PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	The impact of drug diversity on treatment effectiveness in relapsing-remitting multiple sclerosis (RRMS) in Germany between 2010 and 2018: real-world data from the German NeuroTransData Multiple sclerosis registry
AUTHORS	Braune, Stefan; Rossnagel, Fabian; Dikow, Heidi; Bergmann, Arnfin; Study Group, NeuroTransData

VERSION 1 – REVIEW

REVIEWER	Domenico Plantone ASL BA, Neurology Unit
REVIEW RETURNED	26-Feb-2021

GENERAL COMMENTS	In this paper the authors evaluated the impact of drug diversity on treatment effectiveness in relapsing-remitting multiple sclerosis in Germany, analyzing real world data of the NeuroTransData (NTD) MS registry between 1 Jan 2010 and 30 Jun 2019. They considered three time periods: 2010–2012, 2013–2015, and 2016–2018. They found that an increasing proportion of RRMS patients were treated with DMTs and treatment was initiated sooner after diagnosis of MS, between 2010 and 2018. They described the higher percentage of switch induced by the introduction of oral DMTs. Moreover, they also highlighted the continuous decrease of annualized relapse rates, less frequent EDSS progression and increasing periods without relapse, EDSS worsening and with stability of no-evidence-of-disease-activity (NEDA) 2 and 3 criteria, lower conversion rates to secondary progressive MS (SPMS) on oral and on injectable DMTs comparing the three time periods. In my opinion the paper is of great importance and has significant value for all specialists involved in the treatment of multiple sclerosis. However, there are important limitations that should be improved. 1. The three time periods were appropriately chosen. However, when considering the period between 1 January 2010 and 30 June 2019, the 2017 revisions of the McDonald criteria for the diagnosis of multiple sclerosis must be at least mentioned (Thompson AJ et al, 2018). The paper was published online on the 21st of December 2017 and certainly had an impact. 2. The authors need to define “high-disease activity DMTs” 3. When they consider the decrease of annualized relapse activity it is not clear what they want to say. Moreover orals may be discussed separately in this context. 4. The definition of NEDA 2 and NEDA 3 should be discussed in the methods.

	5. The definition of SPMS and therefore the criteria to diagnose it has been matter of debate in the 2010-2018 time period and therefore the authors should clarify how they diagnosed SPMS.

REVIEWER	D Baronchini Sant'Antonio Abate Hospital Gallarate, Multiple Sclerosis Study Center
REVIEW RETURNED	15-Mar-2021

GENERAL COMMENTS	This paper aims to describe how the availability of new DMTs has changed multiple sclerosis (MS) management and prognosis. Subjects of the research are german MS patients enrolled in a large national registry. Three time periods are compared (2010-2012, 2013-2015, 2016-2018), corresponding to new DMTs approval in Germany. The results show that prognosis is improving over time, as well as therapy management (e.g. treatment allocation, persistence on therapy). This study tried to answer a very important question, but there are crucial methodological concerns that, unfortunately, make it uninformative. Moreover, data presentation is frequently not clear or poor, especially in text and tables, and English language should be widely revised. The major methodological concern is the lack of inferential statistical analyses: it seems that the authors decided to use only descriptive statistics, but this prevents to draw any conclusion about the differences between the time periods examined. In particular, in time to event analyses it is essential to run a multivariate analysis to avoid bias. Other important limitations are lack of inclusion and exclusion criteria (how the authors chose the 17,000 subjects over the 68,400 in the registry?), lack of a clear definition of what the three time periods were about (MS onset? MS diagnosis? First DMT initiation?), and lack of a clear explanation of important outcomes (e.g. NEDA-2 and NEDA-3, baseline timepoint with respect to the time to EDSS progression, secondary progression MS definition criteria). Also, it is not correct to “compare” ARR during therapy without considering ARR pre-therapy; actually, the higher ARR found in 13-15 index period could be secondary to chance, because MS patients receiving infusion at that time were intrinsically more active than MS patients in the other index periods). In results section there are important discrepancies between the data, for example: • In table 2 the total number of included patients is 12,181, while in the text is 17,553 • In table 2, observing months of MS duration, it seems that DMTs were started later in index period 13-15 and 16-18 than in 10-12 (as “index event” is defined as DMT initiation), but in the text is stated the opposite; • In table 4 is indicated a time to EDSS progression of 209 months for index period 16-18, about 17 years…how can be possible with an observation of 2-3 years?? Maybe, their MS onset occurred many years before DMTs initiation? If it is so, why so many years passed before starting a DMTs? Maybe it wasn’t the first DMT, but in that case, how can be attributed any effect of MS improving to index period 16-18?

