Objective medication adherence and persistence in people with multiple sclerosis: a systematic review, meta-analysis, and meta-regression

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What is already known about this subject

- Suboptimal medication adherence occurs in approximately 50% of people who require regular medication administration across chronic diseases and is linked with poorer health outcomes and increased healthcare utilization.

- People with multiple sclerosis may be prescribed disease-modifying therapy, which is administered through self-injectable, oral, or intravenous administration routes; injectable and oral administration routes are associated with suboptimal adherence and persistence.

What this study adds

- Medication adherence (12-month comparison) was significantly higher for oral compared to injectable disease-modifying therapies, with no difference in discontinuation rates for oral and injectable disease-modifying therapies.

- Medication adherence remained suboptimal for both oral and injectable disease-modifying therapies despite higher adherence with oral medication, which highlights the ongoing need for medication compliance initiatives.

- Differences in study methodologies, including measurement methods, definitions, and observation lengths, limited the comparative analysis that could be undertaken. The limitations highlight that future research would benefit from protocol consistency.

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ABSTRACT

BACKGROUND: Medication adherence is critical for the realization of pharmacotherapy benefits and reduced healthcare expenditure. Studies have shown up to 60% of people with Multiple sclerosis (MS) experience suboptimal medication adherence, which is associated with poorer health outcomes and subsequent discontinuation. The current systematic review reported on objectively measured adherence and discontinuation rates for self-administered oral and injectable disease-modifying therapies (DMTs).

OBJECTIVES: To identify whether, in people with MS, the introduction of oral DMTs has improved medication adherence when compared with injectable DMTs. The secondary aim was to report synthesized objectively measured medication adherence and persistence rates for both oral and injectable DMTs in MS across varying study durations.

METHODS: Literature searches were conducted through PubMed, Web of Science, Scopus, and PsycINFO. Inclusion criteria were limited to English, peer-reviewed, objective, self-administered DMT articles, published between July 1993 to December 2019. Publications reporting combined intravenous and self-administered DMT data, or that did not account for DMT switching in discontinuation rates, were excluded. Data were synthesized into observation lengths ranging from less than 8 months to greater than 36 months. Meta-analysis and meta-regression were undertaken on both oral and injectable 12-month adherence and discontinuation data.

RESULTS: In total, 61 articles were included; 46 articles examined adherence and 26 examined discontinuation. Twelve-month adherence ranged between 53.0% to 89.2% for oral (N=7) and 47.0% to 77.4% for injectable DMTs (N=7). Results from the meta-analysis and meta-regression show significantly higher pooled mean medication possession ratio (MPR) adherence for oral DMTs (91.0%) when compared to injectable DMTs (77.0%) over 12 months (β=−0.146; 95% CI: −0.263 to −0.029). Results indicate major asymmetry across studies (LFK index: −5.18), proposing the presence of significant publication bias. Mean discontinuation over 12 months was between 10.5% to 33.3% for oral (N=7) and 15.2% to 50.8% for injectable DMTs (N=10), with meta-analysis results indicating the presence of significant heterogeneity (I2 Injectable: 99.5%; I2 Oral: 93.1%) between studies included in each subgroup. However, no appreciable difference in mean discontinuation rates across groups (Injectable: 27%; 95% CI: 19.0%-34.0%; Oral: 24%; 95% CI: 17.0%-31.0%) was found.

CONCLUSIONS: Medication adherence for oral DMTs suggests a significant improvement compared to adherence for injectable DMTs. No significant difference in discontinuation rates between oral and injectable DMTs was found. Oral DMT adherence and persistence studies are limited, given their relatively recent introduction. Suboptimal medication adherence and discontinuation issues remain present for both oral and injectable DMTs. Future studies would benefit from improved consistency in methodology, such as comparable adherence and persistence definitions.

Multiple sclerosis (MS) is a chronic, neurodegenerative disease with a reported 10.4% increase in global prevalence between 1990 and 2016, to over 2.2 million cases.[1,2] While there is no cure for MS, disease-modifying therapies (DMTs),[3,4] reduce annualized relapse rates by 18.0% to 66.0%[5,6] and disability progression by 12.0% to 41.0%.[6]

Optimal medication adherence is crucial to maximize drug efficacy and reduce unnecessary healthcare expenditure. However, World Health Organization[7] data estimates approximately 50% of people with chronic diseases experience suboptimal medication adherence. Medication adherence in MS is no exception. Adherence rates for self-injectable DMTs are reported as between 41% to 88% across varying measurement types,[8] and between 30% to 60% of people with MS discontinue self-injectable DMTs within two years.[9-11]

The introduction of oral DMTs has not resolved the problem. A study assessing one-year adherence and persistence to oral DMTs—fingolimod (FTY), teriflunomide (TFN), and dimethyl fumarate (DMF)—reported that the adherence rate, measured by proportion of days covered (PDC), was less than 80% in 24.6% to 46.9% of participants with discontinuation rates between 25.6% to 50.3%.[12] Studies consistently showed an increased likelihood of suboptimal medication adherence or discontinuation with increasing treatment durations.[13-15]

Medication adherence is "The extent to which a patient acts in accordance with the prescribed interval, and dose of a dosing regimen."[16] Persistence is "The duration of time from initiation to discontinuation of therapy."[16] Discontinuation is the cessation of therapy, which may be initiated by either the clinician or patient.[17] Suboptimal medication adherence may be intentional or unintentional. Intentional suboptimal adherence has been linked to perceived inefficacy,[18] cost,[19] and medication side effects. Side effects vary by DMT, but they may include fatigue, headache, nausea, or diarrhea. Specific to route of administration, injectable DMTs may incur injection site reactions and needle phobia.[3] Forgetting is the most common unintentional reason for suboptimal medication adherence. Factors such as physical disability, cognitive impairment, and depression—all common in MS patients—contribute to medication adherence difficulties.[3,18] Medication adherence may be assessed objectively, using, for example, pharmacy records, or via patient self-report.

