ADHERENCE AND PERSISTENCE OF ONCE- OR TWICE-DAILY ORAL DMDS IN MS:

A SYSTEMATIC REVIEW AND META-ANALYSIS

ISPOR Europe

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Disclosures

- **JN** has received consulting fees for speaking, advising and consulting from: Biogen Idec, EMD Serono, Genzyme, Genentech, Multiple Sclerosis Society of America, MS World and Novartis. She has received research grants from Genzyme, Biogen and Novartis
- **NCE and RAE** are employees of Health Services Consulting Corporation
- **AD** is an employee of Fair Dynamics Consulting and worked on behalf of Health Services Consulting Corporation. Health Services Consulting Corporation received funding from EMD Serono, Inc. to run the analysis
- **MG and ALP** are employees of EMD Serono, Inc., Rockland, MA, USA (a business of Merck KGaA, Darmstadt, Germany)

Background

- Medication adherence remains a challenge among patients with MS
  - Recent studies have demonstrated that real-world adherence and persistence with oral DMDs currently available in the US (fingolimod, dimethyl fumarate, and teriflunomide) may be similar to that of self-injectable DMDs[1–5]
  - Improvements in DMD adherence have the potential to reduce patient and payer burden in terms of improved clinical outcomes and lower medical resource utilization[4,6–8]
- A systematic review and quantification of the overall real-world adherence and persistence with once- or twice-daily oral DMDs would be helpful in understanding the extent of the inadequacies in regards to adherence and persistence
  - Kantor et al. (2018)[9] conducted a systematic review and meta-analysis of real-world persistence with fingolimod
    - The meta-analysis focused on fingolimod, included published studies (n=7) and conference posters (n=17), and only captured studies through 2015
  - This current meta-analysis evaluates all once- or twice-daily oral DMDs, evaluates both adherence and persistence, only includes published studies, and captures studies through April 2018

DMD, disease modifying drug; MS, multiple sclerosis

1. Lanzillo R, et al. *J Neurol.* 2018;265(5):1174–1183; **2.** Ferraro D, et al. *Curr Med Res Opin.* 2018;10:1–12; **3.** Munsell M, et al. *Patient Prefer Adherence.* 2017;11:55–62; **4.** Burks J, et al. *Clinicoecon Outcomes Res.* 2017;9:251–260; **5.** Longbrake EE, et al. *Mult Scler J Exp Transl Clin.* 2016;ePub ahead of print; **6.** Gerber B, et al. *Mult Scler Relat Disord.* 2017;18:218–224; **7.** Yermakov S, et al. *J Med Econ.* 2015;18(9):711–720; **8.** Lizan L, et al. *Patient Prefer Adherence.* 2014;8:1653–1664; **9.** Kantor D, et al. *J Neurol Sci.* 2018;388:168–174.

Objectives

- To conduct a systematic literature review to assess the availability and variability of data on reported once- or twice-daily oral maintenance DMD adherence and/or persistence rates across 'real-world' data sources; and
- To conduct meta-analyses of the rates of adherence and persistence of once- or twice-daily oral maintenance DMDs in patients with MS

DMD, disease modifying drug; MS, multiple sclerosis

Methods – Systematic Literature Review

- A systematic literature review of all studies published between January 2010 and April 2018 that evaluated adherence and/or persistence with oral DMDs was performed
- The search strategy employed DMD product names and various terms for adherence
- *A priori* exclusion criteria were: no primary data (narrative reviews, systematic reviews, meta-analyses, editorials, or reports of study design were excluded); no primary real-world DMD adherence/persistence data; once- or twice-daily oral maintenance DMD adherence/persistence not reported; pediatric studies; non-English studies; and abstract only available
- Two screeners independently reviewed search results and reference lists of selected articles to identify appropriate studies, and a third individual adjudicated any disagreements. Data extraction was also conducted in this manner
- The quality of selected studies was evaluated using a modified version of the Newcastle-Ottawa Scale (per Cochrane Collaboration)
  - Studies were categorized as poor, partial or full quality, based on attainment of criteria such as study design validity, appropriate patient selection and characterization, outcome assessment, and follow-up

