AdverseEvents
REDEFINING DRUG SAFETY

SPECIAL REPORT

The Comparative Safety of Multiple Sclerosis Medications:

An Analysis Utilizing AdverseEvents Explorer

JUNE 2014

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Contents

Drugs Covered

The drugs examined here are **interferon beta-1a (Avonex), interferon beta-1a (Rebif), interferon beta-1b (Betaseron), interferon beta-1b (Extavia), glatiramer (Copaxone), dimethyl fumarate (Tecfidera), fingolimod (Gilenya), teriflunomide (Aubagio),** and **natalizumab (Tysabri).**

Key Findings

- In general, the older-generation drugs, particularly the interferons (Rebif, Avonex, Betaseron), have inferior safety profiles when compared to newer drug regimens

- Tecfidera has a very positive safety profile compared to its peers (except for elevated disproportionality regarding flushing and gastrointestinal issues)

- While a significant portion of MS patients exhibit cognitive deficits due to the disease itself, we found two MS drugs, Tysabri and Avonex, that exhibited elevated reporting for "cognitive disorder" and "memory impairment" when compared to their peers

- Controversy surrounds possible links to interferon treatments and suicide. The results here show an elevated association with "suicidal behavior" for only one interferon drug, Rebif. Additionally, both Rebif and Extavia showed increased associations with "depression and suicide/self-injury" when compared to their peers.

- Patients on Gilenya might need monitoring for lymphocyte and cardiac abnormalities

- Rebif and Extavia should be prescribed with caution to patients prone to optic nerve disorders

- The known link between PML and Tysabri was confirmed

Market/Treatment Implications

According to EvaluatePharma® analysis (May 2014) [1], current sales figures and future estimates on the disease modifying MS drugs suggest that new oral agents like **Tecfidera, Gilenya** and **Aubagio** are taking away market share from the **interferons** like **Betaseron, Rebif,** and **Avonex.** These estimates project that **Betaseron's** sales will shrink at a rate of 19% in the US in 2014, while **Tecfidera** will grow 122% and **Gilenya** will grow 16%. **Tecfidera** is trending toward blockbuster status with over $2 billion in sales expected in 2014.

It appears then, that neurologists are becoming more comfortable using **Tecfidera** as a first-line treatment instead of the **interferons** – likely because of the oral convenience (versus injection) and the assumed similar or slightly worse safety profile. Our analysis here confirms that this trend is likely to continue, as the safety profile of **Tecfidera** looks favorable compared to its **interferon** peers

In addition, **Gilenya** appears to be a safer alternative to **Tysabri** according to this analysis, which may make it a more favorable second-line treatment option after relapse for patients initially treated with traditional interferon therapy or **Copaxone**.

Overview

- Multiple sclerosis (MS) is a chronic neurological disease characterized by myelin damage, inflammation, and degeneration in both the brain and spinal cord.

- Relapse-remitting multiple sclerosis (RRMS) is the most common form of the disease and strikes almost twice as many women as men.

- RRMS medications have different routes and frequency of administration and varied success rates with regard to reducing relapse rates and limiting neurological dysfunction.

- Adverse events linked to the administration of RRMS drugs can range from mild fatigue to death.

- New generation drugs do not have a long history of use, but in general they appear to have better safety profiles than the older generation drugs.

- A drug's safety profile is never fully elucidated until post-marketing adverse events are examined in detail.

- The following report is a detailed examination of post-marketing adverse event data across major, disease-modifying RRMS drugs.

The importance of post-marketing safety surveillance

The pre-approval clinical trial process suffers from many limitations including: homogenous groups of patients, limited drug exposure times, ever-increasing exclusion criteria, lack of gender-specific analyses, inadequate testing of the elderly and different races, etc. All of these restrictions can result in very different reactions, especially with regard to side effects, in clinical trial subjects versus real-world consumer populations [1]. Accordingly, the true side effect profile of a drug is almost never realized until many months, or even years, after Food and Drug Administration (FDA) approval [2, 3]. As a consequence, all FDA approved drugs have the potential to trigger various side effects not revealed during pre-approval investigations. For more detail please see a White Paper we recently produced, "Post FDA-approval drug safety data: why they are vital and how they can be made accessible, actionable, and predictable."

Adverse events (AEs) from FDA approved drugs are a major public safety concern. In fact, almost one million new AE reports are currently reported to the FDA each year, across ~2,000 approved drugs [4].

Because of the noted limits of pre-approval safety processes, AdverseEvents believes that post-marketing side effect analysis can supply our clients with the real-world data they need to make informed coverage, formulary, and prescribing decisions.

Careful and continuous post-approval monitoring is therefore vital to the evaluation of a drug's true safety profile. That is exactly what we specialize in at AdverseEvents.

To obtain such data, we leverage the FDA's Adverse Event Reporting System (FAERS), a centralized, computerized information database that is broadly used by the FDA and other pharmacovigilance experts for post-marketing drug safety surveillance [1, 5-20]. The FDA uses FAERS analyses to make post-marketing regulatory decisions such as the issuance of warnings, label changes, and/or market removal [21]. International government and related organizations (Australia's "Therapeutic Goods Administration," Canada's "Vigilance Adverse Reaction Online Database," Europe's "EudraVigilance," Japan's "Pharmaceuticals and Medical Devices Agency," The United Kingdom's "Yellow Card Scheme," France's "pharmacovigilance database," and The World Health Organization's "VigiBase") also use spontaneous AE databases to identify post-approval drug safety concerns.

Challenges to using FAERS data, however, have been reported to include "underreporting," the "Weber Effect" [22, 23], and "stimulated reporting" [24-28]. With regard to underreporting, recent efforts by both FDA and the healthcare industry are helping to increase AE reporting rates. Indeed, almost one million AE reports will be added to both the EudraVigilance [29] and FAERS databases this year alone [4]. FAERS now has a total of over seven million reports. With regard to the "Weber effect," a recent study has demonstrated that it may be of less concern than it was in the past, likely due to the aforementioned modern focus on the importance and utility of post-approval AE reporting by both the FDA and key health care players [30]. We have recently examined modern FAERS trends to determine the magnitude of "stimulated reporting" after an FDA-issued AE warning. We analyzed over 100 recent FDA Alerts and found little evidence to support the hypothesis that "stimulated reporting" is widespread within FAERS (article submitted).