Two previous systematic reviews have been undertaken addressing medication adherence and persistence to self-administered injectable DMTs in people with MS,[8,15] both of which predated studies that assessed medication adherence and persistence in oral DMTs. Two recent reviews of oral DMT adherence and discontinuation rates did not compare oral and injectable DMTs to quantify whether oral

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DMTs show improved compliance.[20,21] Given the changed landscape of DMT options, our primary aim was to identify whether oral DMTs, when compared with injectable DMTs, have increased medication adherence and persistence to self-administered DMTs in people with MS. Secondarily, we synthesized objectively measured medication adherence and persistence rates for self-administered oral and injectable DMTs in MS across varying study durations.

Methods

SEARCH STRATEGY

Literature searches were conducted through PubMed, Web of Science, Scopus, PsycINFO, CINHAL (via EBSCOhost), and the Cochrane Library. Key publication reference lists were also searched. The search included articles published from the first approved DMT, on July 23, 1993,[22] through December 31, 2019. The search strategy included all US Food and Drug Administration approved MS DMTs to capture studies reporting both intravenously (IV) and self-administered DMTs, although IV administered DMT data were excluded.

Search terms included: multiple sclerosis, medication adherence, adherence, compliance, concordance, persistence, disease-modifying therapy, disease-modifying treatments, oral medication, treatment, therapy, therapeutics, and drug therapy, as well as each of the DMT generic and brand names. Six search strings were constructed from the search terms incorporating truncations (eg, disease-modifying therap*).

STUDY SELECTION

Inclusion was limited to peer-reviewed articles, in English, assessing medication adherence and persistence for all self-administered oral or injectable DMTs, in adults with MS (≥18 years; any subtype) taken on a regular basis (≥once every two weeks). Studies that did not explicitly account for switching methods were excluded. We additionally excluded conference proceedings abstracts.

DATA EXTRACTION

Abstracts were screened for relevance by two independent investigators (JM, LG), who mutually agreed upon differences. Inter-rater reliability was calculated. Following full-text screening, data were extracted including patients, study, measurement instrument characteristics, adherence and/or persistence/discontinuation results, correlations between adherence/discontinuation, and differences between groups. Extracted adherence values included mean medication possession ratio (MPR) and proportion of days covered (PDC), binary adherence cut-off score, reported at least 80% adherence unless otherwise specified, or effect sizes (ES) and standard errors. Where unavailable, the standard errors were calculated from the standard deviation and sample size. The MPR is the sum of the days' supply for all fills of a given drug in a particular time period, divided by the number of days in the time period. The PDC is the ratio of the number of days covered by the medication in a period, divided by the total number of days in the period. Studies that reported adherence using medication event monitoring systems (MEMS) bottle caps and electronic autoinjectors typically utilized the MPR calculation: medication administered divided by expected medication. Adherence measures that differed from the above were reported according to the specific calculation.
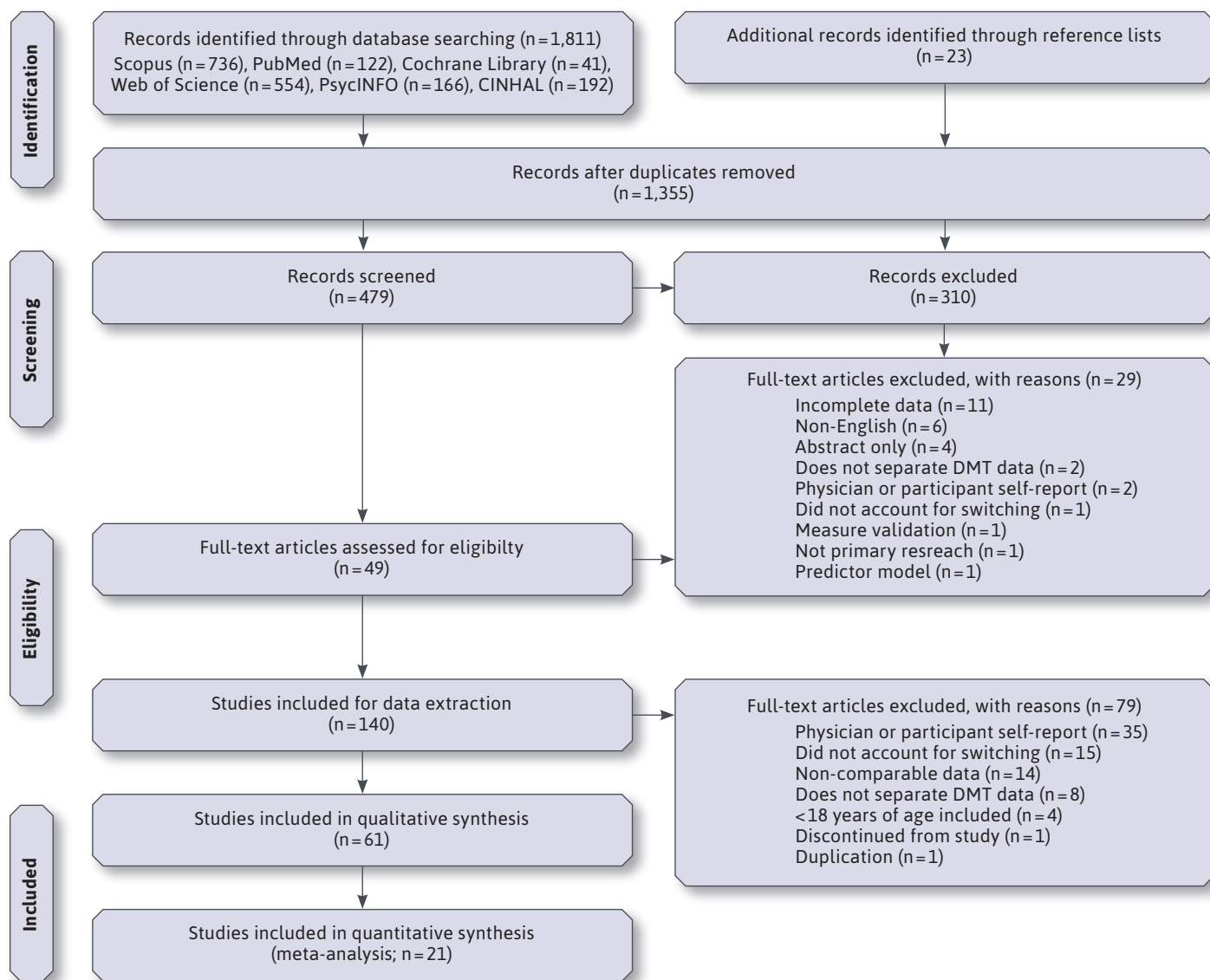
DATA SYNTHESIS AND ANALYSIS

