaxone 20mg | Teva | SC | Chemical | December 1996 |
| Interferon beta-1a | Rebif | EMD Serono | SC | Biological | March 2002 |
| Natalizumab | Tysabri | Biogen | IV | Biological | November 2004 |
| Interferon beta-1b | Extavia | Novartis | SC | Biological | August 2009 |
| Fingolimod hydrochloride | Gilenya | Novartis | PO | Chemical | September 2010 |
| Teriflunomide | Aubagio | Sanofi | PO | Chemical | September 2012 |
| Dimethyl fumarate | Tecfidera | Biogen | PO | Chemical | March 2013 |
| Glatiramer acetate 40 mg | Copaxone 40mg | Teva | SC | Chemical | Jan 2014 |
| Peginterferon beta-1a | Plegridy | Biogen | SC | Biological | August 2014 |
| Alemtuzumab | Lemtrada | Sanofi | IV | Biological | November 2014 |
| Glatiramer acetate 20mg | Glatopa 20mg | Sandoz | SC | Chemical | April 2015 |
| Ocrelizumab | Ocrevus | Genentech | IV | Biological | March 2017 |
| Glatiramer acetate 20 mg | Glatiramer acetate 20 mg | Mylan | SC | Chemical | October 2017 |
| Glatiramer acetate 40 mg | Glatiramer acetate 40 mg | Mylan | SC | Chemical | October 2017 |
| Glatiramer acetate 40 mg | Glatopa 40mg | Sandoz | SC | Chemical | February 2018 |
| Cladribine | Mavenclad | EMD Serono | PO | Chemical | March 2019 |
| Siponimod fumaric acid | Mayzent | Novartis | PO | Chemical | March 2019 |
| Diroximel fumarate | Vumerity | Biogen | PO | Chemical | October 2019 |
| Ozanimod hydrochloride | Zeposia | Celgene | PO | Chemical | March 2020 |
| Monomethyl fumarate | Bafiertam | Banner Life Sciences | PO | Chemical | April 2020 |

Abbreviations: SC, subcutaneous; IM, intramuscular; IV, intravenous; PO, *per os* (oral).

Injectable (subcutaneous and intramuscular) and oral therapies are typically self-administered, while infusion (intravenous) therapies are provider-administered.

Since the first DMT's approval in 1993, the therapeutic arsenal for MS has widened considerably with a gradual stream of new approvals.⁴ However, the majority of these newly

available agents are branded products. Out of all agents approved for the treatment of MS, only glatiramer faces direct competition from generic versions. Currently, there are 4 generic glatiramers in the DMT market. The first generic glatiramer—glatiramer 20mg (Glatopa 20mg)—was approved by the FDA in April 2015.²⁸ This was the only available generic until October 2017, when 2 new generic glatiramer formulations manufactured by Mylan (both 20mg and 40mg) were approved. Finally, a fourth formulation of generic glatiramer—glatiramer 40mg (Glatopa 40mg)—was approved in February 2018.²⁸

1.3 Pricing and Spending on Disease-Modifying Therapies for Multiple Sclerosis

Over the last two decades, prices of DMTs for MS have increased drastically in the US, at rates that far outpace general inflation.²⁹⁻³⁶ The mean annual cost of treatment with DMTs for MS has increased from approximately \$10,000 in 2000 to more than \$86,000 in 2019.³¹ Large price increases within the DMT category can be explained by a combination of rising prices of existing therapies and the entry of newer more expensive drugs.^{37,38}

Escalating prices of DMTs have led to substantial increases in pharmaceutical spending.^{37,38} Because of this, as of 2018, MS constituted one of the top therapeutic classes by pharmaceutical spending across all types of health insurance.³⁸ Escalating prices have particularly affected Medicare Part D,³⁰ the single largest purchaser of DMTs for MS in the US.³¹—it is estimated that nearly 30% of individuals with MS in the US are covered by Medicare through disability insurance.³⁹ Between 2006 and 2016, Medicare Part D spending on self-administered DMTs increased by more than 10-fold from almost \$400 million to \$4.4 billion.³⁰ Importantly, high annual cost of treatment of DMTs pushes most Medicare Part D

beneficiaries treated with a MS agent into the catastrophic coverage phase. A study by Trish et al. estimated that in 2012 practically all (96%) Medicare Part D beneficiaries treated with a MS agent reached the catastrophic threshold by the end of the calendar year.⁴⁰ Furthermore, rising prices of DMTs have translated into dramatic increases in out-of-pocket costs for Medicare Part D beneficiaries with MS.^{30,37,41,42} Out-of-pocket spending for Medicare Part D beneficiaries on self-administered DMTs increased from approximately \$19 million in 2006 to more than \$149 million in 2016,³⁰ with an estimated mean out-of-pocket spending across all DMTs in 2019 of almost \$7,000 per year.³⁴ Ultimately, growing out-of-pocket costs of DMTs for MS limit patients' affordability, reducing access and adherence to these essential medications,³³ which can negatively affect health outcomes.⁴³

1.4 The Impact of Competition in Prescription Drug Prices

Classic economic theory affirms that competition should reduce or stabilize prices as more products enter the market. Thus, enhancing competition is often discussed as a potential policy strategy to address the pressing issue of increasing prices of prescription drugs.^{44,45} There are 2 fundamental forms of competition in the prescription drug market: generic (within molecule competition) and branded (across molecule or within class) competition.

1.4.1 Generic or Within Molecule Competition

The passage of the Hatch-Waxman Act in 1984 established an abbreviated approval pathway for generic drugs, facilitating the entry of generic competition after the loss of market exclusivity of small molecule branded drugs.^{46,47} Following the entry of generics into the market,

brand manufacturers typically experience fast and abrupt declines in their market share as drug utilization shifts toward the much less expensive generic products that offer the same clinical benefits.⁴⁸ Furthermore, several reports have consistently found that, after the initial generic entry, generic drug prices further decline with additional generic competition.^{46,47,49,50} For instance, a recent study by Dave *et al.* found that prices of generics compared to their branded alternative were, on average, 13% lower for drugs with one generic manufacturer, 33% lower for drugs with two generic manufacturers and up to 80% lower when there are 10 or more generic manufacturers in the market.⁴⁹ However, there is no evidence of reductions in price of original branded drugs following the market entry of generic competitors. In fact, studies examining the impact of generic competition on original branded drugs prices in the US have shown that prices of original branded drugs increased following the market entry of generics,^{46,51} in a phenomenon often referred to as the generics paradox.⁵² Prices of brand name drugs can increase following the entry of generics entry because the consumers who continue to use brands once generic alternatives are available are more price insensitive.⁴⁶

1.4.2 Branded or Across Molecule Competition

Branded competition occurs when there are multiple branded drugs approved for the same indication that can be used relatively interchangeably; typically, distinct active ingredients with either identical or varying mechanisms of actions. It has been theorized that entry of new branded therapeutic alternatives may lead to lower prices for incumbent agents.⁵³ While this has been the case for a few isolated therapeutic classes, such as the new direct-acting antiviral drugs for hepatitis C, in many instances incumbent branded drugs maintain or increase their prices following the introduction of competing treatments.^{30,46,53-55} For instance, in prior work, we

demonstrated that price trends of existing tumor necrosis factor inhibitors significantly increased after the market entry of each new agent between 2006 and 2016.⁵⁴

1.4.3 Competition in the Disease-Modifying Therapies for Multiple Sclerosis Market

Since the approval of interferon beta-1b in 1993, the first DMT for MS, multiple new agents have entered the market of DMTs for MS. However, despite the increased availability of newer treatment options, drug prices within the DMT class have only continued to increase.

Two studies, both by Hartung et al., have evaluated the impact of competition in the DMT for MS market. The first of them described a rapid price escalation for all DMTs for MS between 2002 and 2013, finding that the entry of new branded DMTs only accelerated the price growth of incumbent agents.³⁵ These findings are consistent with the price-increasing effect described by prior literature for branded competition across different disease states.^{53,54} This study also found that prices of most branded DMTs grew in parallel, at similar rates across different agents.³⁵ In a more recent study using 2011-2017 data, Hartung et al. found that price growth of most DMTs for MS did not slow down following the introduction of the first generic glatiramer in 2015.³⁶ On the contrary, the authors described a significant price level increase for original glatiramer 20mg immediately after the launch of the first generic glatiramer. This initial level increase was followed by a significant, yet mild, slowdown of original glatiramer 20mg price growth. These findings are consistent with prior US studies that described increases in prices of original branded drugs following the market entry of generics.^{46,51}

Additionally, a recent study by Rome et al. evaluated the excess US spending associated with delayed generic competition related to the introduction of the new 40mg-version of branded glatiramer that extended the brand manufacturer's market exclusivity for that product version.⁵⁶

This study estimated that the 2.5 years of delayed competition from generic glatiramer 40mg was associated with \$4.3 billion to \$6.5 billion in excess spending in the US.

1.5 Evidence Gaps

Prior research evaluating trends in prices and the role of competition in the DMTs for MS market employed measures of list prices (wholesale acquisition cost or average wholesale price),³⁰⁻³⁴ or adjusted by average rebates reported by major public programs,^{35,36} which do not capture actual changes in rebates and other concessions from manufacturer to payers in the DMT category. The lack of specific discount data constitutes a key limitation because discounts have increased in parallel to list prices. Specifically, we previously estimated that increases in manufacturer discounts offset 64% of the list prices increases in 2007-2018 for DMTs.²⁹ Thus, it is necessary to incorporate estimates of manufacturer discounts in the evaluation of the role of generic competition in prices of incumbent DMTs.