	Moreover, the discussion lacks some basic points, such as an initial paragraph summarizing the results, a paragraph dedicated to the limitations of the study (too many!), an adequate contextualization of the main results with respect to the scientific literature on the subject. In conclusion, although research goals were very interesting and the chosen outcomes were correct, there are too many methodological limitations to significantly address those goals. Furthermore, data presentation is rather confusing.

REVIEWER	Dejan Jakimovski State University of New York at Buffalo
REVIEW RETURNED	22-Mar-2021

GENERAL COMMENTS	The manuscript by Braune et al. presents real-world treatment data derived from the German NeuroTransData multiple sclerosis (MS) registry which cumulatively included ~230.000 visits from 17.500 relapsing-remitting (RR)MS patients. The manuscript is well written and provides important information for MS care providers, researchers, and industry partners alike. I congratulate the German effort in developing a unified reporting system that can produce such analysis. My comments for further improvement of the manuscript can be found hereafter: 1. The Authors should expand on the findings that the trend of lower annualized relapse rate is present in all medications (except the infusion-type). For example, the injectable treatments have not significantly changed since their implementation in the field and such incremental efficacy cannot be expected purely from the DMT intervention alone. Given that the annual relapse rate (and disability progression) is apparently decreasing as a natural course of the disease, how are these factors accounted for? Some example references: - Steinvorth SM, Rover C, Schneider S, Nicholas R, Straube S, Friede T. Explaining temporal trends in annualised relapse rates in placebo groups of randomised controlled trials in relapsing multiple sclerosis: systematic review and meta-regression. Mult Scler 2013;19:1580-1586. - Nicholas R, Straube S, Schmidli H, Pfeiffer S, Friede T. Time-patterns of annualized relapse rates in randomized placebo-controlled clinical trials in relapsing multiple sclerosis: a systematic review and meta-analysis. Mult Scler 2012;18:1290-1296. - Nicholas RS, Han E, Raffel J, Chataway J, Friede T. Over three decades study populations in progressive multiple sclerosis have become older and more disabled, but have lower on-trial progression rates: A systematic review and meta-analysis of 43 randomised placebo-controlled trials. Mult Scler 2019;25:1462-1471. This can be due to various non-DMT-related reasons including better physical care with exercise, diet and psychological interventions, better management of comorbidities, smoking cessation, etc. 2. The lack of such ARR and CDP decline in RRMS patients that were treated with infusion-based treatments (natalizumab and alemtuzumab) can be attributed to the nature of the aggressive