FAERS data (after extensive organization and cleanup through algorithms and our analysts) forms the cornerstone of our product offerings. At the time of this analysis, publicly available FAERS data were only current through Q3 2013. To provide our clients with the most up to date information we obtained non-publicly available FAERS data through Freedom of Information Act inquiries in order to be current to May 12, 2014.

Multiple Sclerosis

Myelin is a waxy, fat-like substance that is wrapped around your nerve fibers, somewhat analogous to the rubber coverings that protect electric wires. By insulating nerve fibers, myelin helps them propagate vital electrical signals throughout the body. Damage to this insulation can lead to loss of nerve signaling and sensory perceptions as well as impairments to both movement and cognition.

Multiple sclerosis (MS) is a chronic neurological disease characterized by myelin damage, inflammation, and degeneration in both the brain and spinal cord. The damage MS wreaks on myelin can be visualized as distinct brain lesions upon MRI examination. The origins of MS remain elusive (genetic, environmental, viral and other causes may play a role).

The forms of MS and their approximate incidences are relapsing-remitting (defined relapses with full, or almost full, recovery and no disease progression between attacks - 85%), secondary-progressive (most patients with relapsing-remitting transition to this form of the disease which is characterized as progression with or without attacks), primary-progressive (occasional plateaus with some minor improvements possible - 10%), and progressive-relapsing (disease is progressive from the start and continues during relapse intervals - 5%).

The most common, and the focus of this report, is relapse-remitting MS (RRMS) which strikes twice as many women as men and usually manifests itself between 20 and 30 years of age. As mentioned, most cases of RRMS unfortunately develop into secondary-progressive which is even more debilitating. Unexpected and recurring relapses or "attacks" are the hallmark of RRMS. A relapse is defined as the worsening of existing MS symptoms and/or the appearance of new symptoms. These episodes typically last from days to weeks and then mostly, or totally, disappear only to flash up again at a later date.

Such relapses are driven by increased myelin inflammation that acutely disrupts nerve transmission and thereby triggers various MS symptomologies. Severe attacks that affect a patient's mobility, functioning, and/or safety are typically treated with corticosteroids. Such compounds, however, are not believed to affect the disease itself.

Visual disturbances, difficulty with walking and performing other tasks that require coordination, fatigue, and loss of bowel and bladder control can occur. Central pain, cognitive dysfunction, and various psychiatric disorders can also occur in MS patients. For more information on the clinical course of MS please see [31, 32].

While often considered mainly an inflammatory and demyelinating disease new evidence from imaging techniques is suggesting that damage to neuronal structures can occur even early on in the progression of RRMS [33, 34]. However, the mechanisms that underlie such neurodegeneration remain obscure [35].

Diagnosis

A detailed clinical history and physical exam are usually the first steps in the diagnostic process. RRMS can be diagnosed if the patient shows evidence of two separate areas of myelin damage that have occurred at different times – e.g. "dissemination in space and time." Multiple confirmatory laboratory procedures are used such as electrophysiology, MRI scans, blood tests, and cerebrospinal fluid analysis, etc.

After a first diagnosis regular moderate physical activity / therapy may be advised as well as cooling devices to help reduce fatigue. Drugs, discussed below, are used in the majority of MS patients.

Therapy

There is currently no cure for MS and until the 1990's the disease was untreatable. Now, the use of MRI has revolutionized MS diagnosis and monitoring, environmental influences are better elucidated, MS-associated genes have been mapped, and physicians can chose from many disease-modifying agents for RRMS.

Two decades ago, the introduction of the first Disease Modifying Therapies (DMTs) (**beta-interferons** and **glatiramer**) was a game-changing event for MS treatment. These early drugs are still widely used for MS but have fairly nonspecific mechanisms of action. They are generally believed to have favorable track records for both efficacy and safety but suffer from high discontinuation rates [36].

Recently, **monoclonal antibodies** have been developed as DMTs. While this new class of drugs has good efficacy, they can sometimes be associated with serious AEs. New **orally available medications** are now a DMT option for MS patients as well. They also show suitable efficacy, but long-term safety profiles are not yet known. For more information regarding current MS drug development efforts please see [37, 38].

DMTs are designed to target the body's immune system. They are usually started immediately after diagnosis and are the current standard of care. Due to the diverse manifestations of MS symptoms and disabilities, as well as the highly variable disease course, deciding on a therapy is complicated by many factors. Moreover, DMTs differ extensively in route and frequency of administration, tolerability, risk of major toxicities, and pregnancy-related risks.

DMTs for RRMS alter a patient's immune system in such a way as to reduce inflammation and thereby inhibit both the frequency and severity of relapses and associated disabilities. The medications are prescribed on a long-term basis and have also been shown to reduce the accumulation of lesions within the brain and spine.

The medications may also slow the progression of disabilities and the disease itself.

The most common therapeutic strategy for RRMS is sequential DMT monotherapy, where patients are prescribed their first DMT and thereafter monitored for efficacy, safety, and tolerability. Therapy continues until a breakthrough relapse occurs or an increased lesion load is detected by MRI. The treatment regimen is consequently revised based on the physician's judgment of when and how treatment failure has occurred.

Interferons and/or **glatiramer** are often the first DMT drugs to be prescribed. Corticosteroid therapy is usually recommended for patients undergoing relapses that include functional impairment (steroid drugs of this type are not, however, included in the present analysis). Other drugs are sometimes prescribed to address urinary urgency, incontinence, nocturia, erectile dysfunction, neuropathic pain, sleep issues, and spasticity/convulsions.

Treatment options are far less advanced for the neurodegenerative characteristics of more advanced stages of the disease. Clinical trials, and therefore drug development efforts, are unfortunately difficult to conduct in advanced forms of MS [39].

Of the 10 currently approved DMTs for RRMS, all of them were evaluated in this report except for **mitoxantrone (Novantrone)**, which was excluded because it is indicated for treating two of the progressive forms of MS in addition to treating worsening RRMS. In the setting of RRMS therapy, the role of **mitoxantrone** is reserved for patients with rapidly advancing disease who have failed other therapies.