DMD, disease modifying drug

Methods – Meta-Analysis

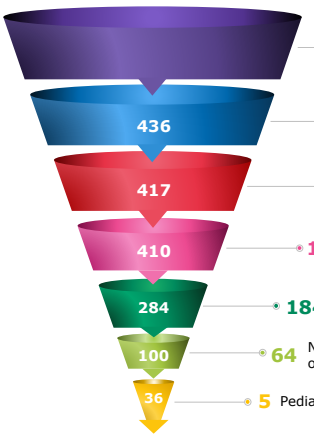
- The endpoints selected for evaluation in the meta-analysis were driven by the availability of data in the published, peer-reviewed literature
- Adherence was evaluated during the follow-up period using the medication possession ratio (MPR) and the proportion of days covered (PDC)
- Discontinuation was evaluated as the proportion of patients that either switched or discontinued all medication. All definitions of discontinuation were considered
- Analyses were conducted for five separate endpoints during a 1-year follow-up period:
  - Mean MPR for patients overall
  - Mean PDC for patients overall
  - Proportion of patients 'adherent' defined as proportion with MPR ≥80%
  - Proportion of patients 'adherent' defined as proportion with PDC ≥80%
  - Proportion of patients who discontinue the initial treatment

Methods – Meta-Analysis Cont'd

- Tests for statistical heterogeneity were used to decide on methods for combining studies
  - Cochran's Q test: if the test is significant, it indicates that heterogeneity exists between the estimates of the population parameter
  - The I^2 statistic was used to help discern the source of the heterogeneity
    - I^2 statistics quantify the share of dispersion across the effects that are due to true heterogeneity rather than sampling error
    - If the I^2 is >50%, then the random effects model (REM) is required to calculate pooled summary estimates of nonadherence by the specific adherence measures
- Egger's test was used to detect publication bias
- A leave-one-out sensitivity analysis was performed by iteratively removing one study at a time to confirm that the findings are not driven by any single study
- Subgroup analyses included US/Ex-US and prospective cohort versus retrospective chart review versus retrospective claims database evaluation

Results – Systematic Literature Review: Study Selection

508
abstracts from published articles + 2 abstracts from referenced lists



74 Published before 2010

19 Non-English studies

7 Non peer-reviewed publications

126 No primary data (106 narrative reviews, 11 systematic reviews, 6 meta-analysis/network meta-analysis, 2 study design with no data, 1 expert opinion

184 No real-world adherence or persistence data

64 No data for oral DMDs (either no oral DMD data or DMDs not evaluated separately)

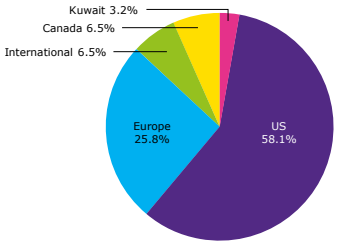
5 Pediatric studies

31 Studies were included in the meta-analysis

DMD, disease modifying drug

Results – Systematic Literature Review: Study Characteristics (n=31)

Origin of Studies*



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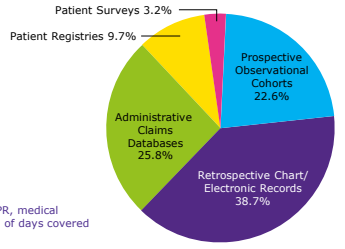
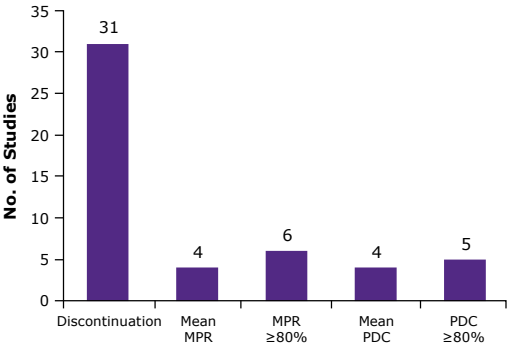


United States
Europe
International
Canada
Kuwait

DMD, disease modifying drug; MPR, medical possession ratio; PDC, proportion of days covered