	disease that requires such DMTs. Since not all patients start equal when prescribed a DMT (severity of the attack, topographical differences between transverse myelitis-type of relapse when compared to optic neuritis), these DMTs are reserved for severe patients that have worse future outlook. 3. Based on Table 1, I can assume that there is a significant influx of newly-diagnosed MS patients that significantly influence the clinical landscape (younger age, lower disability, shorter disease duration). The early disease period in new patients is commonly free of disability progression and can significantly skew the findings to favor the 16-18 group. This should be accounted for in the analysis and commented on in the Discussion section. 4. The decrease in RRMS patients switching to SPMS is similarly biased by the newly diagnosed patients in the later groups. This also seen by the fact that the time to SPMS remains 18 years, something that is reported as part of the natural history of the disease. Confavreux C, Vukusic S (2006) Natural history of multiple sclerosis: a unifying concept. Brain 129:606–616 For example, a report by the EPIC study showed that the transition of SPMS has significantly decreased where ~15-20 of patients transition to SPMS over 18 years. University of California SFMSET, Cree BA, Gourraud PA, et al. Long-term evolution of multiple sclerosis disability in the treatment era. Ann Neurol 2016;80:499-510. Therefore, I would personally suggest removing this from the abstract and additionally discussing the limitations of such analysis in the Discussion part of the manuscript. Lastly, clarification regarding the operational criteria for the transition of SPMS is needed. Moreover, many patients potentially switch to SPMS in concurrence with DMT discontinuation, or the DMT discontinuation occurs before the transition. How were these aspects accounted for by the analysis of patients switching to SPMS while on DMT? 5. Page 8, line 44: Please clarify the sentence regarding the ratio of DMT types by the application. Were in the 10-12 period the DMT distribution included 88% injectables, 13% oral, and 12% infusion? The percentages don't add up for any time-period or DMT type. Similarly for Page 9; line 4. 6. What is the proportion of untreated RRMS patients throughout the different periods? Is this population present in the database and how were they incorporated? 7. Please double-check the female ratio during the 2016-2018 period in Table 1.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

1. ***The three time periods were appropriately chosen. However, when considering the period between 1 January 2010 and 30 June 2019, the 2017 revisions of the McDonald criteria for the diagnosis of multiple sclerosis must be at least mentioned (Thompson AJ et al, 2018). The paper was published online on the 21st of December 2017 and certainly had an impact****.***

The 2017 revision of the McDonald criteria for the diagnosis of MS, published in 2018, redefined criteria for MRI criteria to fulfill dissemination in time and space and the role for diagnosis of CSF specific oligoclonal bands. In summary the changes enabled an earlier diagnosis of proven MS. Traditionally in Germany almost all MS suspected patients undergo CSF diagnostic, which limits the impact of this revision on daily routine in our German cohort. The last period analyzed covers patients treate between 2016 to 2018. All RRMS patients, not only newly diagnosed patients were included. So it can reasonably expected, that only a very small number of patients of the total cohort was added based on the new criteria. There is no reason to expect, that the choice of treatments is affected by the new diagnostic criteria.

Also based on other suggestions in the reviews a section on definition of patient populations was added.

2. ***The authors need to define "high-disease activity DMTs"***
   Definition was added.

3. ***When they consider the decrease of annualized relapse activity it is not clear what they want to say. Moreover orals may be discussed separately in this context*.**
   Wording was optimized.

4. ***The definition of NEDA 2 and NEDA 3 should be discussed in the methods*.**
   Definitions of NEDA 2 and 3 were added in the methods section.

5. ***The definition of SPMS and therefore the criteria to diagnose it has been matter of debate in the 2010-2018 time period and therefore the authors should clarify how they diagnosed SPMS.***
   A section on definition of patient populations was added including the definitions oft he MS subpopulations.

Reviewer: 2

The major methodological concern is the lack of inferential statistical analyses: it seems that the authors decided to use only descriptive statistics, but this prevents to draw any conclusion about the differences between the time periods examined. In particular, in time to event analyses it is essential to run a multivariate analysis to avoid bias.

This study is descriptive by nature. The intention of this study was not to perform a statistical comparison of clinical efficacy between the periods of time. Such an analysis requires a complete different approach, for example including state of the art propensity score matching of baseline characteristics of the different populations. On the other hand we did not intend to draw conclusions from a sample and generalize them a more genral population. While descriptive statistics focus on describing the visible characteristics of a dataset (a population or sample), inferential statistics focus on making predictions or generalizations about a larger dataset, based on a sample of those data. Therefore inferential statistics use a random sample of data taken from a population to describe and make inferences about the total population. This is not the intention of this analysis.

Other important limitations are

lack of inclusion and exclusion criteria (how the authors chose the 17,000 subjects over the 68,400 in the registry?)