To summarize, MS medications have different routes and frequency of administration, diverse adverse event profiles, and varied success rates with regard to reducing relapse rates and limiting neurological dysfunction

The DMTs we analyzed here are injectable i**nterferons (interferon beta-1a (Avonex)**, **interferon beta-1a (Rebif)**, **interferon beta-1b (Betaseron)**, **interferon beta-1b (Extavia)**, **injectable glatiramer (Copaxone)**, o**ral dimethyl fumarate (Tecfidera)**, **oral fingolimod (Gilenya)**, **oral teriflunomide (Aubagio)**, and **infused natalizumab (Tysabri)**.

Side Effects associated with Multiple Sclerosis regimens

While the efficacy traits of these drugs are fairly well known from their respective clinical trial programs, the compounds all have differing half-lives, metabolites, molecular sizes, non-specific binding sites, and pharmacokinetic characteristics. Oftentimes it is these differences that can result in a variety of adverse events.

The true safety profile of FDA-approved medications is not known until after they have been introduced to a wide variety of real-world patient populations. For more detail please see our White Paper "Post FDA-approval drug safety data: why they are vital and how they can be made accessible, actionable, and predictable" (http://info.adverseevents.com/whitepaper-post-fda-approval).

Table 1: A selection of quotes from the academic literature regarding the safety profiles for some of the main RRMS drugs

Drug Name	Quotes
dimethyl fumarate	"The most prevalent side effects were transient flushing and gastrointestinal tract irritation." [40] "The most common side effects are cutaneous flushing and gastrointestinal symptoms, with the highest incidence in the first month after starting treatment. No serious safety signals were seen during the phase II and III trials, including no increased risk of opportunistic infections or cancer." [41]
fingolimod	"The use of fingolimod in clinical practice has been limited by concerns for cardiac effects, infection, and macular edema as well as the relative lack of long-term safety data for this drug with a novel mechanism of action. Additional clinical trial and postmarketing data suggest that fingolimod is a safe, effective, and well-tolerated treatment option when patients are selected and monitored appropriately." [42]
interferon beta and glatiramer acetate	"Moreover, there is no doubt that these older agents are both effective and very safe - something which has not always proven true about the newer therapies. Consequently, there will continue to be a place for these injectable treatments, even as we move into an era where physicians are confronted with many treatment possibilities."[43]
natalizumab	"The only adverse events that were more frequent with natalizumab monotherapy than with placebo were fatigue and allergic reactions. The main safety and tolerability issue with natalizumab is the incidence of progressive multifocal leukoencephalopathy (PML)." [44] "These positive effects have to be balanced against potential adverse events. In this respect, allergic reactions, hematologic abnormalities, melanoma, lymphoma, infections, and most importantly, progressive multifocal leukoencephalopathy (PML) are discussed." [45]

Progressive multifocal leukoencephalopathy (PML) is a rare, but very serious brain infection caused by the John Cunningham (JC) virus that damages myelin. PML typically results in death or severe disabilities. The "JC Virus Test" is used to identify the presence of the virus that can lead to the development of PML. While **natalizumab** has been repeatedly linked to PML by the FDA [46], **fingolimod** has also been linked to at least one case [47]. For more information regarding **natalizumab** and PML please see [48-50].

Fingolimod was also suspected in a patient death that occurred immediately after first dosing of the drug. While FDA could not conclusively link the drug to that event they have discussed possible cardiovascular issues from **fingolimod** administration [51]. **Fingolimod** has been suspected of lowering heart rates, usually within 6-20 hours after the first dose and is therefore contraindicated for patients with heart conditions as well as those who are on antiarrhythmics. Fingolimod also has requirements for monitoring specific laboratory and ophthalmological parameters.

A list of potential AEs for some of the main MS drugs can be found in Rommer et al [52]. Their list includes: **glatiramer acetate** (flushing, chest pain, dyspnea, palpitations, urticaria, and skin necrosis); **interferon beta** (flu-like symptoms, injection-site necrosis, depression, allergic reactions, hepatic injury, neutropenia, and lipoatrophy); **natalizumab** (PML, fever, joint pain, liver disease, melanoma, and allergic reactions);

fingolimod (bradycardia, heart failure, fever, diarrhoea, liver disease, macular oedema, skin cancers, and encephalitis); **teriflunomide** (hepatic injury, elevated liver enzymes, infections, and polyneuropathy); and **dimethyl fumarate** (lymphopenia and gastrointestinal side effects).

Other authors found that "there was a lower rate of depression in patients taking **interferon beta-1a (Rebif)** compared with the other interferons based on limited trial data. I**nterferon beta-1a IM (Avonex)** was associated with the highest rates of flu-like syndrome compared with the other beta interferons. **Interferon beta-1b SC (Avonex)** was associated with the lowest rates of injection site reactions whereas **interferon beta-1b SC (Betaseron)** and **interferon beta-1b SC (Rebif)** had similar rates" [53].

For further review of known adverse events please see Parfenov et al. [54] and Oh and O'Connor [55].

In order to 1) test current safety assumptions, 2) gain a deeper insight into the comparable safety profiles of RRMS medications, and 3) assist neurologists in their drug selection risk/benefit analyses we used multiple analytic platforms to analyze **post-marketing** safety signals associated with these drugs.

Methods & Results

In order to better understand the post-approval safety data available on MS drugs we conducted a detailed review of FAERS. For additional details on each of these drugs please see the Appendix.

To import and filter data from FAERS pre-processing techniques were used to normalize and qualify textual data, such as removal of non-alphanumeric characters, whitespaces, and line breaks. Filtering processes included: i) a system for automated name matching which corrected drug name misspellings and incorrect data within major fields (e.g., the inclusion of dosages or routes of administration as part of the drug name field); ii) aggregation of generic and non-U.S. brand name drugs under a single brand name; iii) separation of "primary suspect" and "all suspect" designations, iv) removal of duplicate case reports; and v) identification of common adverse event and condition types.

Automated data pre-processing and scrubbing workflow provided an initial assignment of a 'raw' FDA FAERS drug names. The automated matching process was accomplished by a combination of fuzzy string matching, string distance, and phonetic matching algorithms. Drug name text-mapping was accomplished as previously described [56]. Textual drug name data were validated by text-mapping of brand drug names and active ingredient names to the RxNorm database [57] and manual curation.