Adherence/Persistence Outcome Evaluated



Number of studies by DMD

- Fingolimod – 25
- DMF – 19
- Teriflunomide – 10

*Values rounded

Results – Systematic Literature Review: Study Quality

Reference	Study Design and Patient Selection			Outcome Evaluation		
	Ascertainment Intervention/ Study Validity	Patient Selection	Outcome Not Present at Start	Appropriate Measure of Adh/Persist	Adequate Duration of Follow-up	All Patients Accounted Followed Up
Lanzillo R, et al. *J Neurol*. 2018;265(5):1174–1183.	P	F	F	F	F	F
Ferraro D, et al. *Curr Med Res Opin*. 2018;34(10):1803–1807.	P	F	F	F	F	F
Granqvist M, et al. *JAMA Neurol*. 2018;75(3):320–327.	F	F	F	F	F	F
Hua LH, et al. *Mult Scler*. 2018 Mar 1;1352458518765656.	P	P	F	F	P	F
Eriksson I, et al. *Eur J Clin Pharmacol*. 2018;74(2):219–226.	F	F	F	F	F	F
Williams MJ, et al. *Curr Med Res Opin*. 2018;34(1):107–115.	F	P	P	F	F	F
Ernst FR, et al. *Curr Med Res Opin*. 2017;33(12):2099–2106.	P	F	F	F	P	F
Lattanzi S, et al. *J Neurol*. 2017;264(11):2325–2329.	P	F	F	F	F	F
Gerber B, et al. *Mult Scler Relat Disord*. 2017;18:218–224.	F	P	P	F	F	F
Zimmer A, et al. *Patient Prefer Adherence*. 2017;11:1815–1830.	P	F	P	P	P	F
Hersh CM, et al. *Mult Scler J Exp Transl Clin*. 2017;3(3):2055217317715485.	P	F	F	F	F	F
Vollmer B, et al. *Mult Scler J Exp Transl Clin*. 2017;3(3):2055217317725102.	P	P	P	F	P	F
Johnson KM, et al. *J Manag Care Spec Pharm*. 2017;23(8):844–852.	F	P	P	F	F	F
Smoot K, et al. *Mult Scler*. 2017;24(7):942–950.	F	F	F	F	F	F
Burks J, et al. *Clinicoecon Outcomes Res*. 2017;9:251–260.	F	P	P	F	F	F
Munsell M, et al. *Patient Prefer Adherence*. 2016;11:55–62.	F	P	P	F	F	F
Hersh CM, et al. *Mult Scler Relat Disord*. 2016;10:44–52.	P	P	F	F	F	F
Zhovtis Ryerson L, et al. *Ther Adv Neurol Disord*. 2016;9(6):454–461.	P	F	F	F	F	F
Nazareth T, et al. *BMC Neurol*. 2016;16(1):187.	F	F	F	P	F	F
Wicks P, et al. *BMC Res Notes*. 2016;9(1):434.	P	F	F	F	P	P
Warrender-Sparkes M, et al. *Mult Scler*. 2016;22(4):520–32.	F	P	F	F	P	F
Lapierre Y, et al. *Can J Neurol Sci*. 2016;43(2):278–83.	P	P	P	F	F	F
Braune S, et al. *J Neurol*. 2016;263(2):327–333.	F	F	F	F	F	P
Frisell T, et al. *Mult Scler*. 2016;22(1):85–93.	F	P	F	F	F	F
Longbrake EE, et al. *Mult Scler J Exp Transl Clin*. 2016 Jan–Dec;2.	P	P	F	F	P	F
He A, et al. *JAMA Neurol*. 2015;72(4):405–13.	F	F	F	P	F	F
Hersh CM, et al. *Int J Neurosci*. 2015;125(9):678–85.	P	F	F	F	P	F
Bergvall N, et al. *J Med Econ*. 2014;17(10):696–707.	F	P	P	F	F	F
Al-Hashel J, et al. *CNS Drugs*. 2014;28(9):817–24.	P	F	F	P	P	F
Agashivala N, et al. *BMC Neurol*. 2013;13:138.	F	P	P	F	F	F
Ontaneda D, et al. *J Neurol Sci*. 2012;323(1–2):167–72.	P	P	F	F	P	F

