

Study on Prescription Preference of Neurologists
Concerning the Disease Modifying Therapies Used in
Treatment of Multiple Sclerosis in Pune

By

Jasmine Lamba

*Dissertation submitted for the partial fulfillment of the
MBA Pharmaceutical Management*

Academic year, 2017-2019



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TO WHOMSOEVER MAY CONCERN

This is to certify that **Jasmine**, student of MBA Pharmaceutical Management from The IIHMR University, Jaipur has undergone internship training at **Eisai India Limited** from **31st January 2019 to 1st May, 2019**.

The Candidate has successfully carried out the study designated to her during internship training and her approach to the study has been sincere, scientific and analytical.

The Internship is in fulfillment of the course requirements.

I wish her all success in all her future endeavors.



Dr. Sandeep Narula
Dean In-charge
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Dr. Abhishek Dadhich

Professor
IIHMR University, Jaipur

CERTIFICATE BY SCHOLAR

This is to certify that the dissertation titled **A study on prescription preferences of neurologists concerning the Disease Modifying Therapies used in treatment of Multiple Sclerosis in Pune** submitted by Jasmine Lamba, Enrollment No. 0101 under the supervision of **Dr. Abhishek Dadhich** for award of MBA in Pharmaceutical Management of the University carried out during the period from 31st January to 1st May, 2019 embodies my original work and has not formed the basis for the award of any degree, diploma associate ship, fellowship, titles in this or any other institute or other similar institution of higher learning.



Signature

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Signature

ABSTRACT

Title of Report: A study on perception preferences of neurologists concerning Disease Modifying Therapies used in treatment of Multiple Sclerosis in Pune

Mentor: Mr. M. Jaya Rao

Name of the Student: Jasmine Lamba

Background –

Multiple Sclerosis (MS) is a long term, inflammatory neurological disorder. The main features of MS are demyelination and neurodegeneration in the central nervous system. It is the most common cause of non-traumatic neurological disability in young adults, troubling at least 2.5 million people worldwide. Prevalence of MS is 7 to 10/100,000 and could be higher as MRI facility is not available for many. MS Prevalence in India is in the range of 0-35 /100,000. Mean age of onset is 27-34. Approximate time from initial contact with medical system to diagnosis is 11-20 weeks. Number people with MS in India is approximately 60000 to 90000. At present, there is no cure for MS, but the disease course can be altered by a range of disease-modifying therapies (DMTs). Such therapies have gone through some notable changes in recent years as research progresses, with most therapies only indicated for the treatment of RRMS. The MS therapeutics market has entered an exciting phase, with an upsurge of available treatment options.

Availability of cheaper bioequivalents has affected the multiple sclerosis market posing risk of brand erosion.

ACKNOWLEDGEMENT

I would first like to thank my mentor Mr. M. Jaya Rao, Zonal Manager, Eisai India Limited. The door to her office was always open whenever I ran into a trouble spot or had any question. She consistently allowed this project to be my own work but steered me in the right direction whenever she thought I needed it.

I would also like to acknowledge Dr. Abhishek Dadhich, my guide from IIHMR University, Jaipur. I am gratefully indebted to him for his very valuable comments on this project.

I would also like to express my profound gratitude to my parents for providing me with unfailing support and continuous encouragement. This accomplishment would not have been possible without them.

Jasmine Lamba

MBA-PM (2017-2019)

Roll No: 0101

LIST OF SYMBOLS AND ABBREVIATIONS:

MS: Multiple Sclerosis

DMTs: Disease modifying therapies

CIS: Clinically isolated syndrome

RRMS: Relapsing-remitting multiple sclerosis

Gd+: Gadolinium enhancing lesion

PML: Progressive multifocal Leukoencephalopathy

ARR: Annual relapse rate

INTRODUCTION:

Multiple Sclerosis (MS) is a progressive, autoimmune disorder which results in damage to the myelin sheath in the Central Nervous System (CNS). The disease is described originally by incidence of revocable neurologic deficits, followed by progressive neurological deterioration over time. Depending upon the site of demyelination, there may be deterioration in the cognitive or emotional functioning and/or accompanied by disability progression. Protection of functioning is the clinical goal of the treatment. MS attacks may lead to inflammation and injury to the myelin sheath causing blocked or slowed nerve signals which may lead to difficulty in vision, muscle coordination, strength, sensation and other bodily functions.