Utilizing the AdverseEvents Explorer platform we analyzed the drugs with: 1) RxFilter (a big data analytic that optimizes FAERS and Adverse Event Data received from FOIA requests and makes it user-friendly and fully searchable) [56], 2) a disproportionality measure (a mathematical analysis that compares "expected" versus "unexpected" rates of adverse events) [58], and 3) the RxScore system (a proprietary algorithmic drug-safety ranking analytic).

RxFilter™ Analysis

In order to make FAERS data accessible to broad groups of healthcare professionals, AdverseEvents analyzes and categorizes the extensive database by using a combination of computer algorithms and in-house data analysis, called **RxFilter.** Our **AdverseEvents Explorer** platform makes FAERS data easy to search and understand [56], and feeds clean data into our other analytics. It accurately standardizes approximately 5 million FAERS case reports, from 1997 on, linked to over ~2,000 FDA approved drugs, enabling health plan administrators, health systems analysts, and pharmaceutical

companies rapid access to fully-searchable and organized FAERS information in order to supplement their own sources of drug safety data.

FAERS data was queried from a drug's approval through the most recently available date. All drugs included in the current analysis have data through May 12, 2014 because we petitioned FDA, via a Freedom of Information Act (FOIA) request, for updated case reports on those specific drugs. 89,060 new case reports were received, processed, and added to the 256,244 cases we already had in our database for the nine MS drugs analyzed here. Integrating data received from FOIA requests into the AE Explorer platform is a valued added service we provide for our clients. For more detail on the process please see http://www.adverseevents.com/foia/

For each of the four categories, below, the drug with the highest percentage of case reports is shaded **red**, while the lowest total is shaded **green**.

Table 1: Top-level analysis of MS medications

Drug Name	Approval Date	Primary Suspect Cases	Life-Threatening Cases (%)	Hospitalization Cases (%)	Disability Cases (%)	Death Cases (%)
dimethyl fumarate (Tecfidera)	3/27/2013	14,790	4 (0.03%)	620 (4.19%)	6 (0.04%)	27 (0.18%)
Fingolimod (Gilenya)	9/21/2010	14,068	189 (1.34%)	1,754 (12.47%)	210 (1.49%)	134 (0.95%)
glatiramer acetate (Copaxone)	12/20/1996	8,191	170 (2.08%)	2,230 (27.23%)	96 (1.17%)	344 (4.20%)
interferon beta-1a (Avonex)	5/17/1996	71,856	154 (0.21%)	29,915 (41.63%)	96 (0.13%)	4,137 (5.76%)
interferon beta-1a (Rebif)	3/7/2002	25,971	459 (1.77%)	10,368 (39.92%)	581 (2.24%)	1,027 (3.95%)
interferon beta-1b (Betaseron)	7/23/1993	11,947	216 (1.81%)	4,573 (38.28%)	339 (2.84%)	1,088 (9.11%)
interferon beta-1b (Extavia)	8/14/2009	1,258	14 (1.11%)	310 (24.64%)	26 (2.07%)	29 (2.31%)
Natalizumab (Tysabri)	11/23/2004	105,872	288 (0.27%)	13,533 (12.78%)	179 (0.17%)	1,546 (1.46%)
Teriflunomide (Aubagio)	9/12/2012	2,291	6 (0.26%)	266 (11.61%)	13 (0.57%)	14 (0.61%)

Disproportionality Analysis

Data mining algorithms based on disproportionality can be used to estimate the relative frequency of an AE associated with the use of a specific drug. The Reporting Odds Ratio (ROR) is a disproportionality measure commonly used by drug safety professionals to help identify AE / drug pairs that are reported more frequently than expected. The method compares expected reporting frequencies (based upon all drugs and all AEs in the FAERS database) with the amount of given AEs reported

An ROR score of ≥1.0 indicates that there is a higher than normal reporting rate for a given AE / drug combination. While there is no widely accepted benchmark regarding a numerical level at which disproportionality analysis yields a "safety signal," many in the drug industry assume that results above 1.5-2.0 warrant attention. We derived ROR by the use of standard formulas [58].

The tables below list the number of "primary suspect" case reports for each drug and how many of those reports fall into corresponding Medical Dictionary for Regulatory Activities (MedDRA) "Preferred Term" (PT), "High-Level Term" (HLT), "High-Level Group Term" (HLGT), and "Standardized MedDRA Queries" (SMQ) adverse event categories. With regard to the latter, MedDRA and the Council for International Organization of Medical Sciences (CIOMS) created and validated categories of related AEs known as "Standardized MedDRA Queries" (SMQ) (http://www.meddra.org/how-to-use/tools/smqs). SMQs are standardized sets of MedDRA terms that are commonly used to support both safety signal detection and monitoring. SMQs contain either "narrow" or "broad" concept terms. Narrow terms are defined by MedDRA as being "cases highly likely to be the condition of interest" and are therefore the SMQ terms we analyze. Please see the tables below for the AE terms and AE groupings that were searched.

Disproportional reporting was assessed for "primary suspect" cases reported for each AE / drug pair. The table lists corresponding ROR results and case counts (in parenthesis). For each AE the drug with the highest disproportional reporting is shaded **red**, while the lowest total is shaded **green**.

Table 2: PTs – ROR (Total Primary Suspect Cases)