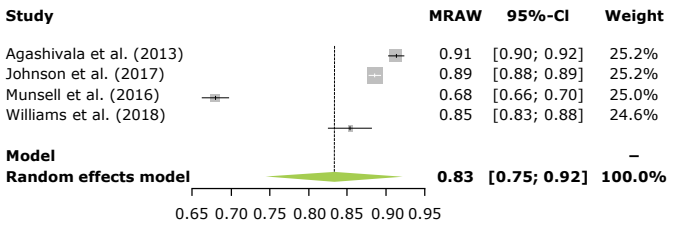
Adh, adherence; Persist, persistence

= full quality = partial quality = poor quality

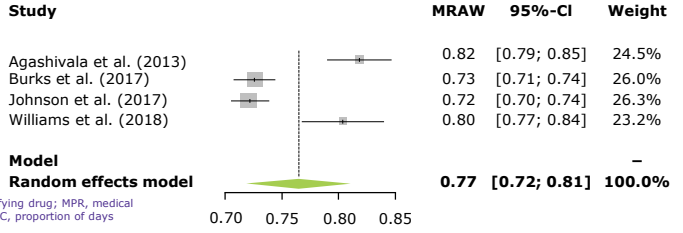
Results – Meta-Analysis: Mean MPR and PDC

At 1 year approximately 1 in 5 patients with MS do not adhere to once- or twice-daily oral maintenance DMDs

Mean Medication Possession Ratio (MPR)



Mean Proportion of Days Covered (PDC)

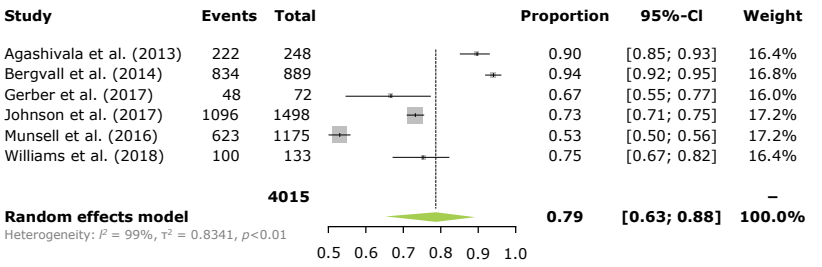


CI, confidence interval; DMD, disease modifying drug; MPR, medical possession ratio; MS, multiple sclerosis; PDC, proportion of days covered

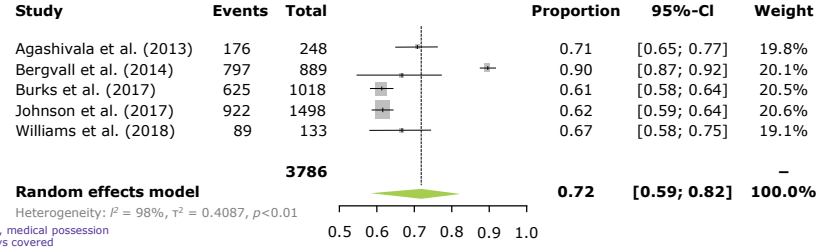
Results – Meta-Analysis: MPR and PDC ≥80%

The pooled MPR ≥80% adherence rate across studies (n=6) was 78.5% and the pooled PDC ≥80% adherence rate (n=5 studies) was 71.8%