There are two key gaps in the evidence on pricing and the role of competition in the DMTs for MS market:

- It is unclear to what extent manufacturer discounts have offset increases in list price of each individual product within the DMT category.
- The impact of the two waves of generic glatiramer entries on price trajectories of incumbent branded DMTs remains unknown.

2.0 OBJECTIVES

- Objective 1.** To describe 2010-2019 product-level trends in list prices, net prices and discounts of branded self-administered DMTs for MS and evaluate to what extent increases in list prices have been offset by increases in manufacturer discounts.
- Objective 2.** To test whether the introduction of generic competition was associated with a change in list and/or net price trajectories of incumbent branded self-administered DMTs for MS.
- Objective 3.** To quantify Medicare Part D savings associated with the entry of generic competition into the market of branded self-administered DMTs for MS.

3.0 METHODS

3.1 Data Sources

3.1.1 Prescription Drug Net Pricing Data

We obtained January 2010 through September 2019 pricing data from the investment firm SSR Health,⁵⁷ which has been used in prior peer-review literature.^{29,58-61} This dataset contains quarterly pricing data for the majority of branded prescription drugs with US sales reported by publicly traded companies, including list prices, estimates of net prices, discounts for Medicaid, and discounts for payers other than Medicaid.

For each product and quarter, the investment firm first estimates the net price per unit by dividing company-reported sales by the number of units sold in the US, obtained from Symphony Health.⁶² This dataset contains the number of units sold for each product in retail pharmacy, inpatient and other clinical settings. Symphony Health samples over 5,000 hospitals and 840,000 practitioner suites, capturing 93% of the prescriptions dispensed across the US. Estimates of net price reflect the mean manufacturer revenue for each drug after accounting for all concessions to purchasers, including rebates, prompt pay discounts, volume discounts, coupon cards, and any other concessions accounted for by manufacturers in the reporting of sales.⁵⁷ Importantly, net prices are not what payers or patients pay but rather the net revenue received by manufacturers per unit of product.²⁹

For each product and quarter, the investment firm estimates total discounts by dividing the difference between the list price and the estimate of net price (numerator) by the list price (denominator).⁵⁷ The estimation of separate discounts for Medicaid and for payers other than Medicaid follows a four-step process. First, the Medicaid unit rebate amount for each drug and

quarter is calculated as the sum of the basic rebate (23.1% of average manufacturer price for branded drugs) and the inflation rebate for price increases above the Consumer Price Index.⁶³ Second, discounts to Medicaid are estimated as the product of the Medicaid rebate per unit and the number of units sold to Medicaid that quarter, obtained from Medicaid state drug utilization reports.⁵⁷ Third, discounts to payers other than Medicaid are calculated for each drug and quarter as the difference between total discounts and the discounts to Medicaid. Finally, the discount per unit for payers other than Medicaid is estimated by dividing discounts for payers other than Medicaid (numerator) by the number of units sold to payers other than Medicaid (denominator). Because of this estimation methodology, supplemental rebates negotiated by Medicaid state programs or Medicaid managed care organizations are not captured under estimates of Medicaid discounts but instead under discounts for payers other than Medicaid. Besides, the methodology for estimating Medicaid discounts is unable to account for any discount derived from the Medicaid best price provision.

Since estimates of net prices are calculated by dividing net sales as reported by manufacturers by the number of units sold in the US, these estimates can be subject to variability introduced by discrepancies between the actual number of units sold by a manufacturer in a given quarter and the number of units sold in that same quarter as captured by Symphony Health. Variability in estimates of net prices introduced by inventory fluctuation tends to be higher in the immediate quarters following a product's approval. For products approved throughout our study period, we excluded all pricing and discount data in their year of approval to minimize the variability in estimates of net prices. We conducted a sensitivity analysis including these data points. This sensitivity analysis is described in section 3.6. Inventory fluctuation can also lead to estimates of net prices greater than list prices. In order to address this issue, we excluded

quarterly records when the net price was greater than the list price as previously done in the literature.^{29,59} This methodology has been employed previously.²⁹

3.1.2 Medicare Part D Drug Event File

We obtained April 2015 through December 2018 Part D drug event files for a 5% random sample of Medicare beneficiaries from the Centers for Medicare and Medicaid Services (CMS). The Part D drug event files contains service date, brand name, generic name, quantity dispensed and days of supply of all transactions covered by Medicare Part D, including both Stand Alone Prescription Drug plans and Medicare Advantage Prescription Drug plans.

3.2 Study Sample

We identified all branded self-administered DMTs for MS approved by the FDA before October 2018 and extracted all pricing data for these agents from SSR Health. We only included agents approved prior to October 2018 in order to have at least one full year of follow-up. Our sample included 8 products: interferon beta-1b (Betaseron; Bayer; approved in July 1993), interferon beta-1a subcutaneous (SC) (Avonex; Biogen; approved in May 1996), glatiramer acetate (Copaxone; Teva; approved in December 1996), interferon beta-1a intramuscular (IM) (Rebif; EMD Serono; approved in March 2002), fingolimod (Gilenya; Novartis; approved in September 2010), teriflunomide (Aubagio; Sanofi; approved in September 2012), dimethyl fumarate (Tecfidera; Biogen; approved in March 2013), and peginterferon beta-1a (Plegridy; Biogen; approved in August 2014). We limited our sample to self-administered products because these are most likely to compete against each other for formulary placement,³⁶ since they are

covered under the pharmacy benefits of an insurance policy. Our analyses did not include interferon beta-1b (Extavia) due to lack of data.

3.3 Independent Variable

For our descriptive analyses of trends in list prices, net prices, and discounts, the independent variable was calendar year. For our analyses evaluating the impact of generic competition on price trajectories of incumbent agents, the independent variable was the time of generic entry. The self-administered DMTs for MS market has only experienced the entry of 4 generics, all of them generic glatiramers. The first generic glatiramer (Glatopa 20mg) was approved by the FDA in April 2015 (Q2 2015). Two additional glatiramers (Mylan's glatiramer acetate 20mg and 40mg) were approved in October 2017 (Q4 2017) and another one (Glatopa 40mg) in February 2018 (Q1 2018). We defined Q2 2015 as the time of first generic entry. Since the entry of the last 3 generic glatiramers occurred over a short lapse of time, we considered them as one event and defined Q4 2017 as the time of the second wave of generic glatiramers entries.

3.4 Outcomes

Our study included 5 main outcomes: list price, net price, discount for Medicaid, discount for payers other than Medicaid, and Medicare Part D savings associated with the entry of generic competition. List prices were expressed as wholesale acquisition costs, which reflect manufacturers' prices to wholesalers or direct purchasers but do not capture any discounts. As

described in the data sources section, net prices reflect the mean revenue accrued by manufacturers for each product after all concessions. Thus, estimates of net prices and discounts capture all manufacturer concessions and not solely rebates from manufacturers to payers. We expressed price outcomes as the annual cost of treatment for patients with MS. We used the FDA-approved recommended dosing to calculate the number of units needed for an annual course of treatment with each self-administered DMT for a standard MS patient. For each product and quarter, we calculated list and net estimates of the annual cost of treatment by multiplying the number of units needed for an annual course of treatment by, respectively, the list and net price per unit in that quarter. Estimates of the annual cost of treatment were expressed in nominal dollars.

In estimating Medicare Part D savings associated with the entry of generic competition, we calculated two intermediate outcomes: net price to payers other than Medicaid, as an approximation to net price to Medicare Part D; and number of years of treatment provided by Medicare Part D, as a measure of drug utilization within the program. First, we calculated net prices to payers other than Medicaid for each included DMT and quarter by applying estimates of discounts in payers other than Medicaid to list prices. We employed this approximation because we were unable to ascertain specific net prices for Medicare Part D. This methodology had been previously employed in the literature.⁶¹ Then, for each included agent and quarter, we multiplied the price of the drug by the number of person-years of that drug received by enrollees in Medicare Part D plans (nationally) between April 2015 and December 2018. This yielded an estimate of total spending incurred by Medicare. We calculated person-years by dividing the total number of days of supply of each product (indexed by p) and quarter (indexed by q), obtained from the 5% random sample of Medicare Part D drug event files, by 365 days in a year.

Given that we only had access to a 5% data sample, we inflated by 20 the number of years of treatment provided to represent national totals in Medicare Part D.

$$Years\ of\ treatment_{p,q} = \frac{20 \cdot \sum Days\ of\ supply_{p,q}}{365}$$

To estimate aggregate savings to Medicare attributable to generic entry, we applied estimates of net prices with and without generic entry (described in section 3.5) to this estimate of person-years of treatment, which we hold fixed across scenarios.

3.5 Analyses

In descriptive analyses, for each product and year, we first calculated list price, net price, and discounts for Medicaid and payers other than Medicaid as the mean across four quarters. For each product, we further calculated absolute and relative changes in list and net prices, and the percentage of list price increases offset by manufacturer discounts.