Adverse Event	dimethyl fumarate	fingolimod	glatiramer acetate	Avonex	Rebif	Betaseron	Extavia	natalizumab	teriflunomide
Breast Cancer	0.16 (12)	0.88 (62)	1.76 (72)	2.48 (875)	1.86 (241)	1.15 (69)	1.27 (8)	0.53 (288)	0.53 (288)
Cognitive Disorder	2.42 (92)	4.56 (155)	1.00 (21)	5.33 (876)	2.64 (166)	2.20 (64)	5.26 (16)	9.38 (2,030)	4.22 (23)
Diarrhoea	5.85 (2,166)	1.14 (461)	0.43 (104)	0.44 (947)	0.51 (386)	0.64 (225)	0.63 (23)	0.44 (1,394)	7.59 (421)
Fall	0.76 (208)	2.03 (502)	1.27 (188)	4.15 (4,867)	3.37 (1,490)	2.52 (524)	4.65 (99)	2.87 (5,079)	3.79 (153)
Fatigue	2.06 (960)	5.43 (2,157)	0.69 (190)	1.48 (3,401)	2.14 (1,743)	1.77 (673)	1.77 (673)	4.99 (14,296)	3.44 (240)
Headache	1.70 (853)	2.81 (1,290)	0.78 (225)	1.20 (2,968)	1.72 (1,503)	1.59 (643)	3.87 (153)	2.04 (7,076)	2.67 (203)
Heart Rate Decreased	0.17 (5)	25.82 (666)	0.54 (9)	0.96 (142)	1.41 (75)	1.26 (31)	2.72 (7)	0.49 (109	N/A (2)
Influenza Like Illness	1.73 (163)	2.46 (220)	1.16 (61)	23.01 (7,455)	12.50 (1,858)	10.44 (745)	18.28 (133)	1.47 (996)	3.58 (52)
Jc Virus Test Positive	N/A (0)	17.14 (21)	N/A (4)	3.13 (19)	5.43 (12)	N/A (2)	N/A (0)	125.60 (311)	N/A (2)
Lymphocyte Count Decreased	2.50 (25)	56.54 (440)	N/A (0)	0.67 (32)	0.70 (12)	1.65 (13)	N/A (0)	0.13 (9)	N/A (0)
Memory Impairment	2.90 (265)	3.48 (299)	0.49 (25)	6.58 (2,635)	2.40 (380)	2.28 (167)	4.06 (32)	8.23 (4,518)	3.81 (56)
Multiple Sclerosis Relapse*	7.35 (457)	14.74 (830)	23.81 (755)	21.88 (4,950)	28.20 (2,546)	14.99 (714)	52.91 (234)	42.20 (9,710)	27.70 (247)
Progressive Multifocal	N/A (0)	2.04 (14)	N/A (2)	0.31 (11)	N/A (1)	N/A (3)	N/A (0)	25.13 (854)	N/A (0)
Rectal Cancer	N/A (0)	N/A (1)	N/A (1)	2.77 (37)	1.83 (9)	N/A (2)	N/A (1)	0.29 (6)	0.29 (6)
Secondary Progressive Multiple Sclerosis*	6.09 (9)	7.77 (11)	28.77 (23)	23.24 (129)	17.54 (43)	16.06 (19)	N/A (4)	44.80 (250)	N/A (2)
Suicidal Behaviour	N/A (0)	N/A (1)	N/A (1)	N/A (4)	12.66 (86)	N/A (1)	N/A (0)	N/A (3)	N/A (1)

* = Likely to relate to either drug ineffectiveness or disease progression.

Table 3: HLTs

Adverse Event	dimethyl fumarate	fingolimod	glatiramer acetate	Avonex	Rebif	Betaseron	Extavia	natalizumab	teriflunomide
Cardiac Signs And Symptoms Nec	0.92 (618)	2.48 (1,475)	1.20 (440)	0.61 (2,032)	0.92 (1,087)	1.04 (561)	1.72 (94)	0.66 (3,244)	1.56 (159)
Hepatic Neoplasms Malignant	N/A (0)	N/A (1)	0.81 (6)	0.74 (48)	0.55 (13)	1.11 (12)	N/A (0)	0.16 (16)	N/A (0)
Injection Site Reactions	N/A (1)	0.02 (7)	6.67 (1,454)	3.05 (6,291)	7.70 (5,062)	7.45 (2,297)	11.93 (349)	0.06 (193)	N/A (2)
Ischaemic Coronary Artery Disorders	0.28 (191)	1.38 (849)	1.63 (578)	0.83 (2,696)	0.88 (1,019)	1.17 (618)	0.73 (42)	0.31 (1,550)	0.74 (79)
Meningiomas Benign	N/A (0)	N/A (0)	N/A (3)	12.91 (21)	10.64 (7)	N/A (2)	N/A (0)	N/A (4)	N/A (0)
Meningiomas malignant	N/A (0)	N/A (0)	N/A (0)	N/A (0)	N/A (0)	N/A (0)	N/A (0)	N/A (0)	N/A (0)
Nausea And Vomiting Symptoms	4.14 (3,213)	1.32 (1,154)	0.79 (415)	0.56 (2,645)	0.78 (1,311)	0.84 (639)	1.10 (87)	0.52 (3,620)	2.62 (356)
Neutropenias	0.04 (7)	0.26 (45)	0.06 (6)	0.04 (35)	0.11 (37)	0.13 (19)	N/A (2)	0.02 (26)	N/A (1)
Optic Nerve Infections And Inflammations	2.97 (36)	11.66 (128)	7.20 (47)	11.87 (594)	38.01 (656)	10.51 (99)	24.11 (24)	7.67 (574)	10.56 (21)
Peripheral Vascular Disorders Nec*	28.32 (4,318)	0.74 (160)	2.22 (270)	0.29 (322)	0.43 (170)	0.66 (121)	1.00 (19)	0.49 (807)	1.18 (41)
Psychiatric Symptoms Nec	0.68 (38)	0.92 (48)	4.26 (127)	0.51 (137)	0.49 (48)	1.13 (50)	1.50 (7)	0.52 (207)	0.72 (6)
Uterine Neoplasms Benign	N/A (2)	0.88 (10)	1.82 (12)	7.36 (390)	11.47 (227)	2.81 (27)	N/A (3)	1.40 (119)	N/A (1)
Uterine neoplasms malignant NEC	N/A (0)	N/A (2)	4.46 (9)	4.47 (76)	5.55 (35)	3.38 (10)	N/A (0)	20 0.75 (20)	N/A (1)
Uterine neoplasms malignant NEC	N/A (3)	0.76 (15)	2.44 (28)	5.59 (528)	8.30 (290)	2.69 (45)	N/A (3)	1.05 (157)	N/A (2)

* = most of these cases are “flushing”