A section „patient population“ with inclusion and exclusion criteria as as well as diagnostic criteria was added. In addition to information already provided elsewhere, it was stated for further clarification also in this section, that for the analysis of treatment effects patients with RRMS were included in whom treatment with a DMT was initiated in one of the three time periods defined.
The number of 68.400 patients was wrong and deleted. In an copy and paste error the sums of all columns in this table were calculated, which was not correct for the total number of patients, as patients were observed over longer periods of time. The definition of the different patient groups was made clearer in the manuscript.

lack of a clear definition of what the three time periods were about (MS onset? MS diagnosis? First DMT initiation?)

The rational for the definition of the three time periods is given in the section „Data analysis“. Each period reflects different spectra of DMTs available during the respective period. Patients in whom a treatment with a DMT was initiated in one of the three periods were identified and included. The manuscript was revised to clarify this more clearly.

lack of a clear explanation of important outcomes (e.g. NEDA-2 and NEDA-3, baseline timepoint with respect to the time to EDSS progression, secondary progression MS definition criteria).

The definitions of NEDA-2 and NEDA-3 were added in the Methods section.
The definition of secondary progressive MS was added in the new section „patient population“.

Also, it is not correct to “compare” ARR during therapy without considering ARR pre-therapy; actually, the higher ARR found in 13-15 index period could be secondary to chance, because MS patients receiving infusion at that time were intrinsically more active than MS patients in the other index periods).

The intention of this study was not to perform a statistical comparison of clinical efficacy between the periods of time. Such an analysis requires a complete different approach, for example including state of the art propensity score matching of baseline characteristics. This is a descriptive approach to demonstrate changes in overall populations being treated in times with different choices of DMTs. The aim was not provide a comparison between different DMTs, but to describe the effects also of ARR of a broader choice of DMTs over time.

In results section there are important discrepancies between the data, for example:

- ***In table 2 the total number of included patients is 12,181, while in the text is 17,553***

The manuscript was revised and definitions of the different populations should now be clearer.

Definitons were added in the new section „patient population“. Also in the results section the manuscript was improved to improve understanding of the population referred to.

- ***In table 2, observing months of MS duration, it seems that DMTs were started later in index period 13-15 and 16-18 than in 10-12 (as "index event" is defined as DMT initiation), but in the text is stated the opposite;***

It is correct that mean times between diagnosis of MS and initiation of a DMT were longer in time periods 2013-2015 and 2016-2018 versus 2010-2012, including all DMTs at all stages of disease. The statement in the text refers to the time interval between first symptom of MS and the start of the very first DMT in individual patients showing a continous decline of this interval between time periods.

- ***In table 4 is indicated a time to EDSS progression of 209 months for index period 16-18, about 17 years…how can be possible with an observation of 2-3 years?? Maybe, their MS onset occurred many years before DMTs initiation? If it is so, why so many years passed before starting a DMTs? Maybe it wasn't the first DMT, but in that case, how can be attributed any effect of MS improving to index period 16-18?***

The legend of table 4 states „months from first symptom of RRMS to 6mCDP in these strata.“. So the 209 months refer to the time from first symptom of RRMS until reaching a 6mCDP with a minimum EDSS of 5 in this column. The stratification by the occurence of the index event in one of the three time periods is of course not identical with the overall observation periods of patients. The mean duration of follow-up was 5.07 years (SD 4.46) (see section data quality). Typically date of first symptom is captured in most patients before start of clinical documentation in the registry. Homogenetity of follow-up documentation is shown in Table 1.

***Moreover, the discussion lacks some basic points, such as an initial paragraph summarizing the results, a paragraph dedicated to the limitations of the study (too many!), an adequate contextualization of the main results with respect to the scientific literature on the subject*.**

The section on strength and limitations of this study was added after the abstract.

The discussion starts with a brief section on the ongoing discussion on why there is a need and how real-world data can potentially fill the efficacy-effectiveness gap between RCTs and real world usage. We see this as important to define the current scientific and socioeconomic state of discussion as framework for the data presented. Up-tp-date references are provided.