Medication Possession Ratio (MPR) ≥80%



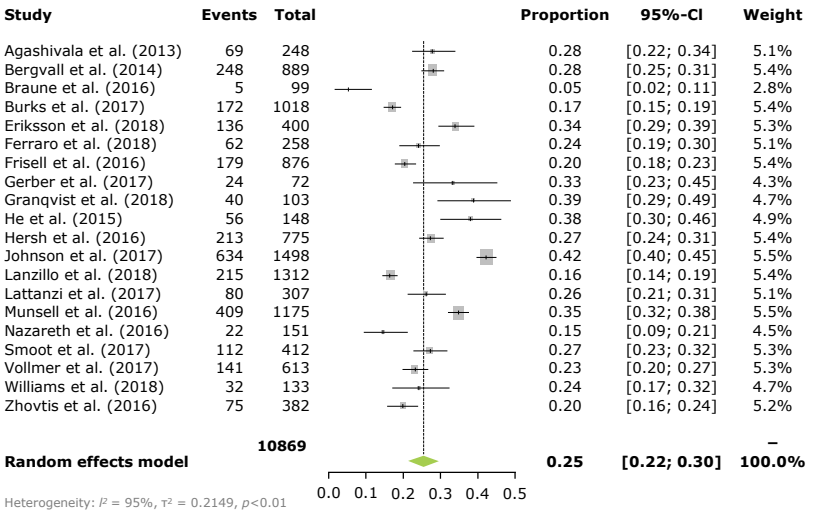
Proportion of Days Covered (PDC) ≥80%



CI, confidence interval; MPR, medical possession ratio; PDC, proportion of days covered

Results – Meta-Analysis: % 1-Year Discontinuation

Approximately 1 in 4 patients with MS discontinue DMD before 1 year



Study	Events	Total	Proportion	95%-CI	Weight
Agashivala et al. (2013)	69	248	0.28	[0.22; 0.34]	5.1%
Bergvall et al. (2014)	248	889	0.28	[0.25; 0.31]	5.4%
Braune et al. (2016)	5	99	0.05	[0.02; 0.11]	2.8%
Burks et al. (2017)	172	1018	0.17	[0.15; 0.19]	5.4%
Eriksson et al. (2018)	136	400	0.34	[0.29; 0.39]	5.3%
Ferraro et al. (2018)	62	258	0.24	[0.19; 0.30]	5.1%
Frisell et al. (2016)	179	876	0.20	[0.18; 0.23]	5.4%
Gerber et al. (2017)	24	72	0.33	[0.23; 0.45]	4.3%
Granqvist et al. (2018)	40	103	0.39	[0.29; 0.49]	4.7%
He et al. (2015)	56	148	0.38	[0.30; 0.46]	4.9%
Hersh et al. (2016)	213	775	0.27	[0.24; 0.31]	5.4%
Johnson et al. (2017)	634	1498	0.42	[0.40; 0.45]	5.5%
Lanzillo et al. (2018)	215	1312	0.16	[0.14; 0.19]	5.4%
Lattanzi et al. (2017)	80	307	0.26	[0.21; 0.31]	5.1%
Munsell et al. (2016)	409	1175	0.35	[0.32; 0.38]	5.5%
Nazareth et al. (2016)	22	151	0.15	[0.09; 0.21]	4.5%
Smoot et al. (2017)	112	412	0.27	[0.23; 0.32]	5.3%
Vollmer et al. (2017)	141	613	0.23	[0.20; 0.27]	5.3%
Williams et al. (2018)	32	133	0.24	[0.17; 0.32]	4.7%
Zhovtis et al. (2016)	75	382	0.20	[0.16; 0.24]	5.2%
		10869			–
Random effects model			**0.25**	**[0.22; 0.30]**	**100.0%**

Heterogeneity: I^2 = 95%, τ^2 = 0.2149, p<0.01

- Among the 31 studies reporting discontinuation, 21 studies reported 1-year discontinuation. Of these studies, 20 were included in the analysis (1 study [Lapierre et al 2016] was excluded because it was not a strictly observational study)