Table 4: HLGTs

Adverse Event	dimethyl fumarate	fingolimod	glatiramer acetate	Avonex	Rebif	Betaseron	Extavia	natalizumab	teriflunomide
Bacterial Infectious Disorders	0.22 (65)	0.62 (166)	0.69 (107)	1.25 (1,693)	2.36 (1,128)	2.38 (524)	1.49 (35)	0.98 (1,975)	0.82 (37)
Bone And Joint Therapeutic Procedures	0.28 (19)	N/A (4)	0.57 (21)	3.65 (1,084)	1.53 (171)	1.13 (58)	N/A (4)	0.96 (439)	1.87 (20)
Decreased And Nonspecific Blood Pressure Disorders And Shock	0.66 (607)	1.68 (1,376)	1.18 (574)	0.54 (2,414)	0.79 (1,259)	0.83 (606)	1.29 (96)	0.59 (3,930)	1.06 (148)
Encephalopathies	N/A (2)	0.43 (27)	0.19 (7)	0.28 (92)	0.38 (44)	0.81 (43)	N/A (1)	0.22 (105)	N/A (1)
Female Reproductive Tract Infections And Inflammations	0.30 (7)	1.30 (30)	1.24 (16)	1.11 (126)	0.85 (36)	1.05 (20)	N/A (3)	1.94 (319)	N/A (3)
Gastrointestinal Signs And Symptoms	4.53 (5,239)	1.22 (1,825)	0.69 (633)	0.56 (4,637)	0.77 (2,248)	0.90 (1,184)	1.23 (164)	0.49 (6,037)	2.32 (518)
Genitourinary Tract Disorders Nec	1.30 (185)	2.20 (296)	1.97 (154)	2.74 (1,835)	4.83 (1,153)	3.02 (343)	1.65 (21)	4.90 (4,494)	3.20 (69)
Hepatic and hepatobiliary disorders	0.07 (36)	0.47 (216)	0.51 (134)	0.46 (1,070)	0.92 (755)	1.23 (463)	0.47 (20)	0.16 (561)	0.28 (21)
Infections - Pathogen Unspecified	0.59 (746)	1.24 (1,396)	0.84 (566)	1.54 (8,619)	2.27 (4,349)	1.83 (1,669)	2.12 (200)	2.02 (15,809)	1.62 (292)
Nervous System Neoplasms Benign	N/A (2)	1.20 (7)	2.96 (10)	4.06 (116)	5.99 (63)	3.44 (17)	N/A (3)	1.16 (51)	N/A (0)
Reproductive Neoplasms Female Benign	0.18 (5)	0.77 (21)	1.45 (23)	4.81 (634)	7.94 (382)	2.86 (66)	2.47 (6)	1.14 (234)	1.61 (7)
Thyroid Gland Disorders	0.20 (15)	0.88 (62)	1.24 (52)	2.04 (725)	3.90 (495)	3.04 (181)	2.07 (13)	0.69 (371)	1.06 (13)
Vision Disorders	0.70 (238)	4.62 (1,366)	1.27 (236)	1.82 (2,917)	1.92 (1,113)	1.85 (497)	4.01 (108)	1.79 (4,207)	2.73 (144)

Table 5: SMQs

Adverse Event	dimethyl fumarate	fingolimod	glatiramer acetate	Avonex	Rebif	Betaseron	Extavia	natalizumab	teriflunomide
Accidents And Injuries	0.44 (337)	1.13 (810)	0.89 (376)	2.53 (8,474)	1.98 (2,467)	1.47 (882)	2.87 (168)	1.47 (7,673)	2.28 (246)
Anaphylactic/ anaphylactoid Shock Conditions	0.17 (26)	0.15 (21)	3.63 (289)	0.28 (206)	0.41 (108)	0.48 (58)	0.39 (5)	0.32 (349)	N/A (1)
Demyelination*	4.66 (640)	8.90 (1,118)	14.72 (1,030)	20.39 (10,020)	21.41 (4,230)	20.08 (1,924)	28.29 (274)	25.76 (15,714)	18.13 (340)
Depression And Suicide/self-injury	0.44 (249)	0.82 (438)	0.50 (217)	1.03 (3,045)	1.71 (1,629)	1.54 (709)	2.76 (123)	0.79 (3,211)	1.17 (99)
Haemorrhage Terms (excl Laboratory Terms)	0.21 (244)	0.37 (406)	0.68 (426)	1.19 (6,201)	1.33 (2,485)	1.26 (1,091)	1.79 (157)	0.29 (2,418)	0.58 (99)
Hematopoietic Leukopenia	0.39 (121)	3.25 (900)	0.12 (26)	0.24 (398)	0.76 (415)	0.71 (185)	0.45 (12)	0.11 (248)	0.68 (32)
Malignancy Related Therapeutic And Diagnostic Procedures	0.32 (19)	0.43 (25)	0.87 (29)	3.20 (902)	1.32 (140)	1.73 (84)	0.97 (5)	0.73 (319)	0.65 (6)
Malignant Tumours	0.07 (36)	0.71 (382)	1.49 (462)	1.51 (4,084)	1.38 (1,352)	1.36 (619)	0.70 (34)	0.39 (1,621)	0.30 (24)
Myocardial Infarction	0.05 (16)	0.34 (114)	0.50 (96)	1.05 (1,773)	0.94 (577)	1.17 (326)	0.37 (11)	0.13 (333)	0.28 (15)
Optic Nerve Disorders	1.32 (38)	5.93 (161)	3.25 (63)	5.04 (701)	15.40 (718)	5.12 (123)	10.69 (26)	3.31 (658)	5.70 (25)
Ovarian Malignant Tumours	N/A (0)	N/A (4)	2.48 (14)	2.91 (139)	3.26 (58)	3.03 (25)	N/A (1)	0.51 (38)	N/A (1)
Retinal Disorders	0.12 (11)	5.53 (450)	0.57 (28)	0.50 (218)	1.72 (267)	1.10 (79)	1.19 (9)	0.40 (257)	0.89 (12)
Skin malignant tumours	0.18 (7)	4.08 (145)	1.83 (39)	2.17 (400)	2.28 (154)	1.37 (43)	N/A (4)	1.18 (323)	N/A (3)
Torsade De Pointes, Shock-associated Conditions	N/A (0)	1.28 (124)	0.47 (27)	0.17 (87)	0.22 (41)	0.52 (43)	0.57 (5)	0.03 (19)	N/A (2)
Uterine And Fallopian Tube Malignant Tumours	N/A (1)	1.18 (13)	3.45 (22)	3.63 (197)	3.48 (70)	2.79 (26)	N/A (1)	0.92 (77)	N/A (1)

* = Likely to relate to either drug ineffectiveness or disease progression.

RxScore™

We are accustomed to using objective product ranking and scoring platforms such as "Consumer Reports" to guide our purchasing decisions. Drugs, however, have no similar platform, for either efficacy or safety.