We synthesized adherence and discontinuation studies into four observation lengths, ranging from less than 8 months to greater than 36 months (Supplementary Table 1, 2, 3, available in online article). Where applicable, adherence values for two or more injectable or oral DMTs reported within a study were calculated to form a single injectable or oral value utilizing an online calculator . Only baseline (preintervention) data are reported for intervention studies.

EFFECT SIZE POOLING

Due to an appropriate number of comparative studies, meta-analysis and meta-regression were undertaken for 12-month adherence and 12-month discontinuation. ES for studies were pooled using the inverse variance heterogeneity (IVhet) meta-analysis model,[23] which uses a quasi-likelihood model based variance structure without distributional assumptions and has coverage probabilities for 95% confidence intervals (CI). This model has outperformed the random effect (RE) method and is superior to conventional RE and/or fixed-effect models for inter-study heterogeneity,[23,24] as the IVhet model retains correct coverage probabilities and lower observed variance.[23]

Heterogeneity and consistency were evaluated with Cochran's Q and the I2 statistics, respectively. Practically significant heterogeneity was indicated (I2 > 50%). Asymmetry between meta-analysis studies was examined graphically using doi plot and the Luis Furuya-Kanamori (LFK) index,[25] as the doi plot represents an improvement over the classic funnel plot, while the LFK index outperforms Egger's regression P-value for detection of asymmetry.[25] Both doi plot and LFK indicated major asymmetry between studies, indicating heterogeneity between studies from type, combinations of DMTs, methods adopted, study population heterogeneity, or publication bias. As a result, overall pooled estimates for comparing oral vs injectable DMTs were not calculated. Instead, an IVhet meta-regression

FIGURE 1   PRISMA Flow Chart

Identification

Records identified through database searching (n=1,811)
Scopus (n=736), PubMed (n=122), Cochrane Library (n=41),
Web of Science (n=554), PsycINFO (n=166), CINHAL (n=192)

Additional records identified through reference lists (n=23)

Records after duplicates removed (n=1,355)

Screening

Records screened (n=479)

Records excluded (n=310)

Full-text articles excluded, with reasons (n=29)
Incomplete data (n=11)
Non-English (n=6)
Abstract only (n=4)
Does not separate DMT data (n=2)
Physician or participant self-report (n=2)
Did not account for switching (n=1)
Measure validation (n=1)
Not primary resreach (n=1)
Predictor model (n=1)

Eligibility

Full-text articles assessed for eligibilty (n=49)

Included

Studies included for data extraction (n=140)

Full-text articles excluded, with reasons (n=79)
Physician or participant self-report (n=35)
Did not account for switching (n=15)
Non-comparable data (n=14)
Does not separate DMT data (n=8)
<18 years of age included (n=4)
Discontinued from study (n=1)
Duplication (n=1)

Studies included in qualitative synthesis (n=61)

Studies included in quantitative synthesis (meta-analysis; n=21)

Notes: PRISMA Flowchart of search strategy, with the reasons for exclusion.
Adapted from Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement.
BMJ 2009;339(7716):b2535.

model to examine the heterogeneity in the meta-analysis was used.[26] The Huber-Eicker-White-sandwich error variances generated correct standard errors in meta-regression, equivalent to the IVhet model in meta-analysis. For the 12-month adherence meta-regression, studies were divided into two subgroups: oral DMTs (Group-1, N=6) and injectable DMTs (Group-2, N=8).

Discontinuation studies included in this review reported different discontinuation definitions, including continuous discontinuation of medication for more than 30 days, more than 60 days, more than 90 days, or any discontinuation. Due to limited studies that reported these measures in each group, we clubbed them together irrespective of discontinuation definition. Discontinuation studies were

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analysed in two subgroups: oral DMTs (Group-1, eight data sources; N=7 studies) and injectable DMTs (Group-2, 11 data sources; N=10 studies).

SENSITIVITY ANALYSIS

Given high heterogeneity between the studies, we performed sensitivity analyses to explore the effect of excluding individual studies on the overall pooled estimates and level of heterogeneity. The analyses showed no discernible changes (Supplementary Table 5, available in online article).

Meta-analyses were carried out using MetaXL version 5.3. Meta-regression was performed in Stata.

APPRAISAL TOOL FOR CROSS-SECTIONAL STUDIES (AXIS)

Study reporting quality was assessed using the appraisal tool for cross-sectional studies (AXIS),[27] undertaken by one author (JM). The assessment was cross-checked by a second author (LG).