CI, confidence interval; DMD, disease modifying drug

Summary of Meta-Analysis Findings

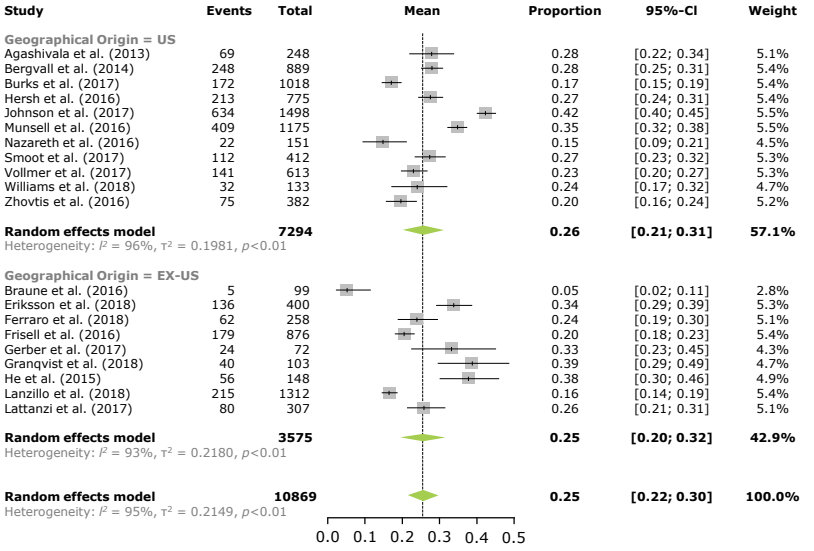
Endpoint*	# Studies	Pooled Value	95%-CI Lower Bound	95%-CI Upper Bound
1-Year mean MPR	4	0.833	0.745	0.921
1-Year mean PDC	4	0.765	0.720	0.811
1-Year MPR ≥80% adherence	6	0.785	0.635	0.885
1-Year PDC ≥80% adherence	5	0.718	0.591	0.819
1-Year discontinuation	20	0.254	0.216	0.297

* Random effects model results

CI, confidence interval; DMD, disease modifying drug; MPR, medical possession ratio; MS, multiple sclerosis; PDC, proportion of days covered

Results – Meta-Analysis: 1-Year Discontinuation Subgroup Analysis US/Ex-US

The geographic subgroup analyses demonstrated that there were essentially no differences between studies with US patients compared to those with ex-US patients

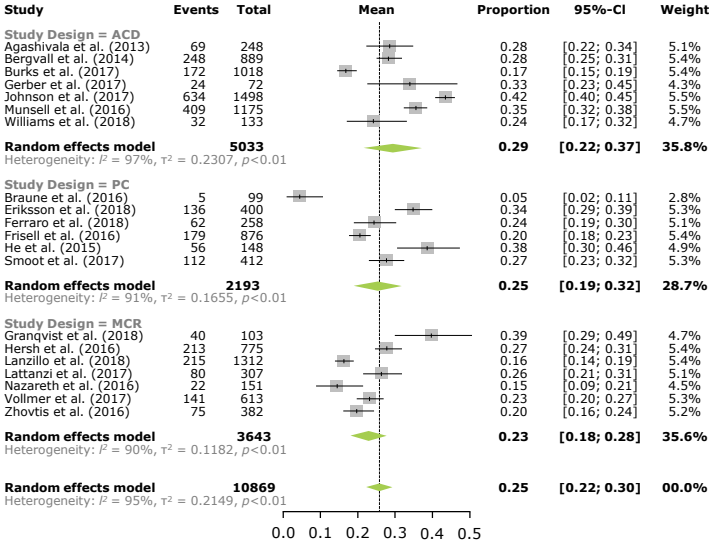


CI, confidence interval

- Among the 31 studies reporting discontinuation, 21 studies reported 1-year discontinuation. Of these studies, 20 were included in the analysis (1 study [Lapierre et al 2016] was excluded because it was not a strictly observational study)

Results – Meta-Analysis: Discontinuation Subgroup Analysis Study Design

The study design subgroup analyses showed overlapping confidence intervals, however numerical differences suggest that this may be an area for further exploration. Administrative claims data may more fully capture discontinuation than prospective cohort studies and retrospective chart reviews.