After this small section the data are presented and discussed. Scientific literature for the contextualization of the main results is scarce as this is the first study to address population effects of a series of newly introduced DMTs in RRMS on adherence and clinical effectiveness. As possible other real-world data based studies were cited. There are several studies investigating the changes of baseline characteristics of clinical studies in MS over time, f.e. as cited by reviewer 3, but their methodological approach does not fit the one of this study.

Reviewer: 3

1. ***The Authors should expand on the findings that the trend of lower annualized relapse rate is present in all medications (except the infusion-type). For example, the injectable treatments have not significantly changed since their implementation in the field and such incremental efficacy cannot be expected purely from the DMT intervention alone. Given that the annual relapse rate (and disability progression) is apparently decreasing as a natural course of the disease, how are these factors accounted for?***

- ***Nicholas R, Straube S, Schmidli H, Pfeiffer S, Friede T. Time-patterns of annualized relapse rates in randomized placebo-controlled clinical trials in relapsing multiple sclerosis: a systematic review and meta-analysis. Mult Scler 2012;18:1290-1296.***

- ***Nicholas RS, Han E, Raffel J, Chataway J, Friede T. Over three decades study populations in progressive multiple sclerosis have become older and more disabled, but have lower on-trial progression rates: A systematic review and meta-analysis of 43 randomised placebo-controlled trials. Mult Scler 2019;25:1462-1471.***

This can be due to various non-DMT-related reasons including better physical care with exercise, diet and psychological interventions, better management of comorbidities, smoking cessation, etc.

There is some literature on changes of ARR during clinical trials over time. Nicholas et al 2012 investigated the ARR during the course of clinical trials within 2 years of trial duration. This is a different perspective than our study. Nicholas RS reported in 2019 reported on progressive MS, not RRMS: „Over three decades, Progressive Multiple Sclerosis populations changed and are now older, with a longer disease duration and more disability, with lower on-trial progression rates.“ Our study included patients with RRMS not progressive MS.

Stellmann et al 2012 concluded: „Up to now all analysed predictors failed to satisfactorily explain the lowering of relapse rates in phase-3 trials over the last decades.“ Smaller changes were observed for EDSS progression in placebo cohorts (Roever et al. 2015), while we looked at patients on DMTs.

In our study baseline characteristics regarding age, EDSS, relapse rate and MS duration differed only slightly between the three patient strata of three time periods (see table 2). There certainly was no trend towards lower relapse activity before treatment initiation between the groups. Mean values for age and MS duration were similar over time. Still disease activity on therapy developed as shown. The impact of non-medical inventions on the course of MS remains unknown. Our registry does not capture such data. The possible impact of unknown confounders was mentioned in the section on „Strength and Limitations“.

2. The lack of such ARR and CDP decline in RRMS patients that were treated with infusion-based treatments (natalizumab and alemtuzumab) can be attributed to the nature of the aggressive disease that requires such DMTs. Since not all patients start equal when prescribed a DMT (severity of the attack, topographical differences between transverse myelitis-type of relapse when compared to optic neuritis), these DMTs are reserved for severe patients that have worse future outlook.

This is exactly also our understanding, that natalizumab and alemtuzumab, used in very highly active patients, achieve very satisfying control of disease activity. In this clearly defined population this effect is constant over time, but also not related to change in a greater choice of DMTs in this segment with these particular patients.

3. Based on Table 1, I can assume that there is a significant influx of newly-diagnosed MS patients that significantly influence the clinical landscape (younger age, lower disability, shorter disease duration). The early disease period in new patients is commonly free of disability progression and can significantly skew the findings to favor the 16-18 group. This should be accounted for in the analysis and commented on in the Discussion section.

The proportion of newly diagnosed RRMS patients per time period can reasonably seen as constant. Mean duration of MS at initation of a new DMT were comparable between the three time periods with a trend to longer durations between diagnosis of MS and initiation of DMT in 2013-2015 and 2016-2018 versus 2010-2012 underlining the constant proportion also of this subgroup of patients. A dysproportionate increase of new MS patients whould have induced decreasing durations of MS on average. The mean younger age in the 2016-2018 group was even associated with a longer MS duration compared the 2010-2013 population.