ETHICS, PROTOCOL REGISTRATION AND REPORTING

This secondary data analysis did not require ethics approval and informed consent. The systematic review was registered with the International Prospective Register of Systematic Reviews (PROSPERO; CRD42019122412) and reported per the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines.[28]

Results

SEARCH SUMMARY

Database searches yielded 1,811 publications (Scopus: 736, PubMed: 122, Cochrane Library: 41, Web of Science: 554, PsychINFO: 166, and CINHAL: 192; Figure 1). Twenty-three additional records were identified from key reference lists. A total of 1,355 duplicates were removed, leaving 479 abstracts screened against inclusion criteria. Inter-rater reliability for abstract inclusion was substantial ($\kappa=0.785$, $P<0.001$).[29] Following mutual adjudication of 46 records, 140 studies underwent full-text screening, and 79 articles were excluded. In total, 38 studies were excluded because they only measured self-reported adherence and/or discontinuation. The remaining 61 studies underwent data extraction and were included in the qualitative synthesis. Forty-six studies examined adherence, and 26 studied examined discontinuation. Twenty-one studies were included in the quantitative analysis.

STUDY CHARACTERISTICS

Study characteristics are displayed in Table 1. Twenty-six studies were conducted in the United States, 10 in Canada,

seven in Italy, three each in Germany, France and Spain, two in Switzerland, and one each in Greece, Sweden, Denmark, as well as one international multisite and two European multisite studies. Forty-four studies were retrospective, 16 prospective, and one had retrospective and prospective observation periods. Data of included studies were primarily collected from database claims (N=22), multicentre or clinic (N=19), database (N=9), administrative (N=6), or clinical data (N=5). Twelve studies examined both injectable and oral DMTs, 40 examined injectable DMTs only, and nine studies examined oral DMTs only. From these studies, 12 examined adherence of oral DMTs and 40 examined the adherence of injectable DMTs. Twenty-six studies examined DMT discontinuation (N=13 oral; N=21 injectable).

Twenty-four studies included participants with relapse remitting MS (RRMS); four included RRMS and secondary progressive MS (SPMS); two included RRMS, SPMS, and primary progressive MS (PPMS); one included RRMS and clinically isolated syndrome (CIS); and one included RRMS, SPMS, and CIS participants. Twenty-nine studies did not report MS subtype. Overall, observation lengths ranged between eight weeks to 18 years, although the majority of studies assessed adherence over 12-month (N=24) and 24-month (N=13) periods. Study sample size ranged between 30 to 50,057 participants. Mean participant age across studies (N=54) ranged between 32.3 to 55.0 years.

BIAS ASSESSMENT

Quality of reporting, assessed with the AXIS[27] (Supplementary Table 4, available in online article), showed studies were clear in their statement of aims. The overall study methodology was appropriate in design, description, and sample size justification. A notable issue with US studies, which could potentially limit generalizability, was the use of insurance claims databases for 20 (76.9%) of 26 studies. One study recruited veterans[30] with a primarily male sample and older mean age than other studies. Ethics approval and consent were obtained for 17 (27.9%) studies, with ethics only obtained for 15 (24.6%), and consent only obtained for six (9.8%) studies. Ethics approval and/or consent was exempt by local laws for 12 (19.7%) studies, while there was no explicit comment about consent or ethics attainment for 11 (18.0%) studies. Study results were adequately described in general. However, as secondary study outcomes, the results were sometimes limited in adherence and/or discontinuation data. Discussions were largely an appropriate reflection of study results, with most studies discussing limitations, albeit some were brief. Generalizability issues were sparsely mentioned. The studies were predominantly funded by pharmaceutical companies (N=35; 57.4%). The authors received honorariums, speaker, consultancy fees or

TABLE 1		Characteristics of Included Objective Studies						
Author, year	Country	Study type	Observation length	Sample size	Age, gender, subtype, MS duration, EDSS	Design/setting	DMT(s)	Comments
Agashivala, 2013[41]	USA	AH, DC	12 months	N = 1,891	Age: M = 45.6, SD = 11.1 years; Gender: 76.4% Female; Subtype: NR; MS duration: NR; EDSS: NR	Retrospective/ database claims	FTY, IFNβ-1b, IFNβ-1a, GA	New oral DMT users
Aungst, 2019[42]	USA	AH	52 weeks	N = 35 (consented); N = 25 (ana-lyzed)	Age: M = 41.1, SD = 11.6 years; Gender: 71.0% Female; Subtype: NR; MS duration: NR; EDSS: NR	Prospective/ multicentre	DMF	
Bayas, 2015[37]	Fifteen European Countries	AH	12 months	N = 912 (safety population); N = 791 (completed)	Age: M = 36.3, SD = 10.3 years; Gender: 73.7% Female; Subtype: RRMS; MS duration: Analyzed subset: N = 710, M = 33.0, SD = 49.8 months; EDSS: M = 1.8, SD = 1.4	Prospective/ multicentre	IFNβ-1a s.c	Commenced IFNβ-1a < 8 weeks prior to study enrollment
Bonafede, 2013[39]	USA	DC	24 months	N = 5,710	Age: M = 44.6, SD = 10.4 years; Gender: 76.6% Female; Subtype: NR; MS duration: NR; EDSS: NR	Retrospective/ database claims	IFNβ-1a, IFNβ-1b, GA, FTY	
Braune, 2016[43]	Germany	DC	24 months; PM: M = 1037.8 (461.2) days	N = 433; PM: N = 198 (99 FTY, 99 iDMT)	Age: M = 40.1, SD = 9.8 years (PM only); Gender: 75.8% Female; Subtype: RRMS; MS duration: M = 7.4, SD = 5.9 years; EDSS: M = 2.3, SD = 1.5	Retrospective/ outpatient clinical data	IFNβ-1a, IFNβ-1b, GA, FTY	1st injectable failed and switched to fingolimod or 2nd injectable. Analysis of 1 and 2 years for persistence; Propensity matched sam-ple persistence and discontinu-ation across available observation days
Bruce, 2010[14]	USA	AH	8 weeks	N = 67	Age: M = 46.2, SD = 10.6 years; Gender: 88.1% Female; Subtype: RRMS; MS duration: M=10.0, SD = 7.8 years; EDSS: M = 2.4, SD = 1.2	Prospective/ MS specialty clinic	GA, IFNβ-1a, IFNβ-1b	
Burks, 2017[13]	USA	AH, DC	12 months	N = 1,018	Age: 18-24 (4.3%), 25-44 (14.2%), 35-44 (30.6%), 45-54 (32.0%), 55-64 (19.0%); Gender: 72.1% Female; Subtype: NR; MS duration: NR; EDSS: NR	Retrospective/ database claims	TFN, FTY, DMF	Injectable data combined intravenous, thus, were excluded