CI, confidence interval

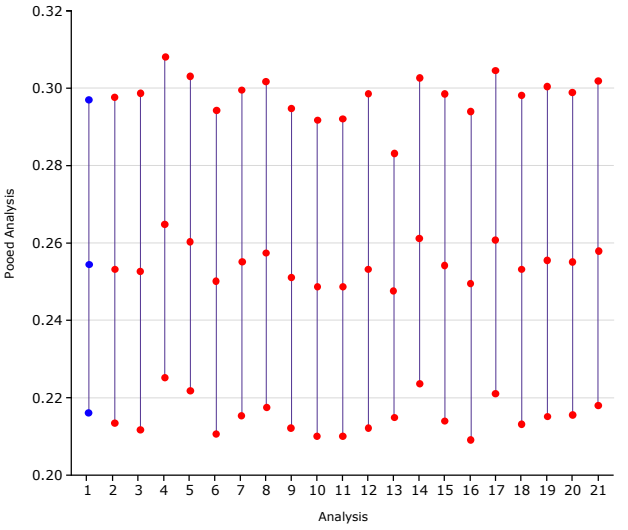
ACD = administrative claims database

PC = prospective cohort

MCR = medical chart review

Results – Meta-Analysis: Discontinuation Leave-One-Out Sensitivity Analysis

The leave-one-out sensitivity analysis confirmed that the findings were not driven by any single study, as removal of individual studies did not affect results.



Analysis Number	Description
1	All 20 documents
2	Omitting Agashivala et al. (2013)
3	Omitting Bergvall et al. (2014)
4	Omitting Braune et al. (2016)
5	Omitting Burks et al. (2017)
6	Omitting Eriksson et al. (2018)
7	Omitting Ferraro et al. (2018)
8	Omitting Frisell et al. (2016)
9	Omitting Gerber et al. (2017)
10	Omitting Granqvist et al. (2018)
11	Omitting He et al. (2015)
12	Omitting Hersh et al. (2016)
13	Omitting Johnson et al. (2017)
14	Omitting Lanzillo et al. (2018)
15	Omitting Lattanzi et al. (2017)
16	Omitting Munsell et al. (2016)
17	Omitting Nazareth et al. (2016)
18	Omitting Smoot et al. (2017)
19	Omitting Vollmer et al. (2017)
20	Omitting Williams et al. (2018)
21	Omitting Zhovtis et al. (2016)

Limitations

- Given that systematic reviews and meta-analyses bring together studies that are diverse both clinically and methodologically, heterogeneity in their results is to be expected (95% confidence intervals showed a wide range of values, particularly for % of patients adherent)
  - Methodological heterogeneity is likely to arise through diversity in patient populations, how measures are defined, treatments administered, duration of follow-up, and study quality
  - This was evident in the assessment of the quality of the included studies, which highlighted how the appraisal of the different studies needed to be adapted for their individual design
  - The significant Cochran's Q result and the I^2 >50% result confirmed the need to use the random effects model
  - The I^2 values with a range of 93.8% to 99.5% are consistent with other published meta-analyses of medication adherence[1–5]
- The limited number of available studies restricted the ability to analyze MPR and PDC adherence in greater detail, and also the ability to perform subgroup analyses across adherence and persistence measures

MPR, medical possession ratio; MS, multiple sclerosis; PDC, proportion of days covered

1. Kantor D, et al. *J Neurol Sci.* 2018;388:168–174; **2.** Durand H, et al. *J Hypertens.* 2017;35(12):2346–2357; **3.** Scheepers LEJM, et al. *Semin Arthritis Rheum.* 2018;47(5):689–702; **4.** Shehab A, et al. *Curr Vasc Pharmacol.* 2018;ePub ahead of print; **5.** Sherrill B, et al. *J Clin Hypertens (Greenwich).* 2011;13(12):898–909

Discussion

- This is the first meta-analysis in MS assessing real-world adherence of multiple oral DMDs
- Findings showed that a proportion of patients with MS do not adhere to once- or twice-daily oral DMDs and a large proportion discontinue DMDs before 1 year
  - Over 1 year, approximately one in five (1/5) patients with MS do not adhere to once- or twice-daily oral maintenance DMDs, and approximately one in four (1/4) discontinue DMDs before 1 year
  - It is essential that healthcare providers understand data on patient adherence, which can help to inform appropriate initial selection of therapeutic agents for patients starting treatment, as well as for those who may need to switch treatment
  - Opportunities to improve adherence and persistence to DMD treatment in patients with MS remain
- With increasing availability of 'real-world' data, future meta-analyses using specific study designs and outcome measures and more homogenous patient populations will allow for more precision in aggregating adherence and persistence data

DMD, disease modifying drug; MPR, medical possession ratio; MS, multiple sclerosis; PDC, proportion of days covered