In addition to describing trends in list prices, net prices, and discounts of branded self-administered DMTs for MS, we sought to formally test whether the introduction of generic competition was associated with a change in the price trajectories of incumbent branded self-administered DMTs for MS. For these analyses, we excluded peginterferon beta-1a—approved in August 2014—to have at least one full year of follow-up before the first generic glatiramer’s approval in April 2015. We divided the study into 3 periods and constructed interrupted time series analyses with linear regression models. We constructed a regression model for all included branded self-administered DMTs. Additionally, we also run a series of regressions, one for each agent. Models regressed annual cost of treatment against a continuous variable for time (quarter),

2 indicator variables for the periods after first and second generic entry, and the second-order interactions between them.

$$\text{Annual Cost of Treatment} = \beta_0 + \beta_1 \cdot q + \beta_2 \cdot P2 + \beta_3 \cdot P2 \cdot q + \beta_4 \cdot P3 + \beta_5 \cdot P3 \cdot q + \varepsilon$$

In these interrupted time series analyses models, *annual cost of treatment* reflects the cost of treating a patient with a branded self-administered DMT for MS for a year, expressed in nominal dollars. q is a continuous variable for time expressed in quarters. Period 2 denotes the time after the entry of the first generic glatiramer (Q2 2015 through Q3 2017) when there was only one generic competitor in the market, Period 3 denotes the time after the second wave of generic glatiramers (Q4 2017 through the end of the study period in Q3 2019) when there were up to 4 generic competitors in the market. β_3 and β_5 are the coefficients of interest. β_3 represents the difference in slopes of price trajectories after the entry of the first generic glatiramer, relative to that of the prior time period (β_1). β_5 reflects the difference in slopes of price trajectories after the second wave of generic glatiramer entries, relative to that of prior time periods ($\beta_1 + \beta_3$).

Furthermore, we aimed to provide an estimate of Medicare Part D savings associated with the entry of generic competition into the market of branded self-administered DMTs for MS. We replicated interrupted time series analyses using as the outcome variable estimates of net prices to payers other than Medicaid. For each DMT with a statistically significant change in trajectories of net price to payers other than Medicaid following generic entry, we calculated quarterly Medicare Part D net spending that would have been expected with and without generic competition. We did so by multiplying, for each product and quarter, the number of years of treatment provided by Medicare Part D by the modeled net annual cost of treatment, with and without generic competition, from interrupted time series analyses of net prices in in payers other than Medicaid.

$$Spending_{p,q} = Years\ of\ treatment_{p,q} \cdot \widehat{Net\ Annual\ Cost\ of\ Treatment}_{p,q}$$

Finally, we estimated Medicare Part D savings associated with the introduction of generic competition between April 2015 and December 2018, overall and for each agent, as the difference between the expected net spending without generic entry and the expected net spending with generic entry.

$$Savings_p = \sum_q Spending\ without\ generic\ entry_{p,q} - \sum_q Spending\ with\ generic\ entry_{p,q}$$

$$Total\ Savings = \sum_p Savings_p$$

This study was approved as exempt by the University of Pittsburgh institutional review board because of the use of deidentified data. We conducted all analyses using statistical software SAS version 9.4 (SAS Institute, Cary, NC).

3.6 Sensitivity Analysis

We performed a sensitivity analysis to test the robustness of our findings to the inclusion of pricing data in the year of approval of the branded DMTs that were approved throughout our study period (fingolimod, teriflunomide, dimethyl fumarate, and peginterferon beta-1a).

4.0 RESULTS

4.1 Changes in List Prices, Net Prices, and Discounts

From 2010 to 2019, list prices of self-administered DMTs for MS increased sharply from a mean (SD) annual cost of treatment of \$35,332 (\$2,032) to \$93,534 (\$6,293), at a mean annual rate of 10% (**Table 2**). Manufacturer discounts varied widely across products within the self-administered DMT category, offsetting 40% of the increases in list prices. Nevertheless, net prices of self-administered DMTs for MS still increased from a mean (SD) annual cost of treatment of \$29,303 (\$2,032) in 2010 to \$68,177 (\$6,293) in 2019, at a mean annual rate of 9%.

For interferon beta-1b, list price increased by 184% between 2010 and 2019, from an annual cost of treatment of \$34,892 to \$98,962 (**Figure 1**), at a mean annual rate of 12%. Discounts offset 55% of list price increases, leading to a 111% increase in the annual net price of treatment, from \$26,106 in 2010 to \$55,054 in 2019. The mean annual growth of net prices was 10%. Across the study period, mean discounts for interferon beta-1b increased from 68% to 97% for Medicaid and from 22.7% to 37% for payers other than Medicaid.

For interferon beta-1a IM, list price increased by 162% between 2010 and 2019, from an annual cost of treatment of \$34,939 to \$91,516, at a mean annual rate of 12%. Discounts offset 5% of list price increases, leading to a 231% increase in the annual net price of treatment, from \$23,234 in 2010 to \$76,915 in 2019. The mean annual growth of net prices was 16%. Across the study period, mean discounts for interferon beta-1a IM increased from 71% to 78% for Medicaid and decreased from 32% to 3% for payers other than Medicaid.

Table 2. Changes in Annual Costs of Treatment and Percentage of List Price Increases Offset by Discounts

| | Interferon beta-1b (Betaseron) | Interferon beta-1a IM (Avonex) | Glatiramer (Copaxone) | Interferon beta-1a SC (Rebif) | Fingolimod (Gilenya) | Teriflunomide (Aubagio) | Dimethyl fumarate (Tecfidera) | Peginterferon beta-1a (Plegridy) |
|---|--------------------------------------|--------------------------------------|--------------------------|-------------------------------------|-------------------------|----------------------------|-------------------------------------|--|
| List Price | | | | | | | | |
| Initial Annual Cost of Treatment, \$ (Year) | 34,892 (2010) | 34,939 (2010) | 38,167 (2010) | 33,331 (2010) | 48,811 (2011) | 48,603 (2013) | 60,610 (2014) | 68,600 (2015) |
| Annual Cost of Treatment in 2019, \$ | 98,962 | 91,516 | 81,427 | 99,429 | 99,669 | 88,783 | 94,988 | 93,498 |
| Relative Change, % | 183.6 | 161.9 | 113.3 | 198.3 | 104.2 | 82.7 | 56.7 | 36.3 |
| Mean Annual Change, % | 12.3 | 11.5 | 9.0 | 13.0 | 9.4 | 10.8 | 9.4 | 8.1 |
| Net Price | | | | | | | | |
| Initial Annual Cost of Treatment, \$ (Year) | 26,106 (2010) | 23,234 (2010) | 35,303 (2010) | 32,568 (2010) | 29,813 (2011) | 43,981 (2013) | 58,057 (2014) | 62,391 (2015) |
| Annual Cost of Treatment in 2019, \$ | 55,054 | 76,915 | 32,582 | 70,596 | 77,539 | 82,015 | 75,689 | 75,030 |
| Relative Change, % | 110.9 | 231.0 | -7.7 | 116.8 | 160.1 | 86.5 | 30.4 | 20.3 |
| Mean Annual Change, % | 9.7 | 15.6 | 0.9 | 9.4 | 13.7 | 11.3 | 5.5 | 5.1 |
| % of List Price Increase Offset by Discounts | 54.8 | 5.1 | 106.3 | 42.5 | 6.2 | 5.3 | 48.7 | 49.2 |

Abbreviations: IM, intramuscular; SC, subcutaneous.

We defined annual cost of treatment based on US Food and Drug Administration dosing recommendations as the average price of treating a patient with multiple sclerosis for a year. List prices are expressed as wholesale acquisition costs, which reflect manufacturers' prices to wholesalers or direct purchasers but do not capture any discounts. Net prices capture all manufacturer concessions including rebates, copay cards, 340B discounts, prompt pay discounts, returns provisions, and any other concessions accounted for in the reporting of net sales. All price estimates are expressed in nominal dollars.

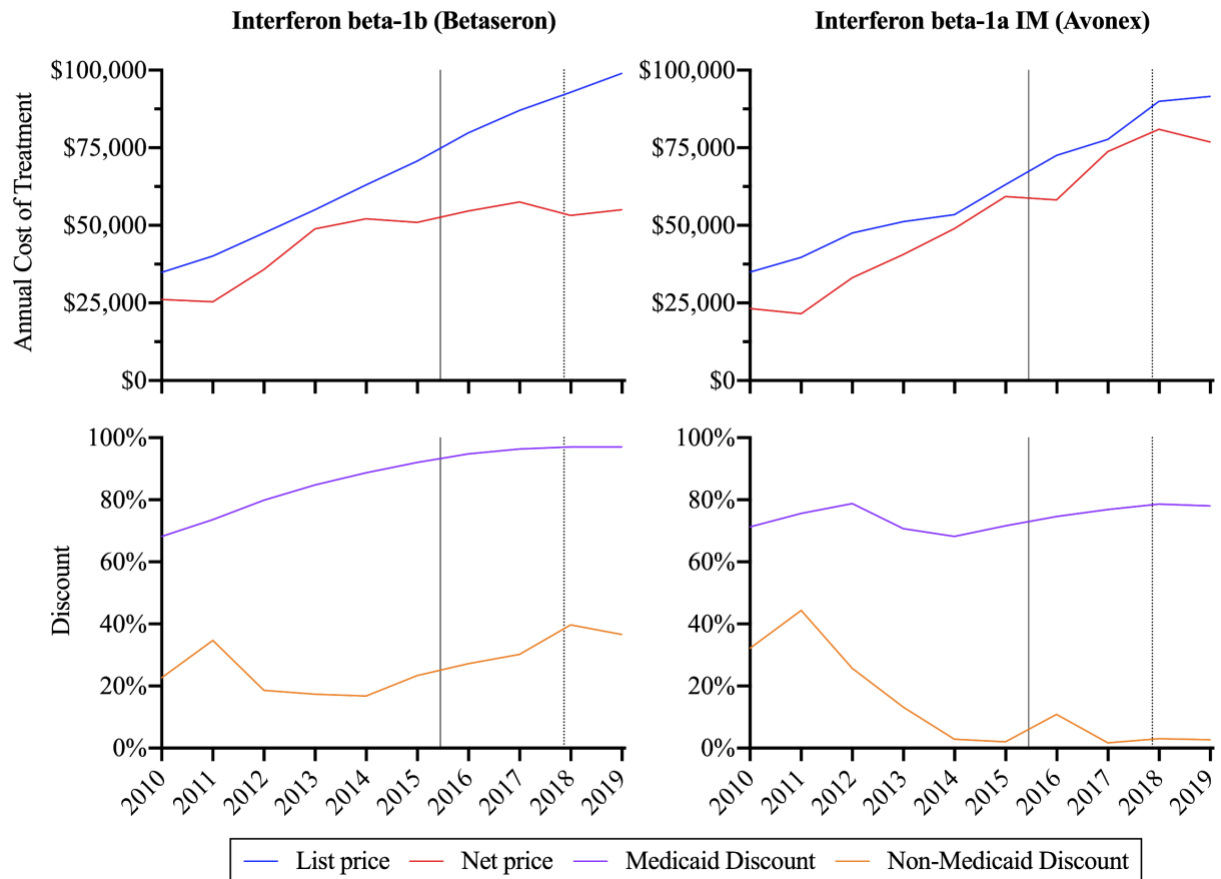


Figure 1. Trends in Prices and Discounts of Interferon Beta-1b and Interferon Beta-1a IM, 2010-2019