MS cannot be cured but treatments that can slow its progression are available and may help with functioning. Onset of MS remains unclear; however, it is recognized that MS can arise during childhood or adolescence. Approximately 2.5 million people worldwide are affected by MS with rates varying widely across races.

Diagnoses and treatments

MS presentation may vary from patient to patient. Some frequently recognized classic MS symptoms include:

- Sensory loss
- Spinal cord symptoms: weakness, spasticity and sensory symptoms
- Optic neuritis
- Pain and fatigue
- Subjective difficulties

There are four categories of clinical MS types:

1) Relapsing-remitting MS (RRMS): Typified by recurrent attacks in which neurologic deficits or shortages appear in different parts of the nervous system and resolve completely or almost

completely over a short period of time, leaving little residual deficit. This is the most common type of MS and 85% of MS cases are patients with RRMS.

2) Secondary progressive MS (SPMS): Approximately 50% of patients convert to a secondary progressive pattern within 10 years of disease onset. This pattern may or may not include relapses, but it is characterized by continued progression over the years.

3) Primary progressive MS (PPMS): This pattern accounts for approximately 10% of all MS cases and function declines steadily without relapses.

4) Progressive relapsing MS (PRMS): Persons with PRMS (<5%) has occasional relapses. Additionally, 70% of patients with Clinically Isolated Syndrome (CIS) (defined as an acute neurological disease suggesting demyelination of the CNS but not fulfilling the criteria for clinically definite MS), if left untreated develop MS within 15 years.

Who gets Multiple Sclerosis?

Anyone may acquire MS but:

- Women are more likely to develop MS as compared to men.
- Genetic risk factors increase the risk of developing MS. However, there is no proof or evidence that MS is genetically passed on.
- Environmental factors like smoking and lack of vitamin D
- More prominent in Europeans

Diagnostic criteria:

Magnetic Resonance Imaging (MRI) : Currently, the McDonald diagnostic criteria are used for diagnosis of MS. MRI is the best tool for detection of asymptomatic dissemination of MS. In certain cases, MRI's may predict progression. Sensitivity of MRI's in detecting MS varies from 81-90%.

Treatments: Currently there is no known cure for MS. Disease modifying agents are used to prolong the demyelination and slow down disease progression. DMTs are approved for RRMS.

Multiple sclerosis in India:

India was identified as a low MS- prevalent nation (<5 cases/100,1000) in 1980s. There is lack of good estimates on the incidence and prevalence of MS in India.

Multiple Sclerosis International Federation's World Multiple Sclerosis Atlas projects a prevalence of 3/100,000; nearly triple the estimate of previous reports. With a current population of >1 billion, it can be estimated that the prevalence of MS in India is higher than reported numbers (i.e. 35,000 patients).

Disease-Modifying Therapies for MS

DMTs are used to decrease relapses and disability progression, which are the stamps of MS. It is thought that the DMTs effect or act on the immune system of body by decreasing the immunological responses that is, the production of white blood cells (b cells and t cells) as these cells are responsible to cause MS by passing through the blood brain barrier. To combat this autoimmune response, DMTs like interferon beta, dimethyl fumarate, teriflunomide etc. acts with their respective mechanism of actions. Classification of DMTs can be done based on mode of administration. It is demonstrated in the table below. Injectables are available mainly as interferons which help in reduction in ARR as well as in disability progression of MS patients. These are to be taken frequently e.g. Avonex is taken once in every week and Plegridy is taken twice in a month.