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TABLE 1 | Characteristics of Included Objective Studies (continued)

Author, year	Country	Study type	Observation length	Sample size	Age, gender, subtype, MS duration, EDSS	Design/setting	DMT(s)	Comments
Cerghet, 2010[44]	USA	AH	12 months	N=214 (eligible); N=163 (completed); N=111 (dispensed a DMT)	Age: M=47.5, SD=9.5 years; Gender: 81% Female; Subtype: RRMS; MS duration: M=8.9, SD=6.4 years; EDSS: M=4.9	Retrospective/database claims	GA, IFNβ-1a, IFNβ-1b	
Cohan, 2018[45]	USA	AH	12 months	N=708; N=531 (no switch); N=177 (switch)	Age: No switch: M=47.5, SD=9.9 years. Switch: M=46.8, SD=9.6 years; Gender: 78.5% Female (Switch and no switch groups); Subtype: NR; MS duration: NR; EDSS: NR	Retrospective/database claims	IFNβ-1a, IFNβ-1b	Participants who switched DMTs versus those who remain consistent on one DMT for 12 months
Cohen, 2015[46]	USA	AH	24 months	N=3,151 (enrolled); N=2,966 (baseline); N=2,410 (completed)	Age: M=49.6, SD=9.9 years; Gender: 80.9% Female; Subtype: RRMS, SPMS, PPMS; MS duration: M=9.6, SD=8.3 years; EDSS: M=3.0, SD=2.5	Prospective/specialty pharmacy	GA, IFNβ-1a, IFNβ-1b	
Condé, 2019[47]	France	DC	24 months	N=346	Age: M=44.2, SD=0.9 years; Gender: 80.3% Female; Subtype: RRMS; MS duration: M=10.1, SD=0.8 years; EDSS: M=1.8, SD=0.1	Retrospective/clinical record	DMF, TFN	
D'Amico, 2019[48]	Italy	DC	24 months	N=903 pwRRMS; N=316 (TFN); N=587 (DMF)	Age: M=42.5, SD=10.6 years; Gender: 67.5% Female; Subtype: RRMS; MS duration: M=109.2, SD=84.6 months; EDSS: TFN: 2.0 (1.5-3.5); DMF: 1.5 (1.0-3.0)	Retrospective/multicentre	DMF, TFN	
Defer, 2018[49]	France	AH	M=11.5 years	N=15,039	Age: NR; Gender: 73.9% Female; Subtype: RRMS, SPMS; MS duration: M=11.5, SD=9.7 years; EDSS: NR	Retrospective/multicentre	IFNβ-1a, IFNβ-1b, GA	Only examines first-line injectable DMTs adherence
Deftereos, 2018[50]	Greece	AH	12 months	N=64 (enrolled); N=47 (complete study)	Age: M=36.2, SD=11.2 years; Gender: 78.1% Females; Subtype: RRMS; MS duration: M=2.1, SD=3.0 years; EDSS: NR	Prospective/multicentre	IFNβ-1a s.c	
Degil Esposti, 2017[40]	Italy	AH, DC	36 months	N=1,698	Age: M=40.0, SD=10.7 years; Gender: 69.0% Female; Subtype: NR; MS duration: M=5.9, SD=6.3 years; EDSS: Range, 0-9	Retrospective/administrative database	IFNβ-1a, IFNβ-1b, GA	