Abbreviations: IM, intramuscular.

Upper panels show 2010-2019 trends in list and net prices. Lower panels show average discounts in Medicaid and in payers other than Medicaid in 2010-2019. Perpendicular lines represent each of the two waves of generic glatiramer entry in Q2 2015 (solid line) and in Q4 2017 (dotted line).

For branded glatiramer, list price increased by 114% between 2010 and 2019, from an annual cost of treatment of \$38,167 to \$81,427 (**Figure 2**), at a mean annual rate of 9%. However, discounts offset more than the totality (106%) of list price increases, meaning that net prices actually decreased by 8%, from \$35,303 in 2010 to \$32,582 in 2019. Across the study period, mean discounts for brand glatiramer decreased from 49% to 43% for Medicaid and increased from 23% to 37% for payers other than Medicaid. The reduction of Medicaid discounts for brand glatiramer is likely an artifact of both the introduction of a new 40mg-formulation in January 2014 and the inability to capture the best price provision in Medicaid discounts estimations.

For interferon beta-1a SC, list price increased by 198% between 2010 and 2019, from an annual cost of treatment of \$33,331 to \$99,429, at a mean annual rate of 13%. Discounts offset 43% of list price increases, leading to a 117% increase in the annual net price of treatment, from \$32,568 in 2010 to \$70,596 in 2019. The mean annual growth of net prices was 9%. Across the study period, mean discounts for interferon beta-1a SC increased from 69% to 83% for Medicaid and from 1% to 26% for payers other than Medicaid.

For fingolimod, list price increased by 104% between 2011 and 2019, from an annual cost of treatment of \$48,811 to \$99,669 (**Figure 3**), at a mean annual rate of 9%. Discounts offset 6% of list price increases, leading to a 160% increase in the annual net price of treatment, from \$29,813 in 2011 to \$77,539 in 2019. The mean annual growth of net prices was of 14%. Across the study period, mean discounts for fingolimod increased from 23% to 65% for Medicaid and decreased from 38% to 19% for payers other than Medicaid.

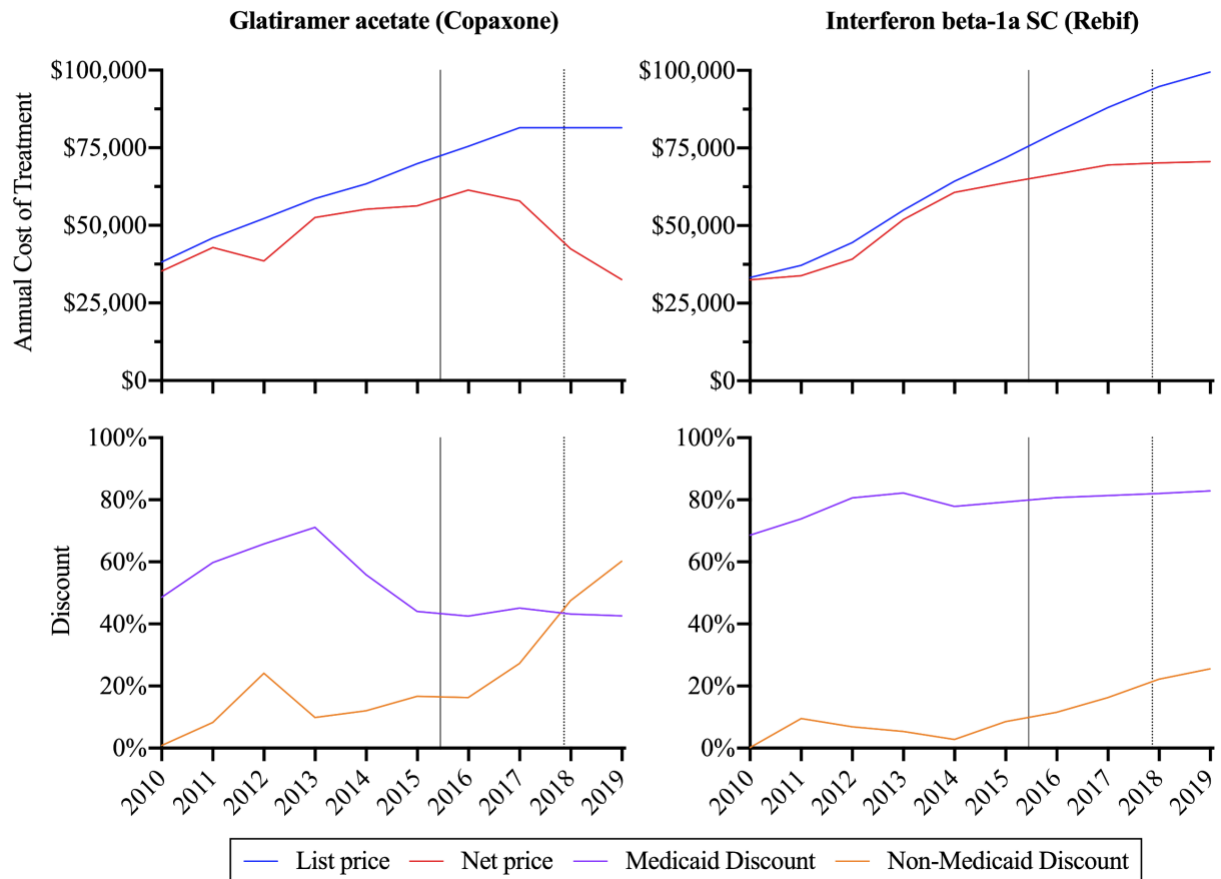


Figure 2. Trends in Prices and Discounts of Glatiramer and Interferon Beta-1a SC, 2010-2019

Abbreviations: SC, subcutaneous.

Upper panels show 2010-2019 trends in list and net prices. Lower panels show average discounts in Medicaid and in payers other than Medicaid in 2010-2019. Perpendicular lines represent each of the two waves of generic glatiramer entry in Q2 2015 (solid line) and in Q4 2017 (dotted line).

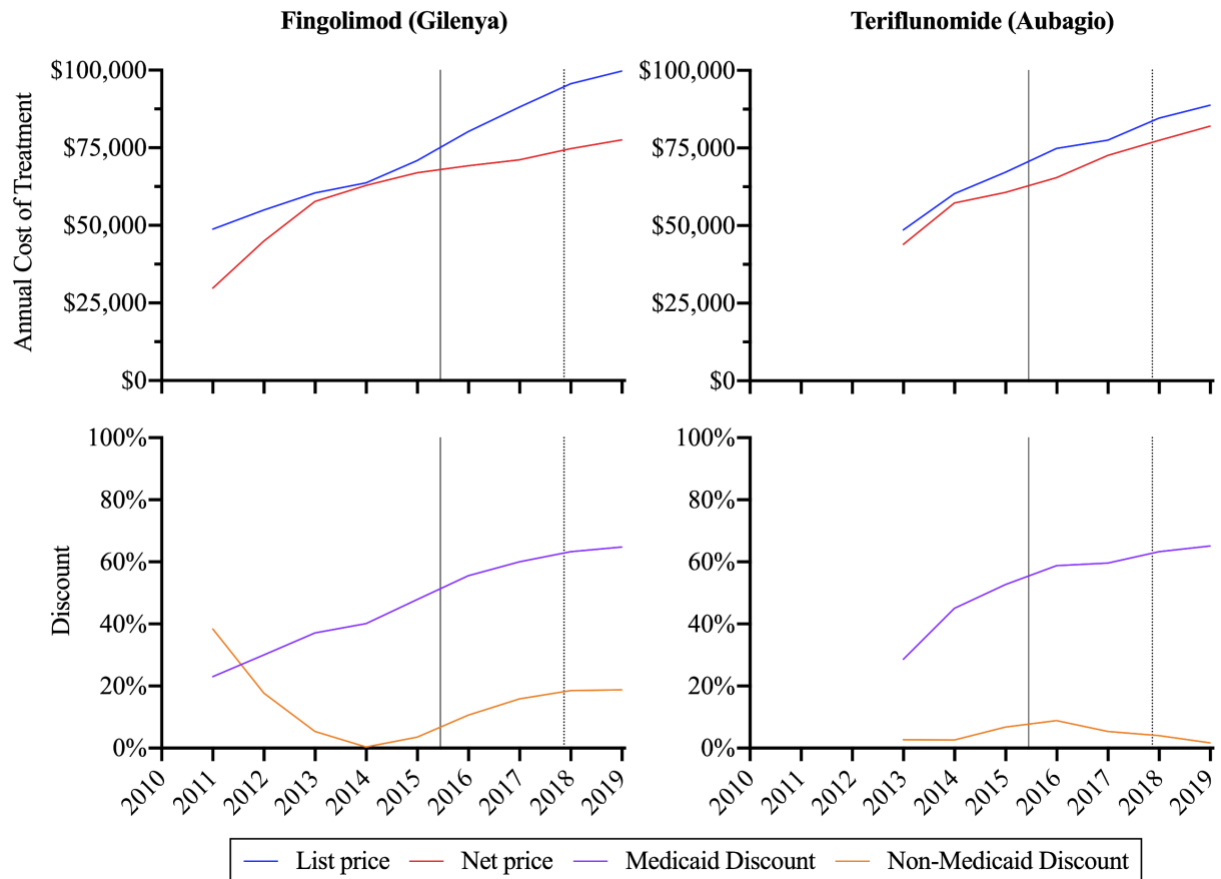


Figure 3. Trends in Prices and Discounts of Fingolimod and Teriflunomide, 2010-2019