Types of DMTs: On basis of mode of administration:

1. Injections
2. Orals
3. IV Infusions

- Injections

Drug (Brand name)	Pharmacological Class
Interferon β -1a (Avonex®, Biogen)	Interferon
Interferon β -1b (Betaseron®, Bayer)	Interferon
Interferon β -1b (Extavia®, Novartis)	Interferon
Glatiramer acetate (Copaxone®, Teva)	Mixed polymer
Interferon β -1a (Rebif®, EMD Serono)	Interferon
Peginterferon β -1a (Plegridy®, Biogen)	Interferon

- Orals

Drug (Brand name)	Class
Fingolimod (Gilenya®, Novartis)	Sphingosine 1-phosphate receptor modulator
Teriflunomide (Aubagio®, Sanofi Genzyme)	Pyrimidine synthesis inhibitor
Dimethyl fumarate (Tecfidera®, Biogen)	Multifactorial
Dimethyl fumarate (Dyfira, Intas)	Bioequivalent of DMF
Dimethyl fumarate (Dimegen, Nuvigen)	Bioequivalent of DMF
Dimethyl fumarate (Sclerogem, Cipla)	Bioequivalent of DMF

- Infusions

Drug (Brand name)	Class
Natalizumab (Tysabri®, Biogen)	Anti α 4 β 1/ α 4 β 7 integrin monoclonal

	antibody
Alemtuzumab (Lemtrada®, Sanofi Genzyme)	Anti-CD52 monoclonal antibody

Each class and each molecule are clearly different in terms of structure and mode of action but are serving same purpose- modifying immune system. It is believed that the basis of MS treatment is individualization of therapy. There is a market for every DMT, depending upon the patient type. Still, some growth drivers influence and favors one type of therapy a little more than others.

Purpose of research

This research is designed to study the perception of neuro physicians of Pune city regarding the DMTs used in the treatment of multiple sclerosis.

- This study will help in obtaining a picture of current market trends in DMT use which is critical to understand as the advent of generic bioequivalents has recently occurred in MS segment.
- The knowledge about prescription preference, route of administration preference can give overall situational analysis which can further help in making marketing strategies and to identify the target customer who is most likely to prescribe a DMT with certain attribute. It may also help to determine the area where new drug research and development should be done.

Problems being investigated

With the arrival of generic bioequivalents of original innovator DMT molecules, MS market scenario should be studied so that strategical and tactical plan can be made accordingly. Hence in this study current prescription preference of DMTs used in MS in Pune are observed.

LITERATURE REVIEW:

- (Jeffrey A. Tice, MD; Rick Chapman, PhD, MS, 2017) In their report ‘Disease-Modifying Therapies for Relapsing Remitting and Primary-Progressive Multiple Sclerosis: Effectiveness and Value’. The report highlighted the therapeutic goal of DMTs is to decrease the frequency of relapses and to prevent the disability that accumulates with disease progression over time. For RRMS, DMTs are intended to decrease relapses and progressive disability, which are the hallmarks of MS. All DMTs are thought to modulate the immune system to decrease the autoimmune damage that is believed to cause the CNS changes responsible for the symptoms of MS.
- (Sorensen & Giovannoni, 2018) In their article ‘Multiple sclerosis care unit’- Treatment of multiple sclerosis (MS) has become increasingly multifaceted and comprises not only a variety of disease-modifying drugs with different mechanism of action but also a wide range of symptomatic therapies.
- (IPSOS Healthcare, 2016) In the article ‘Multiple Sclerosis: The Evolving Competitive Landscape, the Future Challenges & the Opportunities- provides an overview of the current treatment approaches for Multiple Sclerosis (MS), together with an exploration of the current market dynamics and how they have evolved in recent years. It concludes with two case studies: ‘Tecfidera: Still the Wonder Drug?’ and ‘Analyzing Key Market Drivers’.