Determining the overall safety risk of a drug necessarily involves the simultaneous assessment of several safety-related parameters. Choosing these factors, and determining how to weigh their individual contribution within a ranking platform needs careful consideration. To paint a fair picture of the damage done by an AE, it would also need to factor in existing comorbidities that a patient was suffering from *before* a given drug was administered.

To meet these needs, we developed the "RxScore," a proprietary algorithmic scoring model based predominantly on post-marketed safety data from over five million FDA Adverse Event Reporting System (FAERS) reports. RxScore is presented on a 100-point scale meant to reflect both the breadth and seriousness of side effect(s) by incorporating differentially weighted categories including FAERS fields such as "Outcome," "Adverse Event Seriousness," "Report Type," and a disproportionality measure. The score is adjusted by an "importance weighting" of the FAERS "Event Reporter" field in order to assign higher weightings to AE reports provided by physicians, pharmacists, and other healthcare providers compared to non-healthcare providers. Higher weightings were also ascribed to case reports where the subject of the report was only taking one drug versus reports where a subject was taking more than one drug. Both "Indication Seriousness" and a patient's existing comorbidities are also used to negatively adjust the scores. A score of 100 indicates the highest potential adverse event risks. In order to highlight differences between the drugs the tables below list the total score as well as the "percent of maximum" that each drug had across key individual components of the total RxScore.

Our RxScore analysis of MS drugs yielded the following, listed from highest total score to lowest:

Table 6: RxScores and Percent of Key components

Drug	RxScore	Outcome	Adverse Event Seriousness	Disproportionality	Report Priority
interferon beta-1a (Rebif)	55.06	39.63%	47.03%	34.47%	66.77%
interferon beta-1a (Avonex)	54.12	39.84%	47.17%	32.42%	48.31%
interferon beta-1b (Betaseron)	53.18	43.58%	44.34%	29.58%	60.31%
glatiramer acetate	47.36	34.61%	41.24%	28.23%	35.54%
interferon beta-1b (Extavia)	44.91	30.74%	30.00%	28.00%	67.85%
natalizumab	43.38	20.21%	40.72%	32.37%	25.38%
teriflunomide	39.43	26.26%	26.52%	21.12%	49.54%
fingolimod	39.39	26.39%	26.52%	19.30%	43.54%
dimethyl fumarate	33.11	24.92%	18.76%	12.98%	20.77%

RxFilter results, disproportionality measures, and RxScores change over time as a result of new case report procurement. As a result, the data you see in this paper may not reflect the latest update. Clients can access updated results through their AdverseEvents Explorer subscription. If you are not a client, please contact us for more information.

Results Summary

RxFilter analysis

It was noteworthy that **dimethyl fumarate** had the lowest percentage of its' case reports for each of the four categories: "Life-threatening," "Hospitalization," "Disability," and "Death." Three of the four highest percentages were obtained by **interferons**. "Life-threatening" ranged from almost no reports for **dimethyl fumarate** to 2.1% for **glatiramer**. ""Hospitalization" showed a 4.2% for **dimethyl fumarate** but a 41.6% for **Avonex**. The percentage range for "Disability" cases had a low of, again, almost no cases for **dimethyl fumarate** to a high of 2.8% for **Betaseron**. **Dimethyl fumarate** was again lowest for "Death" (0.2%) while **Betaseron** had 9.1% of its' cases in that category.

In general, the older drugs (interferons and glatiramer) had higher percentage reporting of their case counts in these four serious categories - when compared to newer medications.

Disproportionality Results of Note

PTs

- Only one drug, **Avonex**, had a disproportionality total of above 2 for "breast cancer," which is not currently disclosed as an adverse event risk on the drug's label.

- **Glatiramer** had the lowest disproportionality total for "fatigue" at just 0.7 while **fingolimod** had the highest with a 5.4.

- **Teriflunomide** (7.6) and **dimethyl fumarate** (5.9) had much higher associations with "diarrhea" than any other drug examined here (range of 0.4 to 1.1).

- For "heart rate decreased," **fingolimod** was a clear outlier with a 25.8.

- "Influenza like illness" was much higher across the **interferons** than other drugs, with a high of 23.0 registered for **Avonex**.

- As expected, "Jc virus test positive" and "PML" showed very large signals for **natalizumab** but **fingolimod** also had associations of note.

- **Fingolimod** was also an outlier for "Lymphocyte Count Decreased" at 56.5 while no other drug went above 2.5.

- Both "cognitive disorder" (9.4) and "memory impairment" (8.2) appeared selectively elevated for **natalizumab**.

- "Suicidal behavior" was virtually absent from all drugs except for **Rebif**, which had a 12.7 disproportionality total.

HLTs

- **Fingolimod** had the only total above 2.0 for "cardiac signs and symptoms."
- The **interferons** and **glatiramer**, as expected, had elevated (3.1 to 11.9) results for "injection site reactions."
- **Avonex** and **Rebif** were the only drugs to show associations with "meningiomas."
- With regard to both "nausea and vomiting symptoms" and "peripheral vascular disorders Nec" **dimethyl fumarate** was an outlier with a 4.1 and 28.3, respectively.
- All the drugs, except **dimethyl fumarate**, had results over 7.1, and up to 38.0 (**Rebif**) for "optic nerve infections and inflammations."
- Other examples of high disproportionality results included: glatiramer for "psychiatric symptoms nec" and **Rebif** and **Avonex** for "uterine neoplasms benign," "uterine neoplasms malignant NEC," and "uterine neoplasms."

HLGTs

- Outliers in these larger groupings of individual AEs include: **Avonex** for "bone and joint therapeutic procedures;" **natalizumab** and **Rebif** for "genitourinary tract disorders nec;" and **Rebif** for "nervous system neoplasms benign," "reproductive neoplasms female benign," and "thyroid gland disorders."
- As with the PT "diarrhea," both **teriflunomide** (2.3) and **dimethyl fumarate** (4.5) had higher associations than other drugs examined here for "gastrointestinal signs and symptoms."
- **Fingolimod** and **Extavia** were the only drugs that had disproportionality totals above 4.0 for "vision disorders."