Upper panels show 2010-2019 trends in list and net prices. Lower panels show average discounts in Medicaid and in payers other than Medicaid in 2010-2019. Perpendicular lines represent each of the two waves of generic glatiramer entry in Q2 2015 (solid line) and in Q4 2017 (dotted line).

For teriflunomide, list price increased by 83% between 2013 and 2019, from an annual cost of treatment of \$ 48,603 to \$88,783, at a mean annual rate of 11%. Discounts offset 5% of list price increases, leading to an 87% increase in the annual net price of treatment, from \$43,981 in 2013 to \$82,015 in 2019. The mean annual growth of net prices was 11%. Across the study period, mean discounts for teriflunomide increased from 29% to 65% for Medicaid and decreased from 3% to 2% for payers other than Medicaid.

For dimethyl fumarate, list price increased by 57% between 2014 and 2019, from an annual cost of treatment of \$60,610 to \$94,988 (**Figure 4**), at a mean annual rate of 9%. Discounts offset 49% of list price increases, leading to a 30% increase in the annual net price of treatment, from \$58,057 in 2014 to \$75,689 in 2019. The mean annual growth of net prices was 6%. Across the study period, mean discounts for dimethyl fumarate increased from 30% to 58% for Medicaid and from 4% to 17% for payers other than Medicaid.

For peginterferon beta-1a, list price increased by 36% between 2015 and 2019, from an annual cost of treatment of \$68,600 to \$93,498, at a mean annual rate of 8%. Discounts offset 49% of list price increases, leading to a 20% increase in the annual net price of treatment, from \$62,391 in 2010 to \$75,030 in 2019. The mean annual growth of net prices was 5%. Across the study period, mean discounts for peginterferon beta-1a increased from 62% to 77% for Medicaid and from 5% to 14% for payers other than Medicaid.

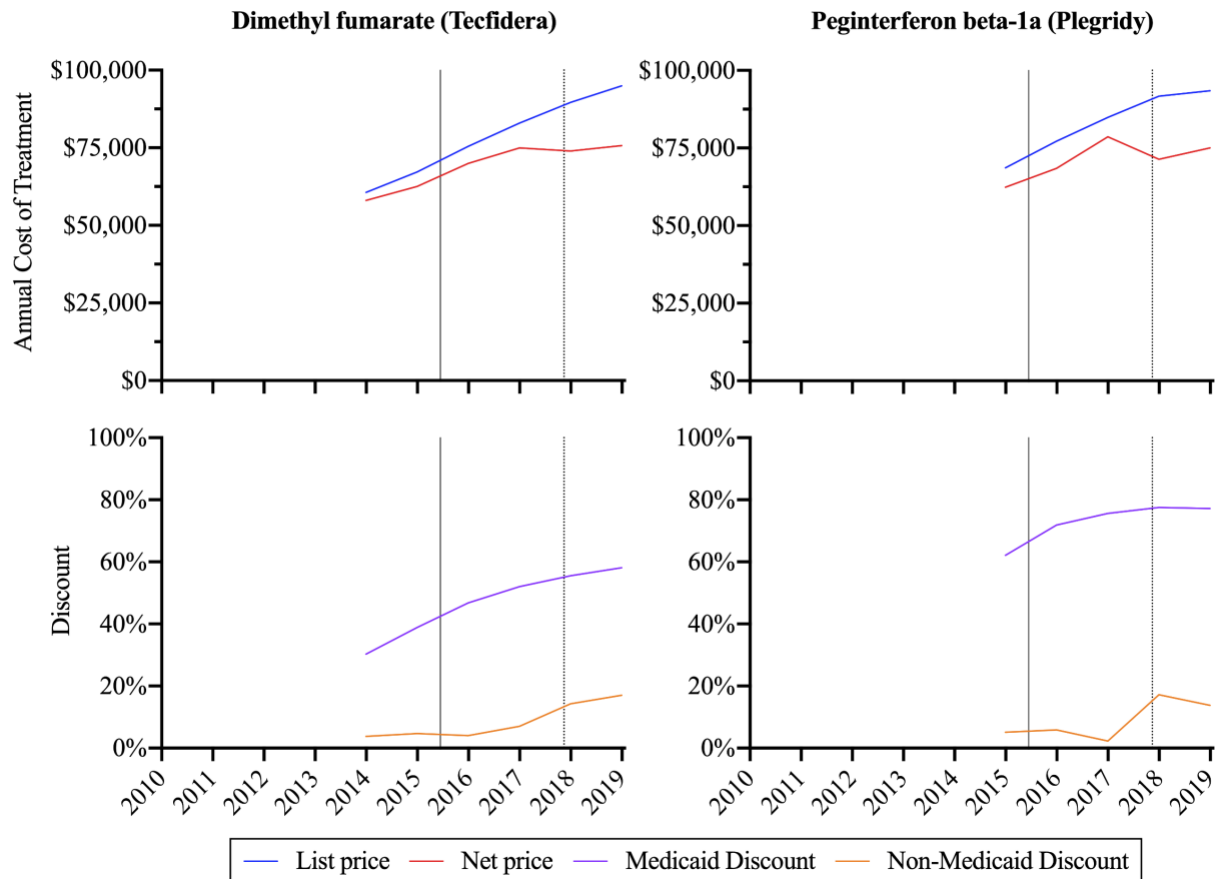


Figure 4. Trends in Prices and Discounts of Tecfidera and Peginterferon Beta-1a, 2010-2019

Upper panels show 2010-2019 trends in list and net prices. Lower panels show average discounts in Medicaid and in payers other than Medicaid in 2010-2019. Perpendicular lines represent each of the two waves of generic glatiramer entry in Q2 2015 (solid line) and in Q4 2017 (dotted line).

4.2 Impact of Generic Competition on Prices of Incumbent Brand Therapies

Results from interrupted time series analyses are shown in **Table 3**. Both list and net prices of all self-administered DMTs increased at a significant rate before the entry of generic competition, except for net prices of dimethyl fumarate. Overall, list prices of self-administered DMTs increased by \$1,929 ($p<0.001$) each quarter over the baseline period, while net prices increased by \$1,559 ($p<0.001$).

4.2.1 Changes after First Generic Entry (Q2 2015)

4.2.1.1 List Prices

Following the entry of the first generic glatiramer, we observed quarterly list price growth rates significantly larger than the observed in the baseline period, of \$282 for interferon beta-1b ($p=0.031$), \$935 for interferon beta-1a IM ($p=0.032$), \$920 for fingolimod ($p<0.001$), and \$985 for dimethyl fumarate ($p<0.001$). In other words, we observed a faster quarterly growth of list prices for these agents over the second period relative to the baseline period. Only list prices of teriflunomide increased at a significantly slower rate each quarter (-\$1,515; $p<0.001$), relative to baseline trends, after the introduction of the first generic.

4.2.1.2 Net Prices

Following the entry of the first generic glatiramer, net prices of original glatiramer (-\$1,190; $p=0.021$), interferon beta-1a SC (-\$1,523; $p<0.001$) and fingolimod (-\$1,944; $p<0.001$) increased at significantly slower rates each quarter relative to baseline trends.

4.2.2 Changes after Second Wave of Generic Entry (Q3 2017)

4.2.2.1 List Prices

Following the second wave of generic glatiramers entry, list prices of interferon beta-1b (-\$514; $p=0.016$), interferon beta-1a IM 1b (-\$1,403; $p=0.049$), original glatiramer (-\$1,463; $p<0.001$), interferon beta-1a SC (-\$721; $p<0.001$) and fingolimod (-\$942; $p<0.001$) increased at significantly slower rates each quarter relative to trends in the prior two periods.

4.2.2.2 Net Prices

Following the second wave of generic glatiramers entry, we only observed significantly different quarterly net price growth rates, relative prior periods, for original glatiramer (-\$2,597; $p<0.001$). This reversed the positive trend from prior periods, leading to an overall decrease in the net price of original glatiramer across the study period. The large magnitude of original glatiramer's net price decrease impacted the overall net price trajectory of the branded self-administered DMT category. Overall, net prices of branded self-administered DMTs increased at a significantly slower rate each quarter (-\$842; $p=0.004$), relative to prior trends, after the second wave of generic glatiramers entry.