METHODOLOGY:

RESEARCH QUESTION:

What is the prescription preferences of neurologists concerning the Disease Modifying Therapies used in treatment of multiple sclerosis?

RESEARCH OBJECTIVES:

- 1. To determine the prescription preferences of neurologists regarding disease modifying therapies used in treatment of Multiple Sclerosis:**
 - To determine the most preferred 1st line DMT by neurologists in newly diagnosed RRMS patients based on route of administration
 - To determine the most preferred oral DMT brand for treatment of RRMS
 - To determine the most preferred dimethyl fumarate brand used by the neurologists
 - To determine the most preferred DMT in patients with high MS disease activity
- 2. To determine the reasons why Neurologists may not prefer Tecfidera.**
- 3. To compare the reasons for patient dropouts and prescription patterns by the key opinion leaders regarding Tecfidera (dimethyl fumarate), Avonex (interferon beta 1a) and Plegridy (peginterferon beta 1a), pre and post generic launch.**

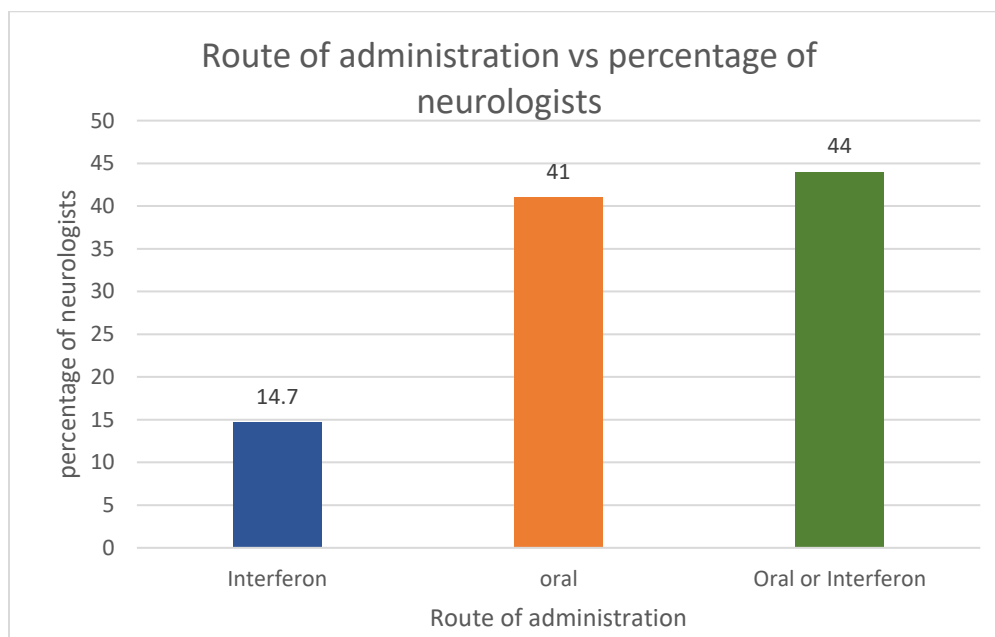
RESEARCH METHODOLOGY:

4. **Type of study:** Descriptive cross-sectional study.
5. **Study population-** Neurologists
6. **Study area-** Pune
7. **Duration of Study–** The study was conducted for the duration of three months of February 2019 to May 2019.
8. **Type of Data-** Quantitative and qualitative
9. **Sample size –** Total sample size was 34 neurologists
10. **Inclusion criteria-** Neurologists with experience of MS treatment
11. **Exclusion criteria-** Chemists
12. **Data collection source -** Primary and secondary
13. **Data collection tool-** Personal interviews
14. **Data entry-** MS Excel

OBSERVATIONS AND RESULTS:

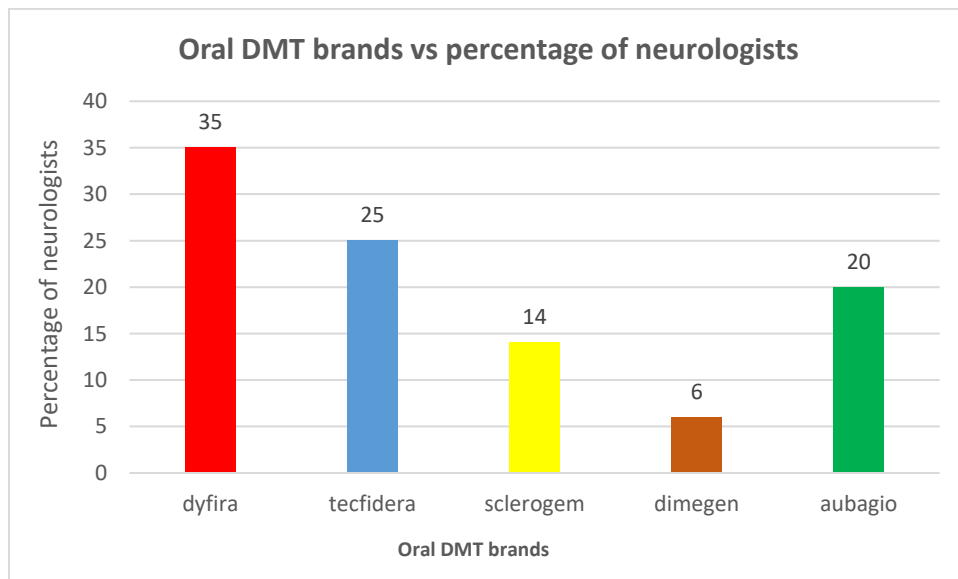
1. To determine the prescription preferences of neurologists regarding disease modifying therapies used in treatment of Multiple Sclerosis:

- Most preferred 1st line DMT by neurologists in newly diagnosed RRMS patients based on route of administration:



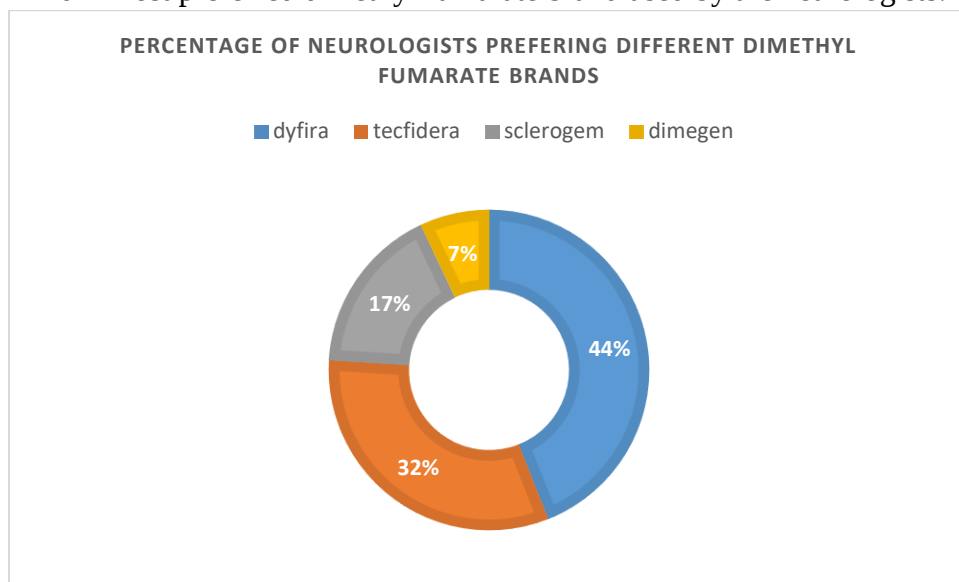
Inference: Majority of neurologists (44%) in study prefer prescribing DMTs having either oral or injection route of administration. However, 41% neurologists prefer only orals as 1st line, this implies the overall prescription preference is towards orals.