SMQs

- **Glatiramer** was the only drug that had an association with "anaphylactic/anaphylactoid shock conditions."
- **Fingolimod** was the only drug that had significantly elevated disproportionality totals for: "hematopoietic leukopenia," "retinal disorders," and "skin malignant tumors."
- Both **Rebif** and **Extavia** showed the only associations over 10.0 for "optic nerve disorders."
- **Rebif**, similarly to its elevated result for the HLGT category of "reproductive neoplasms female benign," and its HLT results for "uterine neoplasms benign," "uterine neoplasms malignant NEC," and "uterine neoplasms," it had the highest association with "ovarian malignant tumors."

RxScore analysis

In parallel to many of the results discussed above, the four **interferons** and **glatiramer** all had higher RxScores than the other, mostly newer, drugs. The four **interferons** and **glatiramer**, as a group, had higher "Outcome" and "Adverse Event Seriousness" totals than the newer drugs a well.

The two interferon beta-1a drugs, **Rebif** and **Avonex**, had higher scores than the two interferon beta-1b drugs, **Betaseron** and **Extavia**.

Dimethyl fumarate was a clear outlier in the fact that it had a much lower RxScore than the other RRMS drugs examined here.

Conclusion

Pre-marketing clinical trials are the established means for determining a drug's safety and efficacy during the approval process, but they are by no means perfect. When a new drug comes to market a more heterogeneous population uses it and, accordingly, real-world side effects begin to appear. Accordingly, healthcare decision makers need safety tools that reflect a given medications effects in these real-life populations. We believe that the use of the platforms discussed here meet such needs.

Given the varied natures of DMTs for RRMS we wanted to explore AE profiles of the drugs, both old and new. Using the methods outlined here we were able to detail real-world side effect data across RRMS medications

Our review of post-approval case report data for RRMS medications suggest disproportionally elevated reporting of many AEs that can adversely affect treatment adherence and quality of life for patients.

Our analyses of post-marketing adverse event data regarding disease modifying RRMS drugs suggest that: 1) in general, the older-generation drugs, particularly the **interferons**, have inferior safety profiles when compared to newer drug regimens, 2) **dimethyl fumarate** has a very positive safety profile compared to its peers (except for elevated disproportionality regarding peripheral vascular disorders and gastrointestinal issues), 3) while a significant portion of MS patients exhibit cognitive deficits due to the disease itself, we found two MS drugs, **natalizumab** and **Avonex**, that exhibited elevated reporting for "cognitive disorder" and "memory impairment" when compared to their peers, 4) there is an elevated association with "suicidal behavior" for only one interferon drug, **Rebif**, and both **Rebif** and **Extavia** showed increased associations with "depression and suicide/self-injury" when compared to their peers, 5) patients on fingolimod might need monitoring for lymphocyte and cardiac abnormalities, 6) **Rebif** and **Extavia** should be prescribed with caution to patients prone to optic nerve disorders, and 7) the link between PML and **natalizumab** was confirmed.

These results are based upon publicly available FAERS data (last update Q3 2013) supplemented with more recent FAERS data obtained via our Freedom of Information Act inquiries (current to May 12, 2014). These efforts to obtain and analyze the most current, non-public, FAERS data underscore our policy of providing clients with the most up to date and relevant post-marketing safety information.

Disclaimers & Limitations

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Given the breadth of systems that MS can affect, some of the AEs analyzed here might be associated with the disease itself and perhaps not directly caused by the administered drug(s). In order to lessen the impact of such disorder-related adverse events, however, we analyzed across drug classes.

In general, post-marketing data may be subjected to biases such as underreporting, stimulated reporting, and confounding by comorbidities. An adverse event report does not definitively ascertain causality. Patients must always first consult with their physician before making any changes, whatsoever, to the medications that they take.

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Appendix – FDA-Approved Indications for each Drug

Drug	Approval Date	Approved Indications
dimethyl fumarate (Tecfidera) *twice-daily delayed-release oral capsule*	3/27/2013	For the treatment of patients with relapsing forms of multiple sclerosis
fingolimod (Gilenya) *once-daily oral capsule*	9/21/2010	For the treatment of patients with relapsing forms of multiple sclerosis to reduce the frequency of clinical exacerbations and to delay the accumulation of physical disability
glatiramer acetate (Copaxone) *dosed daily or 3 times a week depending on strength of SQ injection*	12/20/1996	For the treatment of patients with relapsing forms of multiple sclerosis
interferon beta-1a (Avonex) *once-weekly IM injection*	5/17/1996	For the treatment of patients with relapsing forms of multiple sclerosis to slow the accumulation of physical disability and decrease the frequency of clinical exacerbations. Patients with multiple sclerosis in whom efficacy has been demonstrated include patients who have experienced a first clinical episode and have MRI features consistent with multiple sclerosis.
interferon beta-1a (Rebif) *3 times a week SQ injection*	3/7/2002	For the treatment of patients with relapsing forms of multiple sclerosis to decrease the frequency of clinical exacerbations and delay the accumulation of physical disability
interferon beta-1b (Betaseron) *dosed every other day SQ injection*	7/23/1993	For the treatment of relapsing forms of multiple sclerosis to reduce the frequency of clinical exacerbations. Patients with multiple sclerosis in whom efficacy has been demonstrated include patients who have experienced a first clinical episode and have MRI features consistent with multiple sclerosis.
interferon beta-1b (Extavia) *dosed every other day SQ injection*	8/14/2009	For the treatment of relapsing forms of multiple sclerosis to reduce the frequency of clinical exacerbations. Patients with multiple sclerosis in whom efficacy has been demonstrated include patients who have experienced a first clinical episode and have MRI features consistent with multiple sclerosis.
natalizumab (Tysabri) *dosed every 4 weeks IV infusion*	11/23/2004*	• Tysabri is indicated as monotherapy for the treatment of patients with relapsing forms of multiple sclerosis. • Tysabri is approved for inducing and maintaining clinical response and remission in adult patients with moderately to severely active Crohn's disease with evidence of inflammation who have had an inadequate response to, or are unable to tolerate conventional CD therapies and inhibitors of TNF- α
teriflunomide (Aubagio) *once-daily oral tablet*	9/12/2012	For the treatment of patients with relapsing forms of multiple sclerosis

** natalizumab was originally FDA approved on 11/23/2004 but was withdrawn from the market in 2005 after it was linked to cases of PML upon co-administration with an immunosuppressive drug. It was returned to the US market in 2006.*