Table 3. Interrupted Time Series Regression Coefficients of the Impact of Generic Entry on Prices of Branded Self-administered Disease Modifying Therapies for Multiple Sclerosis

| | Overall | Interferon beta-1b (Betaseron) | Interferon beta-1a IM (Avonex) | Glatiramer (Copaxone) | Interferon beta-1a SC (Rebif) | Fingolimod (Gilenya) | Teriflunomide (Aubagio) | Dimethyl fumarate (Tecfidera) |
|--------------------------|-------------------------------|-----------------------------------|-----------------------------------|-------------------------------|----------------------------------|----------------------------------|-------------------------------|-------------------------------------|
| List Price | | | | | | | | |
| Intercept (β_0) | 19,463*** (15,202, 23,724) | 29,492*** (28,490, 30,495) | 32,137*** (28,803, 35,471) | 35,282*** (34,068, 36,495) | 26,087*** (24,645, 27,528) | 41,727*** (40,093, 43,360) | 8,731** (3,309, 14,153) | 42,202*** (27,067, 57,337) |
| Quarter (β_1) | 1,929*** (1,619, 2,239) | 1,779*** (1,699, 1,859) | 1,282*** (1,017, 1,548) | 1,568*** (1,471, 1,665) | 1,985*** (1,870, 2,100) | 1,217*** (1,100, 1,335) | 2,767*** (2,452, 3,082) | 1,001* (206, 1,795) |
| Period 2 (β_2) | 15,512 (-3962, 34,987) | -4,621 (-11,201, 1,959) | -20,261 (-42,141, 1,619) | 1,535 (-6,427, 9,498) | -118 (-9,577, 9,341) | -18,362*** (-25,519, -11,206) | 31,277*** (22,289, 40,265) | -19,246* (-36,080, -2,411) |
| Quarter*P2 (β_3) | -803 (-1,580, 25) | 282* (25, 539) | 935* (81, 1,788) | -105 (-415, 206) | 59 (-310, 428) | 920*** (633, 1,206) | -1,515*** (-1,929, -1,100) | 985* (144, 1,827) |
| Period 3 (β_4) | 7,655 (-33,638, 48,948) | 14,722* (929, 28,515) | 48,951* (3,086, 94,817) | 44,610*** (27,919, 61,301) | 22,998* (3,169, 42,827) | 30,664*** (15,885, 45,444) | 4,084 (-11,119, 19,288) | 14,121 (-1,515, 29,757) |
| Quarter*P3 (β_5) | -387 (-1,645, 871) | -514* (-934, -94) | -1,403* (-2,800, -6) | -1,463*** (-1,972, -955) | -721* (-1,325, -117) | -942*** (-1,392, -492) | -82 (-545, 381) | -473 (-949, 4) |
| Net Price | | | | | | | | |
| Intercept (β_0) | 32,498*** (30,768, 34,228) | 19,010*** (14,180, 23,840) | 19,010*** (10,433, 20,648) | 29,868*** (24,041, 35,695) | 23,764*** (19,828, 27,701) | 16,368*** (9,742, 22,994) | 13,900* (1,600, 26,201) | 52,711** (15,569, 89,853) |
| Quarter (β_1) | 1,559*** (1,431, 1,686) | 1,732*** (1,337, 2,127) | 1,732*** (1,284, 2,137) | 1,323*** (913, 1,734) | 1,845*** (1,546, 2,145) | 2,505*** (2,027, 2,983) | 2,310*** (1,625, 2,995) | 275 (-1,639, 2,189) |
| Period 2 (β_2) | -6,340 (-15,318, 2,638) | 22,222 (-9,339, 53,784) | 22,222 (-40,829, 24,508) | 26,459* (1,236, 51,682) | 34,367** (11,877, 56,856) | 38,015** (12,690, 63,340) | 4,633 (-11,482, 20,748) | -26,657 (-67,313, 13,999) |
| Quarter*P2 (β_3) | 341 (-14, 695) | -1,214 (-2,449, 21) | -1,214 (-905, 1,662) | -1,190* (-2,198, -182) | -1,523*** (-2,406, -640) | -1,944*** (-2,978, -910) | -506 (-1,295, 282) | 1,371 (-641, 3,383) |
| Period 3 (β_4) | 27,067** (8,382, 45,752) | -41,455 (-160,001, 77,091) | -41,455 (-7,175, 129,701) | 71,063** (19,012, 123,115) | 8,703 (-38,261, 55,667) | -20,509 (-72,352, 31,335) | -391 (-26,097, 25,315) | 15,198 (-19,870, 50,265) |
| Quarter*P3 (β_5) | -842** (-1,411, -273) | 1,061 (-2,498, 4,620) | 1,061 (-3,877, 291) | -2,597** (-4,182, -1,012) | -206 (-1,636, 1,224) | 613 (-965, 2,192) | -91 (-867, 685) | -703 (-1,771, 365) |

Abbreviations: P2, Period 2; P3, Period 3; IM, intramuscular; SC, subcutaneous.

The table shows interrupted time series regression coefficients and 95% CI (in brackets) of the impact of generic entry on prices of branded self-administered disease modifying therapies for multiple sclerosis.

* <0.05; ** <0.01; *** <0.001

4.3 Estimates of Medicare Part D Savings Associated with the Introduction of Generic Competition

Estimates of interrupted time series regression coefficients and 95% CI for the impact of generic entry on net prices of self-administered DMTs in payers other than Medicaid are shown on **Table 4**. Only original glatiramer, interferon beta-1a SC, and fingolimod experienced a significant change in net price trajectories following the entry of generic competition. Specifically, net prices in payers other than Medicaid of original glatiramer (-\$1,165; $p=0.016$), interferon beta-1a SC (-\$1,793; $p=0.006$) and fingolimod (-\$1,730; $p<0.001$) increased at significantly slower rates each quarter relative to baseline trends following the entry of the first generic glatiramer. Additionally, following the second wave of generic glatiramers entry, we only observed significantly different quarterly growth rates of net prices in payers other than Medicaid, relative prior periods, for original glatiramer (-\$2,642; $p<0.001$). For these agents, we show expected trends in net annual cost of treatment with and without the entry of generic competition for payers other than Medicaid in **Figure 5**.

Table 4. Interrupted Time Series Regression Coefficients of the Impact of Generic Entry on Net Prices of Brand Self-administered Disease Modifying Therapies for Multiple Sclerosis in Payers other than Medicaid

| | Interferon beta-1b (Betaseron) | Interferon beta-1a IM (Avonex) | Glatiramer (Copaxone) | Interferon beta-1a SC (Rebif) | Fingolimod (Gilenya) | Teriflunomide (Aubagio) | Dimethyl fumarate (Tecfidera) |
|--------------------------|-----------------------------------|-----------------------------------|-------------------------------|----------------------------------|------------------------------|-----------------------------|----------------------------------|
| Net Price | | | | | | | |
| Intercept (β_0) | 20,234*** (15,691, 24,777) | 20,234*** (10,334, 19,338) | 32,068*** (27,613, 36,524) | 17,654*** (11,254, 24,053) | 16,219*** (9,694, 22,743) | 12,417** (4,857, 19,977) | 49,734** (16,552, 82,916) |
| Quarter (β_1) | 1,654*** (1,270, 2,037) | 1,654*** (1,634, 2,351) | 1,218*** (888, 1,547) | 2,342*** (1,895, 2,790) | 2,579*** (2,058, 3,101) | 2,435*** (1,989, 2,881) | 459 (-1,282, 2,201) |
| Period 2 (β_2) | 24,339 (-5,096, 53,774) | 24,339 (-30,404, 33,182) | 28,142* (4,036, 52,248) | 38,046** (13,972, 62,119) | 32,831** (1,530, 64,131) | 8,549 (-6,595, 23,693) | -23,382 (-60,291, 13,527) |
| Quarter*P2 (β_3) | -1,137 (-2,294, 19) | -1,137 (-1,376, 1,127) | -1,165* (-2,113, -218) | -1,793*** (-2,761, -825) | -1,730* (-2,973, -487) | -636 (-1,316, 43) | 1,256 (-588, 3,100) |
| Period 3 (β_4) | -45,664 (-15,6201, 64,872) | -45,664 (-20,336, 105,883) | 71,806** (21,558, 122,054) | 16,392 (-29,090, 61,873) | -14,979 (-71,902, 41,943) | 782 (-21,766, 23,331) | 14,238 (-20,042, 48,519) |
| Quarter*P3 (β_5) | 1,173 (-2,145, 4,492) | 1,173 (-3,021, 883) | -2,642*** (-4,172, -1,112) | -478 (-1,873, 917) | 413 (-1,346, 2,172) | -74 (-800, 652) | -669 (-1,713, 375) |

Abbreviations: P2, Period 2; P3, Period 3; IM, intramuscular; SC, subcutaneous.

The table shows interrupted time series regression coefficients and 95% CI (in brackets) of the impact of generic entry on net prices of brand self-administered disease modifying therapies for multiple sclerosis in payers other than Medicaid.