- Most preferred oral DMT brand for treatment of RRMS:



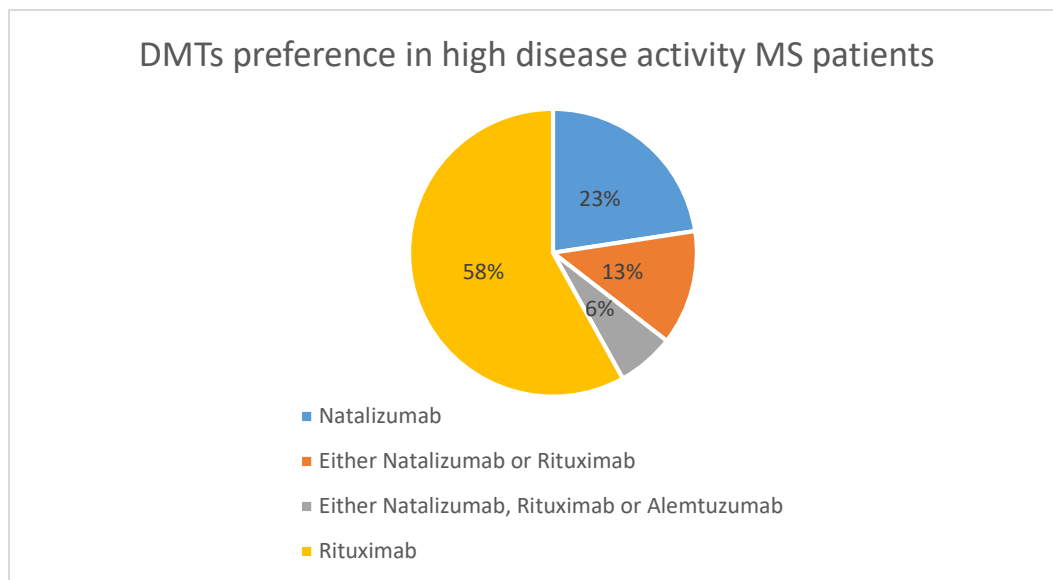
Inference: Among oral DMTs available in the market, Dyfira (bioequivalent) is observed to have maximum preference in prescription as 35% neurologists are preferring it. Tecfidera (25%) and Aubagio (20%) are second and third respectively in order of preference.

- Most preferred dimethyl fumarate brand used by the neurologists:



Inference: As shown in the chart above, Dyfira when compared within dimethyl fumarate products i.e. Tecfidera, Sclerogem and Dimegen, shows maximum preference in prescription by neurologists as 44% neurologists prefer Dyfira more. It is giving close competition to Tecfidera which is an original DMF molecule and is preferred by 32% neurologists.

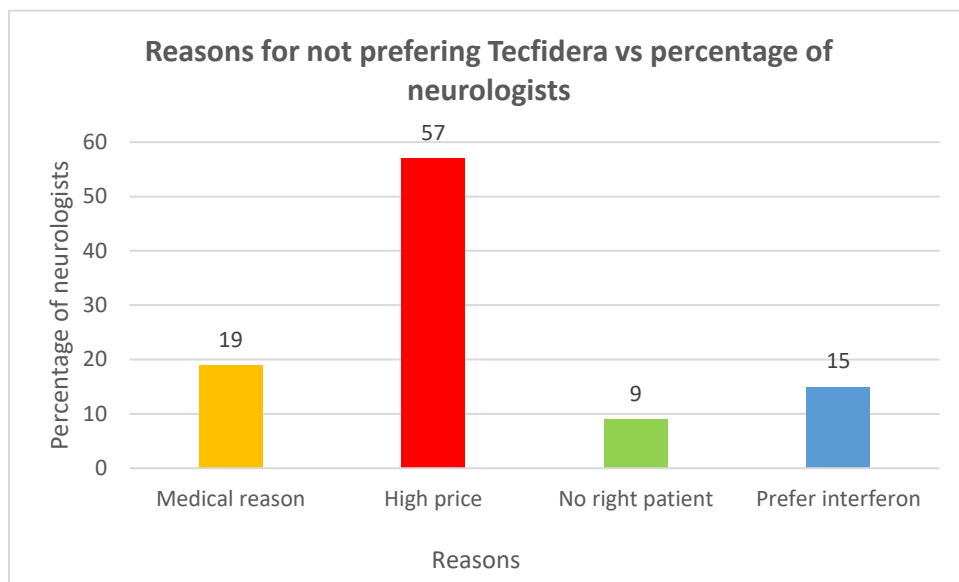
- Most preferred DMT in patients with high MS disease activity:



Inference: Rituximab, an off-label drug for MS is observed to have maximum preference in prescription. 58% neurologists prefer Rituximab in patients with high disease activity MS. 23% prefer Natalizumab (Tysabri) and 13% neurologists are neutral about Natalizumab or Rituximab.

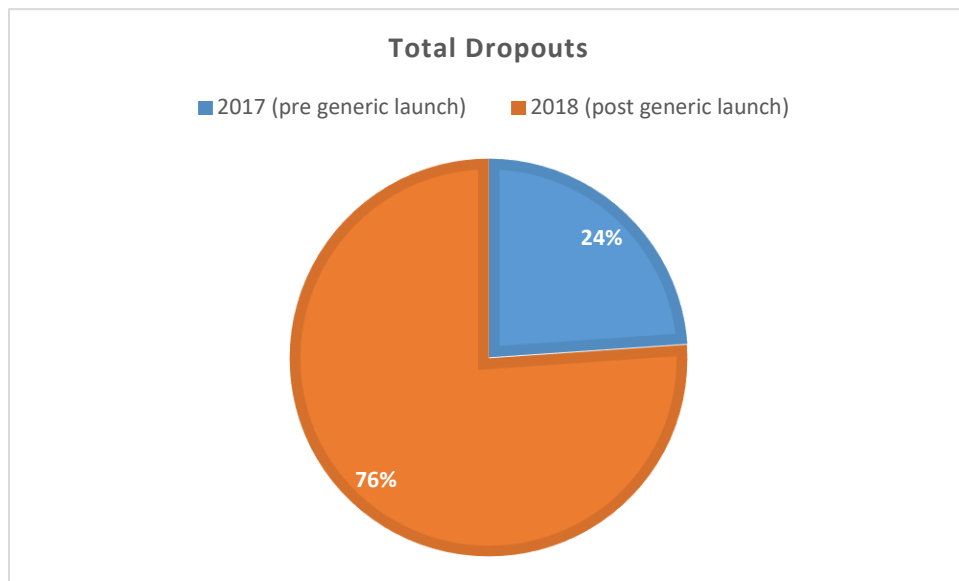
6% neurologists are currently preferring Natalizumab and Rituximab equally but are waiting for Alemtuzumab to be available in market.