TABLE 1	Characteristics of Included Objective Studies *(continued)*							
Author, year	Country	Study type	Observation length	Sample size	Age, gender, subtype, MS duration, EDSS	Design/setting	DMT(s)	Comments
Devonshire, 2016[51]	Canada	AH	12 and 24 weeks	N=162 (enrolled); N=158 (analyzed)	Age: M=37.4, SD=9.8 years; Gender: 75.3% Female; Subtype: RRMS, SPMS; MS duration: M=24.0, SD=57.6 months; EDSS: M=1.8, SD=1.3.	Prospective/ multicentre	IFNβ-1a s.c.	
Duquette, 2019[9]	Canada	AH, DC	24 months	N=26,157 (compliance); N=32,795 (discontinuation)	Age: NR; Gender: NR; Subtype: NR; MS duration: NR; EDSS: NR	Retrospective/ database claims	IFNβ-1a, IFNβ-1b, GA, FTY, DMF, TFN	Demographics not reported
Eriksson, 2018[52]	Sweden	DC	Median=2.5 years	N=400	Age: DMF 1st: M=35.3, SD=9.8. DMF switch: M=40.5, SD=10.1; Gender: DMF 1st: 72.0% Female. DMF switch: 76.0% Female; Subtype: NR; MS duration: NR; EDSS: NR	Retrospective/ regional database	DMF	Compares DMF as 1st line and switch to DMF
Ernst, 2017[53]	USA	DC	24 months	N=450	Age: M=45.5, SD=12.1 years; Gender: 75.8% Female; Subtype: RRMS; MS duration: M=527.6, SD=1600.5 days; EDSS: NR	Retrospective/ administrative data	IFNβ-1a s.c., DMF	
Evans, 2017[54]; 2016[55]	Canada	AH, DC	12-month adherence; M=7.8, SD=4.0 years discontinuation follow-up	N=4,746 (2017); N=4,830 (2016)	Age: M=40.4, SD=10.0 years; Gender: 75.8% Female; Subtype: NR; MS duration: NR; EDSS: NR	Retrospective/ administrative data	IFNβ-1a, IFNβ-1b, GA	Duplicate studies, both included as one reports MPR (2017) and one PDC (2016)
Evans, 2012[56]	Canada	DC	Up to 14 years	N=1,896	Age: M=40.2, SD=9.5 years; Gender: 75.1% Female; Subtype: RRMS, SPMS; MS duration: NR; EDSS: Median, 2.5 (range, 0-8.5)	Retrospective/ MS database	IFNβ-1a, IFNβ-1b, GA	
Fernández, 2016[57]	Spain	AH	Up to 3 years	N=258	Age: M=40.7, SD=9.5 years; Gender: 67.8% Female; Subtype: RRMS; MS duration: M=8.9, SD=6.0 years; EDSS: M=1.8, SD=1.2	Retrospective/ multicentre	IFNβ-1a s.c.	
Fernández-Fournier, 2015[58]	Spain	DC	Median=34 months	N=155	Age: M=37.0, SD=9.0 years; Gender: 68.3% Female; Subtype: RRMS; MS duration: NR; EDSS: Median=1.5-2, IQR=1-3	Retrospective/ clinical records	GA	Compares GA as 1st line and switch to GA
Gerber, 2017[59]	Canada	AH, DC	12 months	N=2,781	Age: <35 (25%), 35-55 (61.7%), 55-65 (11.8%), >65 (1.5%); Gender: 73.8% Female; Subtype: NR; MS duration: NR; EDSS: NR	Retrospective/ administrative data	IFNβ-1a, IFNβ-1b, GA, FTY, TFN, DMF	

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TABLE 1			Characteristics of Included Objective Studies *(continued)*					
Author, year	**Country**	**Study type**	**Observation length**	**Sample size**	**Age, gender, subtype, MS duration, EDSS**	**Design/setting**	**DMT(s)**	**Comments**
Hansen, 2015[10]	Germany	AH	24 months	N = 50,057	Age: NR; Gender: NR; Subtype: NR; MS duration: NR; EDSS: NR	Retrospective/ pharmacy claims database	IFNβ-1a, IFNβ-1b, GA	Demographics not reported
Johnson, 2017[12]	USA	AH	12 months	N = 1,498	Age: M = 48.1, SD = 10.7 years; Gender: 76.7% Female; Subtype: NR; MS duration: NR; EDSS: NR	Retrospective/ database claims	FTY, DMF, TFN	
Jones, 2013[60]	USA	AH	24 months	N = 5,825	Age: M = 44.4, SD = 10.1 years; Gender: NR; Subtype: RRMS; MS duration: NR; EDSS: NR	Retrospective/ shared solution program	GA	Participants were enrolled in a medication support program
Kleinman, 2010[61]	USA	AH	12 months	N = 358	Age: M = 40.7, SD = 5.9 years; Gender: 62.7% Female; Subtype: NR; MS duration: NR; EDSS: NR	Retrospective/ claims database	IFNβ-1a, IFNβ-1b, GA	Participants had to be employed for this study
Kleiter, 2017[62]	Germany	AH	24 weeks	N = 151 (enrolled); N = 143 (analyzed)	Age: M = 41.2, SD = 11.5 years; Gender: 69.2% Female; Subtype: RRMS, CIS; MS duration: (n = 105), M = 15.2, SD = 29.4 months; EDSS: (n = 105) median, 2.0 (range, 0-6.5)	Prospective/ multicentre	IFNβ-1b s.c.	
Kozma, 2014[63]	USA	AH	24 months	N = 4,606	Age: M = 46.0, SD = 9.4 years; Gender: 78.7% Female; Subtype: NR; MS duration: NR; EDSS: NR	Retrospective/ database claims	IFNβ-1a, IFNβ-1b, GA	
Krol, 2017[64]	Netherlands and Germany	AH	Up to 5 years	N = 1,682	Age: M = 40.1, SD = 10.7 years; Gender: 72.5% Female; Subtype: NR; MS duration: NR; EDSS: NR	Retrospective/ multinational	IFNβ-1a s.c.	No demographic data reported for the Netherlands
Lafata, 2008[19]	USA	AH	24 months	N = 224	Age: M = 47.6, SD = 10.4 years; Gender: 77.2% Female; Subtype: RRMS; MS duration: NR; EDSS: NR	Retrospective/ multispecialty practice	GA, IFNβ-1a, IFNβ-1b	Insured patients
Lebrun-Frenay, 2019[65]	France	DC	Up to 5 years	N = 881 (enrolled); N = 852 (analyzed)	Age: M = 39.9, SD = 10.6 years; Gender: 75.8% Female; Subtype: RRMS; MS duration: M = 8.1, SD = 7.5 years; EDSS: M = 2.3, SD = 1.7 (n = 716)	Prospective/ database claims	GA	