* <0.05; ** <0.01; *** <0.001

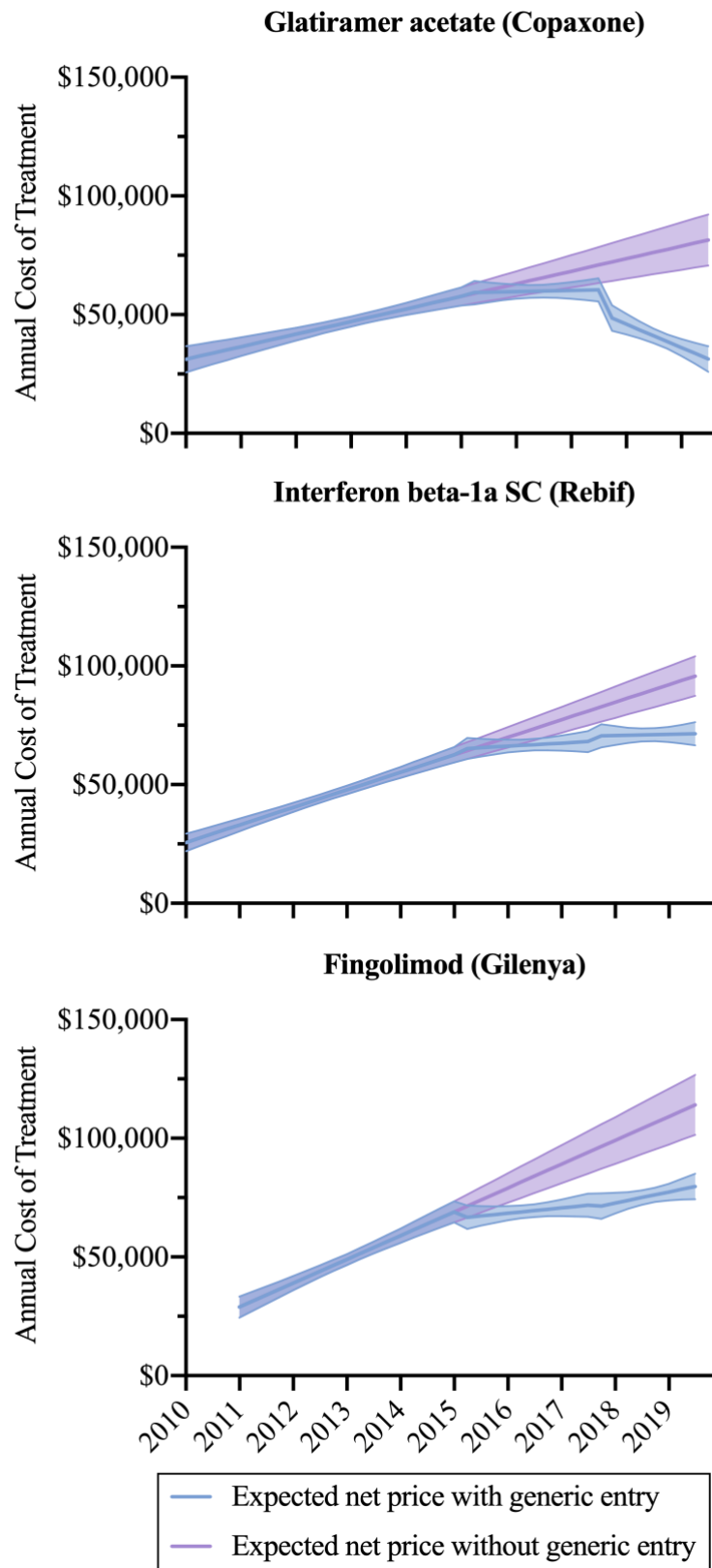


Figure 5. Expected Trends in Net Annual Cost of Treatment and 95% CI with and without Generic Entry for Payers other than Medicaid, 2010-2019

We estimate that 2015-2018 Medicare Part D net spending in the absence of generic competition would have been of \$4.69 billion for original glatiramer, \$1.58 billion for interferon beta-1a SC, and \$1.63 billion for fingolimod (**Figure 6**); while 2015-2018 Medicare Part D net spending with generic entry was estimated at \$3.96 billion, \$1.33 billion and \$1.32 billion, respectively. Thus, the expected savings accrued by Medicare Part D over this 3-year period following the introduction of generic competition were estimated at \$733 million for original glatiramer, \$253 million for interferon beta-1a SC and \$313 million for fingolimod, adding up to overall savings for the Part D program of \$1.30 billion.

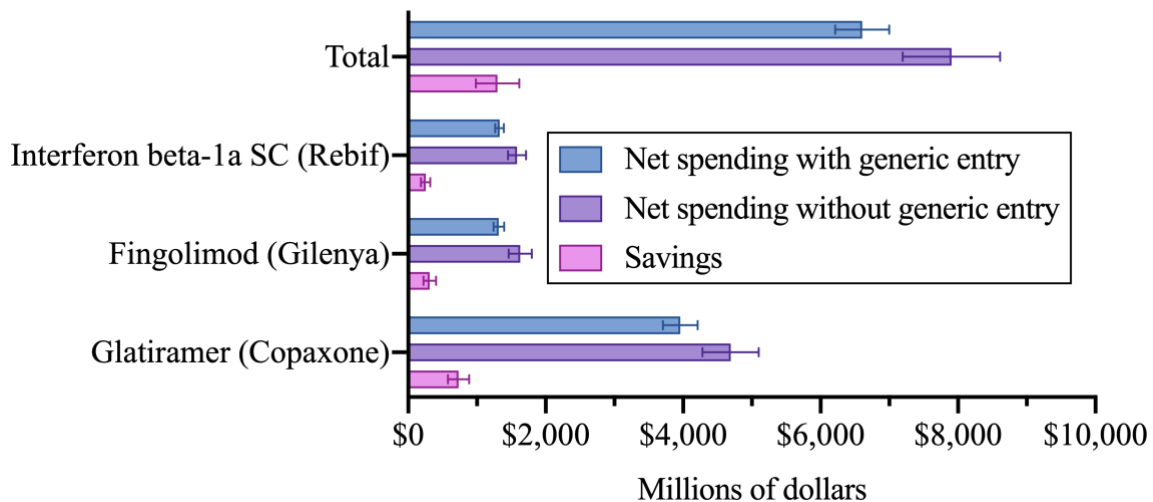


Figure 6. Estimated 2015-2018 Medicare Part D Savings Associated with the Entry of Generic Competition

4.4 Results of Sensitivity Analysis

In our base-case analysis, we exclude all pricing and discount data in the year of approval of brand DMTs approved throughout our study period (fingolimod, teriflunomide, dimethyl fumarate) in order to avoid data variability introduced by inventory fluctuation. In sensitivity analyses, we repeated interrupted time series analyses including these data, obtaining similar findings. Estimates of regression coefficients for the sensitivity analysis are shown in **Table 5**.

Table 5. Sensitivity Analyses without Excluding Pricing Data in the Approval Year

| | Overall | Interferon beta-1b (Betaseron) | Interferon beta-1a IM (Avonex) | Glatiramer (Copaxone) | Interferon beta-1a SC (Rebif) | Fingolimod (Gilenya) | Teriflunomide (Aubagio) | Dimethyl fumarate (Tecfidera) |
|--------------------------|-------------------------------|-----------------------------------|-----------------------------------|-------------------------------|----------------------------------|----------------------------------|-------------------------------|-------------------------------------|
| List Price | | | | | | | | |
| Intercept (β_0) | 19,463*** (15,202, 23,724) | 29,492*** (28,490, 30,495) | 32,137*** (28,803, 35,471) | 35,282*** (34,068, 36,495) | 26,087*** (24,645, 27,528) | 42,710*** (41,358, 44,061) | 11,923*** (7,161, 16,684) | 34,684*** (27,789, 41,579) |
| Quarter (β_1) | 1,929*** (1,619, 2,239) | 1,779*** (1,699, 1,859) | 1,282*** (1,017, 1,548) | 1,568*** (1,471, 1,665) | 1,985*** (1,870, 2,100) | 1,154*** (1,051, 1,256) | 2,593*** (2,308, 2,877) | 1,380*** (990, 1,771) |
| Period 2 (β_2) | 15,512 (-3962, 34,987) | -4,621 (-11,201, 1,959) | -20,261 (-42,141, 1,619) | 1,535 (-6,427, 9,498) | -118 (-9,577, 9,341) | -19,346*** (-26,652, -12,039) | 28,085*** (19,136, 37,035) | -11,728* (-21,865, -1,591) |
| Quarter*P2 (β_3) | -803 (-1,580, 25) | 282* (25, 539) | 935* (81, 1,788) | -105 (-415, 206) | 59 (-310, 428) | 983*** (695, 1,271) | -1,340*** (-1,743, -938) | 606* (126, 1,086) |
| Period 3 (β_4) | 7,655 (-33,638, 48,948) | 14,722* (929, 28,515) | 48,951* (3,086, 94,817) | 44,610*** (27,919, 61,301) | 22,998* (3,169, 42,827) | 30,664*** (15,435, 45,894) | 4,084 (-11,989, 20,157) | 14,121 (-1,639, 29,881) |
| Quarter*P3 (β_5) | -387 (-1,645, 871) | -514* (-934, -94) | -1,403* (-2,800, -6) | -1,463*** (-1,972, -955) | -721* (-1,325, -117) | -942*** (-1,406, -4,78) | -82 (-571, 408) | -473 (-952, 7) |
| Net Price | | | | | | | | |
| Intercept (β_0) | 32,498*** (30,768, 34,228) | 19,010*** (14,180, 23,840) | 19,010*** (10,433, 20,648) | 29,868*** (24,041, 35,695) | 23,764*** (19,828, 27,701) | 16,368*** (9,742, 22,994) | 13,900* (1,600, 26,201) | 52,711** (15,569, 89,853) |
| Quarter (β_1) | 1,559*** (1,431, 1,686) | 1,732*** (1,337, 2,127) | 1,732*** (1,284, 2,137) | 1,323*** (913, 1,734) | 1,845*** (1,546, 2,145) | 2,505*** (2027, 2,983) | 2,310*** (1,625, 2,995) | 275 (-1,639, 2,189) |
| Period 2 (β_2) | -6,340 (-15,318, 2,638) | 22,222 (-9,339, 53,784) | 22,222 (-40,829, 24,508) | 26,459* (1,236, 51,682) | 34,367** (11,877, 56,856) | 38,015** (12,690, 63,340) | 4,633 (-11,482, 20,748) | -26,657 (-67,313, 13,999) |
| Quarter*P2 (β_3) | 341 (-14, 695) | -1,214 (-2,449, 21) | -1,214 (-905, 1,662) | -1,190* (-2,198, -182) | -1,523*** (-2,406, -640) | -1,944*** (-2,978, -910) | -506 (-1,295, 282) | 1,371 (-641, 3,383) |
| Period 3 (β_4) | 27,067** (8,382, 45,752) | -41,455 (-160,001, 77,091) | -41,455 (-7,175, 129,701) | 71,063** (19,012, 123,115) | 8,703 (-38,261, 55,667) | -20,509 (-72,352, 31,335) | -391 (-26,097, 25,315) | 15,198 (-19,870, 50,265) |
| Quarter*P3 (β_5) | -842** (-1,411, -273) | 1,061 (-2,498, 4,620) | 1,061 (-3,877, 291) | -2,597** (-4,182, -1,012) | -206 (-1,636, 1,224) | 613 (-965, 2,192) | -91 (-867, 685) | -703 (-1,771, 365) |