2. Reasons why Neurologists may not prefer Tecfidera:

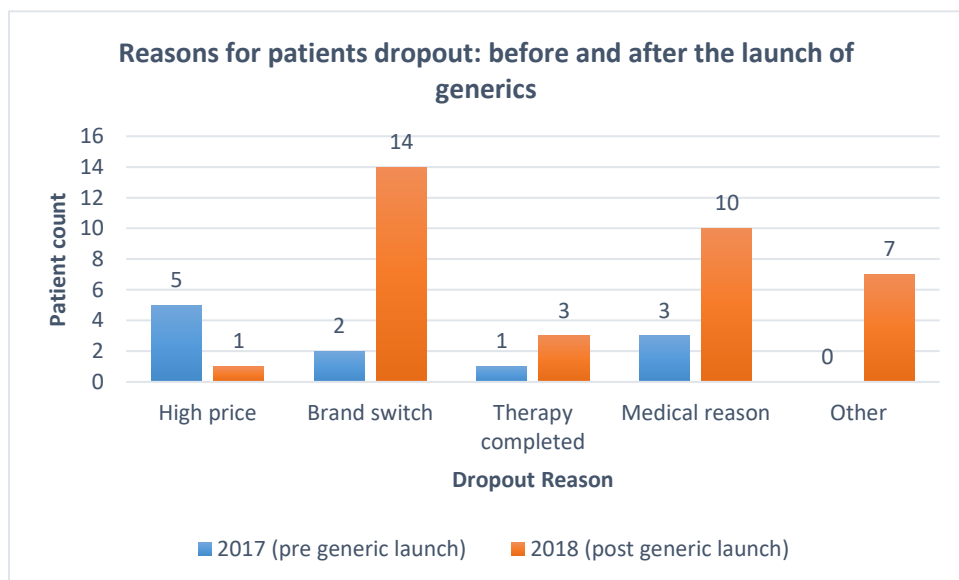


Inference: 57% of neurologists do not prefer Tecfidera due to the high price of therapy. 19% face medical reasons which include lack of efficacy or tolerance. 15% neurologists prefer interferon and 9% may only use Tecfidera when a right patient is there.

3. **Comparison of the reasons for patient dropouts from Tecfidera, Avonex and Plegridy pre and post generics launch:**



Inference: Total dropouts occurred in 2017 before the launch of generics was 24% as compared to after the generic launch when it increased to 76% in 2018.



Inference: 14 dropouts occurred as brand switch in 2018 out of total 35 drop outs.

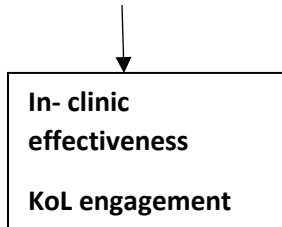
CONCLUSION:

Since route of administration plays important role in adherence and compliance, it is observed from the study that market is shifting towards orals. Interferons are injected subcutaneously, and it is thought to be inconvenient mode as it is associated with injection site reactions and pain. With availability of orals in market, that too at affordable prices, orals use is on a rise. Further study can be done on MS patients to determine if they feel injections are inconvenient and orals can improve their adherence to therapy.

In Pune, MS market has seen a drastic change post generic launch in 2018. It has experienced a shift in prescription trends as before the generic launch, Tecfidera in oral category had monopoly in 1st line orals market of MS. It is observed from the study that Dyfira has quickly become the most preferred oral in 2019. Not only Dyfira but neurologists are also writing Sclerogem and Dimegen. This might be attributed to the price factor as generics have been launched at much cheaper cost. Further research can be done to confirm the factors why Dyfira among generics is most preferred. As a salesperson I have personally observed robust and aggressive promotion by Intas to promote Dyfia so this might be one of the reasons why Dyfira is getting maximum preference.

In patients where 1st line therapy fails or high disease activity patients, stronger molecules are used in them by IV infusion method. Rituximab is being extensively preferred despite being off label in MS. Natalizumab is moderately used but not as much as Rituximab. This may be due to the risk of PML associated with its use and needs a robust marketing plan to combat this mindset, as PML risk is not that common but still neurologists are concerned over it.

Suggestions



- Create a sense of brand loyalty among health care practitioners: **Brand advocates** can be identified and, in this way, correct patient for Tecfidera can be enrolled.
- Increase patient pool by organizing awareness drives along with KoL engagement, increase reach to newer institutions.
- Tactical plans: e.g. world MS day initiatives
 - Radio talks
 - Walkathons
 - Online videos
 - Engaging KoLs in patient awareness programs

Limitations of study:

1. Sample size was less as the MS market is very niche market with very few neurologists treating MS.
2. Due to small sample size of respondents this study only reflects Pune MS market situation and cannot be effectively generalized to overall MS market.
3. Neurologists give very less time to a new sales representative as it takes time to be comfortable and acclimatize hence limited data points could be generated.

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