TABLE 1	Characteristics of Included Objective Studies *(continued)*							
Author, year	Country	Study type	Observation length	Sample size	Age, gender, subtype, MS duration, EDSS	Design/setting	DMT(s)	Comments
Lugaresi, 2012[66]	Italy	AH	12 weeks	N=120 (recruited); N=119 (intent-to-treat population); N=109 (completed study)	Age: M=37.9, SD=9.7 years; Gender: 75.6% Female; Subtype: RRMS; MS duration: M=5.8, SD=5.3 years; EDSS: M=2.1, SD=1.2	Prospective/ multicentre	IFNβ-1a s.c.	
McKay, 2017[67]	Canada	AH	24 months	N=326 (included); N=135 (DMT users)	Age: M=48.7, SD=11.9 years; Gender: 74.5% Female; Subtype: RRMS, SPMS, PPMS; MS duration: M=15.3, SD=9.9 years; EDSS: Median, 2.5 (IQR, 2.0-4.0)	Retrospective/ pharmacy claims	IFNβ-1a, IFNβ-1b, GA	
Melesse, 2017[35]	Canada	AH, DC	M=7.8 years	N=721	Age: M=37.6, SD=9.8 years; Gender: 74.2% Female; Subtype: NR; MS duration: NR; EDSS: NR	Retrospective/ administrative data	IFNβ-1a, IFNβ-1b, GA	Subset study of Evans, 2016; 2017, specific to first DMT prescribed
Moccia, 2016[68]	Italy	DC	>5 years; M=7.9, SD=3.8 years	N=499	Age: M=32.3, SD=8.2 years; Gender: 63.1% Female; Subtype: RRMS; MS duration; M=2.7, SD=2.7 years; EDSS: M=2.0, SD=0.6	Retrospective/ clinical data	IFNβ-1a, IFNβ-1b	Newly commenced on IFNβ-1a & 1b as first DMT
Moccia, 2015[69]	Italy	AH	Up to 4 years	N=114	Age: M=35.8, SD=10.4 years; Gender: 71.1% Female; Subtype: RRMS; MS duration: M=8.1, SD=9.1 years; EDSS: M=2.8, SD=0.8	Retrospective/ clinical data	IFNβ-1a s.c	
Munsell, 2017[70]	USA	AH, DC	12 months	N=8,382	Age: M=43.1, SD=NR years; Gender: 76.7% Female; Subtype: NR; MS duration: NR; EDSS: NR	Retrospective/ claims database	IFNβ-1a, IFNβ-1b, GA, TFN, FTY, DMF	Newly initiated treatment
Oleen-Burkey, 2011[71]	USA	AH	24 months	N=839	Age: M=45.2, SD=10.4 years; Gender: 81.3% Female; Subtype: NR; MS duration: NR; EDSS: NR	Retrospective/ administrative claims data	GA	
Paolicelli, 2016[72]	Italy	AH	24 months	N=384 (recruited); N=343 (12 months); N=150 (24 months)	Age: M=36.0, SD=9.2 years; Gender: 67.2% Female; Subtype: RRMS; MS duration: Median, 74 months (range, 0-398); EDSS: Median, 2 months (range, 0-6)	Prospective/ clinical database	IFNβ-1a s.c.	

TABLE 1	Characteristics of Included Objective Studies *(continued)*							
Author, year	**Country**	**Study type**	**Observation length**	**Sample size**	**Age, gender, subtype, MS duration, EDSS**	**Design/setting**	**DMT(s)**	**Comments**
Pedersen, 2018[73]	Demark	AH	12 weeks	N=60 (recruited); N=54 (analyzed)	Age: M=43.7, SD=7.9 years; Gender: 83.3% Female; Subtype: RRMS; MS duration: M=6.7, SD=4.5 years; EDSS: Median, 2.75 (range, 0-5)	Prospective/multicentre	IFNβ-1a s.c.	
Prosperini, 2019[74]	Italy	DC	12 months	Prematching: N=621; PEG, N=196, DMF, N=265, TFN, N=160	Age: M=41.9, SD=10.7 years; Gender: 69.3% Female; Subtype: RRMS; MS duration: M=11.0, SD=7.4 years; EDSS: PEG (1.0 [0-5.5]); DMF (1.5 [0-0.5]); TFN (2.5 [0-5.5])	Retrospective/multicentre	TFN, DMF, PEG	Data propensity matched; Prematching cohort demographics displayed
Sabido-Espin, 2017[75]	USA	AH, DC	36 months	N=5,956	Age: M=44.0, SD=10.7 years; Gender: 74.7% Female; Subtype: NR; MS duration; NR; EDSS: NR	Retrospective/insurance claims database	IFNβ-1a s.c	
Sanchirico, 2019[76]	USA	AH	12 months	N=7,072	Age: M=55.0, SD=10.0 years; Gender: 78.3% Female; Subtype: NR; MS duration: NR; EDSS: NR	Retrospective/medical and pharmacy claims	GA, IFNβ-1a, IFNβ-1b, TFN, DMF, FTY	
Schreiber, 2018[77]	Denmark	AH	12 months	N=195 (enrolled); N=126 (12 months)	Age: M=41.0, SD=8.7 years; Gender: 66.7% Female; Subtype: RRMS; MS duration: M=9.0, SD=6.0 years; EDSS: M=3.0, SD=1.7	Prospective/multicentre	FTY	Only Includes intervention study, but observational data used
Settle, 2016[30]	USA	AH	6 months	N=30 (recruited); N=13 (routine care); N=17 (intervention)	Age: M=48.0, SD=10.8 years; Gender: 50.0% Female; Subtype: RRMS, SPMS; MS duration: NR; EDSS: Median 3-3.5, range 2.0-8.0	Prospective/veterans' affair medical centre	IFNβ-1a i.m.	Compares usual care to online web-based tool; Veterans' Affair Medical Centre sample
Shao, 2018[78]	USA	AH	M=281.56 days	N=6,003	Age: M=46.0, SD=10.1 years; Gender: 77.5% Female; Subtype: NR; MS duration: NR; EDSS: NR	Retrospective/commercial claims database	IFNβ-1a, IFNβ-1b, GA	
Smith, 2015[79]	USA	DC	M=554.2 days	N=8,107	Age: M=43.1, SD=10.7 years; Gender: 76.2% Female; Subtype: NR; MS duration: NR; EDSS: NR	Retrospective/insurance claims database	IFNβ-1a	Newly commenced IFNβ-1a
Solsona, 2017[80]	Spain	AH	Median, 979 days	N=110	Age: M=38.8, SD=9.3 years; Gender: 66.4% Female; Subtype: NR; MS duration: NR; EDSS: Median, 1.5 (range, 0-4.5)	Retrospective/multiple sclerosis clinic data	IFNβ-1a s.c.	