Abbreviations: P2, Period 2; P3, Period 3; IM, intramuscular; SC, subcutaneous.

The table shows interrupted time series regression coefficients and 95% CI (in brackets) of the impact of generic entry on prices of brand self-administered disease modifying therapies for multiple sclerosis when pricing data from products' approval year were not excluded.

* <0.05; ** <0.01; *** <0.001

5.0 DISCUSSION

In this retrospective descriptive study, we described 2010-2019 trends in list prices, net prices, and discounts of brand self-administered DMTs for MS, and evaluated the impact of the introduction of generic competition on the price trajectories of incumbent agents. Our study yielded 5 main findings. First, we found that list prices of self-administered DMTs for MS grew drastically between 2010 and 2019, increasing in parallel at a mean annual rate of 10%. Second, manufacturer discounts varied widely across different self-administered DMTs. For original glatiramer, manufacturer discounts more than offset list price increases; however, the offsetting was only partial and at different levels for all other agents. Third, despite the discount growth experienced by some agents, net prices of self-administered DMTs for MS still increased substantially between 2010 and 2019 at a mean annual rate of 9%. Fourth, following the introduction of the first generic glatiramer in 2015, the net price growth of original glatiramer, interferon beta-1a SC and fingolimod slowed down significantly, but only original glatiramer experienced a significant decrease in net price after the second wave of generic competitors in 2017. Finally, we estimated that, between 2015 and 2018, the Medicare Part D program accrued \$1.3 billion in savings associated with the entry of competition from generic glatiramers.

To our knowledge, this is the first study to describe specific product-level trends in list prices, net prices, and manufacturer discounts for self-administered DMTs for MS. Multiple studies had evaluated trends in prices of DMTs for MS over the last 2 decades.²⁹⁻³⁶ Consistent with our results, these studies described a rapid price growth at similar rates across brand self-administered DMTs for MS. However, most of these studies employed measures of list prices,³⁰⁻³⁴ or tried to account for manufacturer discounts using aggregated rebates reported by major

public programs.^{35,36} Only a prior study by Hernandez et al. described aggregated changes between 2007 and 2018 in list prices, net prices, and discounts across branded DMTs available before 2007.²⁹ This study found a widening gap between list prices and net prices in the DMT category with more than 60% of the list price increases offset by manufacturers discounts. However, in aggregating pricing outcomes, the authors weighted by the number of units sold in the US to account for the relative utilization of each agent. This translated into aggregated results that track closely original glatiramer trends, given its position of market dominance in the DMT category. Our product-level analyses found a large gap between list and net prices for original glatiramer, interferon beta-1b and interferon beta-1a SC. However, for all other DMTs we found that the magnitude of this gap is much smaller or practically nonexistent, with net prices of products such as interferon beta-1a IM closely tracking list prices.

A prior study by Hartung et al. assessed the role of generic competition in the DMTs market.³⁶ Specifically, this study evaluated the impact of the introduction of the first generic glatiramer (Glatopa 20mg) in April 2015 on trajectories in Medicaid cost per claim of brand self-administered DMTs. The authors found that the market entry of the first generic competitor into the brand self-administered DMTs market had little effect on cost trajectories of incumbent agents, after accounting for aggregated Medicaid discounts. The study found that only original glatiramer 20 mg, interferon beta-1a SC and teriflunomide experienced a significant, yet mild, slowdown in their cost growth. Additionally, the authors reported a significant increase in the price growth of fingolimod following the introduction of the first generic glatiramer. These results by Hartung et al. are consistent with the majority of our results. We also found a slowdown in net price growth for original glatiramer 20 mg, interferon beta-1a SC, and teriflunomide; however, our results were not significant for teriflunomide. Besides, we found a

significant slowdown in the price growth of fingolimod, which contrasts with Hartung et al. findings. This difference is likely due to their use of gross costs adjusted by aggregated rebates as their outcome, which does not capture product-levels changes. In this case, fingolimod's list price growth significantly increased following the introduction of the first generic glatiramer; however, this list price growth was offset by increasing manufacturer discounts which led to the slowdown of net price growth. Additionally, our findings are in line with a recent study by Rome et al. which estimated quarterly US spending on all glatiramer products, both branded and generic. This study found that the delayed introduction of generic competition was associated with \$4.3 billion to \$6.5 billion in excess spending

Despite the evidence of increasing manufacturer discounts for some agents, overall net prices of brand self-administered DMTs still increased dramatically over the study period. Drug manufacturers often argue that high prices reflect the expense of research and development and that high prices constitute a key incentive for innovation. Yet, for some agents such as interferon beta-1b, interferon beta-1a IM, or interferon beta-1a SC—with an approximately two-decade presence in the market—net prices are still high, and for interferon beta-1a IM, even continue growing. Notwithstanding, these year-over-year increases in prices do not represent higher value on the current value-based pricing scheme.

High and rising net prices can be attributed to the absence of direct generic or biosimilar competition for most agents in the category. In fact, our findings revealed that the entry of generic competition into the DMTs market had a profound impact on net prices of original glatiramer, the only agent facing direct competition from generics. Although still high, the rapid net price reductions experienced by original glatiramer following the entry of direct generic competition evidence that generics constitute a fundamental check on rising drug prices in the

DMTs market. Our findings will inform policymakers in the development of policies aiming to spur competition in the specialty drug market. Particularly, those aiming to prevent manufacturer practices that delay or effectively block the introduction of generics and biosimilars, such as drug patent evergreening, and patent litigation or pay-for-delay agreements.

While our results show that manufacturer concessions play a fundamental role in offsetting list prices increases of branded DMTs, discounting practices can have unintended negative effects. Manufacturer discounts to payers are not generally passed on directly to patients, and uninsured patients or those with high deductible plans or in the deductible phase of their benefits coverage are exposed to list prices.²⁹ Thus, the widening gap between list and net prices can exacerbate disparities in medication access between insured and uninsured or underinsured patients. Additionally, the complexity that discounting practices bring to the pharmaceutical reimbursement system can create perverse incentives for utilization of drugs subject to large rebates, even when they may not bring any additional value.²⁹

Our study is subject to several limitations. First, our study sample is limited to branded self-administered DMTs for MS with US sales reported by publicly traded companies. Our sample did not include interferon beta-1b (Extavia) due to lack of data. Second, due to the method of estimating net prices, estimates of net price can be subject to variability. However, our findings were robust to the exclusion of pricing data in the approval year, when data variability tends to be greater. Besides, prior literature had employed and validated this methodology to address variability in net pricing data.²⁹ Third, because of the inability to estimate both supplemental Medicaid rebates negotiated by states or managed care organizations and rebates derived from the Medicaid best price provision, these concessions were captured by estimates of discounts in payers other than Medicaid rather than by estimates of Medicaid discounts. This can

lead to the underestimation Medicaid discounts and the overestimation of discounts for payers other than Medicaid. Fourth, in estimating Medicare Part D savings associated with the introduction of generic glatiramer we employed estimates of discounts to payers other than Medicaid, which includes Medicare Part D, but also other payers such as commercial insurance or the VA. However, estimates of net prices to payers other than Medicaid likely resemble more closely the actual net prices paid by Medicare Part D than the overall estimates of net prices across all payer types, which include the typically substantial Medicaid discounts. Finally, our analyses were unable to isolate the impact of generic competition on prices in the DMT for MS market from that of branded competition or other concomitant forces, such as the increased public awareness and scrutiny of rising prescription drug prices.

In conclusion, we found that after all manufacturer concessions, net prices of self-administered DMTs for MS still increased substantially between 2010 and 2019, at a mean annual rate of 9%. However, the market entry of generic glatiramers led to net price reductions for original glatiramer, the only agent facing direct competition from generic. Our findings are of great public health significance since they evidence that generics constitute a key check to the net price growth of DMTs. Our findings will inform policymakers in the development of policies aiming to facilitate the entry of generics and biosimilars into the specialty drug market, which will reduce access barriers for MS patients, improving adherence and clinical outcomes.

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