4. The decrease in RRMS patients switching to SPMS is similarly biased by the newly diagnosed patients in the later groups. This also seen by the fact that the time to SPMS remains 18 years, something that is reported as part of the natural history of the disease.

Confavreux C, Vukusic S (2006) Natural history of multiple sclerosis: a unifying concept. Brain 129:606–616 For example, a report by the EPIC study showed that the transition of SPMS has significantly decreased where ~15-20 of patients transition to SPMS over 18 years.

University of California SFMSET, Cree BA, Gourraud PA, et al. Long-term evolution of multiple sclerosis disability in the treatment era. Ann Neurol 2016;80:499-510.

Therefore, I would personally suggest removing this from the abstract and additionally discussing the limitations of such analysis in the Discussion part of the manuscript.

The proportion of newly diagnosed RRMS patients per time period can reasonably seen as constant. Mean duration of MS at initation of a new DMT were comparable between the three time periods with a trend to longer durations between diagnosis of MS and initiation of DMT in 2013-2015 and 2016-2018 versus 2010-2012 underlining the constant proportion also of this subgroup of patients. A dysproportionate increase of new MS patients whould have induced decreasing durations on average. Smaller fluctuations of an overall constant number of newly diagnosed MS patients are highly unlikely to cause such a „thinning“ effect to reduce switches from RRMS to SPMS on DMT from 4.25% in 10–12, to 1.97% in 13–15, and to 1.46% in 16–18. Cree et al reported a mean duration from

onset of MS to SPMS of 16.8 years, corresponding with 17.8 years in our study. Thank you for this reference. It was included in the manuscript. Therefore we kept the statement on this trend with reduction of frequencies to progress from RRMS to SPMS over time in the abstract and the discussion section. The necessity to validate this results as longer observation periods on new DMTs will becom available was added to the manuscript.

Lastly, clarification regarding the operational criteria for the transition of SPMS is needed.

The question of diagnostic criteria of SPMS was added to the manuscript in the new section on „Patient population".

Moreover, many patients potentially switch to SPMS in concurrence with DMT discontinuation, or the DMT discontinuation occurs before the transition. How were these aspects accounted for by the analysis of patients switching to SPMS while on DMT?

The effect of DMTs in detail and overall and the question of adherence would be an interesting ans meaningful full new project.

5. Page 8, line 44: Please clarify the sentence regarding the ratio of DMT types by the application. Were in the 10-12 period the DMT distribution included 88% injectables, 13% oral, and 12% infusion? The percentages don't add up for any time-period or DMT type. Similarly for Page 9; line 4.

Numbers are correct with total numbers summing up to more than 100% DMTs per period of time as some patients received more than one DMT in this period of time. The excess beyond 100% correlates with higher switching activity in 2013-2015, and again lower frequency in 2016-2018, as shown on page 9, line 4 ff..

Extra information was included in the manuscript on page 8.

6. What is the proportion of untreated RRMS patients throughout the different periods? Is this population present in the database and how were they incorporated?

Yes, the population of untreated MS patients is also captured in the NTD MS registry. This group of patients was not part of this study. In section „Treatment acceptance" the decreasing proportion of untreated RRMS patients is shown. First insights show very heterogeneous clinical characteristics in this population, as the motivation to refuse disease modyfying therapies is quite heterogeneous. These questions must be adressed in a different project.

7. Please double-check the female ratio during the 2016-2018 period in Table 1.

It is Table 2. Thank you for detecting this error !! Number was corrected

VERSION 2 – REVIEW

REVIEWER	Domenico Plantone ASL BA, Neurology Unit
REVIEW RETURNED	02-Jun-2021

GENERAL COMMENTS	The authors improved the manuscript and I do not have any further critique.

REVIEWER	Dejan Jakimovski State University of New York at Buffalo
REVIEW RETURNED	07-Jun-2021

GENERAL COMMENTS	I thank the Authors for their responses.