TABLE 1	Characteristics of Included Objective Studies *(continued)*							
Author, year	Country	Study type	Observation length	Sample size	Age, gender, subtype, MS duration, EDSS	Design/setting	DMT(s)	Comments
Steinberg, 2010[36]	USA	AH	3 years; reported in 12-month periods	N = 1,606	Age: M = 51.8, SD = 9.8 years; Gender: 76.0% Female; Subtype: RRMS; MS duration: NR; EDSS: NR	Retrospective/ database claims	IFNβ-1a, IFNβ-1b	
Stockl, 2010[81]	USA	AH, DC	8 months	N = 468	Age: M = 53.2, SD = 10.2 years; Gender: 83.3% Female; Subtype: NR; MS duration; NR; EDSS: NR	Retrospective/ insurance database claims	IFNβ-1a, IFNβ-1b, GA	Disease management program compared to retail and specialty pharmacy participant
Tan, 2011[82]	USA	AH	12 months	N = 2,446	Age: M = 41.9, SD = 10.1 years; Gender: 74.9% Female; Subtype: NR; MS duration: NR; EDSS: NR	Retrospective/ insurance database claims	IFNβ-1a, IFNβ-1b, GA	
Vieira, 2019[83]	USA	AH	24 months	N = 4,563	Age: M = 46.7, SD = 9.9 years; Gender: 78.2% Female; Subtype: NR; MS duration: NR; EDSS: NR	Retrospective/ database	FTY, TFN	
Warrender-Sparkes, 2016[84]	International	DC	12 months	N = 2,640	Age: M = 32.9, SD = 10.0 years; Gender: 70.3% Female; Subtype: RRMS, SPMS, CIS; MS duration: NR; EDSS: Median, 2 (IQR 1, 2.5)	Retrospective/ MBase registry	IFNβ-1a, IFNβ-1b, GA, FTY	Newly diagnosed, commencing DMT
Williams, 2018[85]	USA	AH	12 months	N = 381	Age: M = 41.8, SD = 10.9 years; Gender: 82.8% Female; Subtype: NR; MS duration: NR; EDSS: NR	Retrospective/ administrative database claims	FTY, GA	Hispanic and African American sub-groups
Zecca, 2017[38]	Switzerland	AH	9 months	N = 56 (observation); N = 53 (evaluable data)	Age: Median, 49.0 (IQR 38, 55); Gender: 77.4% Female; Subtype: RMMS; MS duration: Median, 6.5 years (IQR, 38, 55); EDSS: Median, 2 (IQR 1,3.3)	Retrospective and prospective/ multicentre	IFNβ-1a s.c	Includes a retrospective and prospective observation period

travel compensation (N = 31; 50.8%), or they were employed by a pharmaceutical company (N = 28; 45.9%). While unsurprising, given pharmaceutical companies interest in understanding real-world adherence figures for their products, this interest warrants remark.

ADHERENCE RATES

Medication adherence was most often measured using the MPR (N = 23), followed by the PDC (N = 13), and electronic autoinjectors (N = 12). In addition, medication adherence was also measured with pill count (PC; N = 3), MEMS (N = 2), and injection count (IC; N = 1).

Binary Adherence (≥80%). Using a binary measure, 32 studies reported injectable adherence and 10 reported oral adherence (see Supplementary Table 1 and 2). For studies with a less than 8-month observation period, autoinjector adherence for injectable DMTs (N = 4) ranged between 80.5% and 93.0%, while one study using MEMS reported

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TABLE 1	Characteristics of Included Objective Studies *(continued)*							
Author, year	Country	Study type	Observation length	Sample size	Age, gender, subtype, MS duration, EDSS	Design/setting	DMT(s)	Comments
Zhang, 2017[86]	Canada	AH	12 months	N = 801	Age: M = 41.5, SD = 9.5 years; Gender: 76.0% Female; Subtype: NR; MS duration: NR; EDSS: Median, 3 (IQR 2,4)	Prospective/ clinical and administrative database	IFNβ-1a, IFNβ-1b, GA	
Zhornitsky, 2015[87]	Canada	DC	18 years	N = 1,471	Age: M = 38.4, SD = 9.3 years; Gender: 75.3% Female; Subtype: RRMS; MS duration: M = 6.0, SD = 6.7 years; EDSS: Median, 2.0 years (IQR: 1.5-3.0; Range, 0-8.0)	Prospective/ MS clinic	IFNβ-1a, IFNβ-1b, GA	
Zimmer, 2017[88]	Switzerland	AH, DC	24 months	N = 98	Age: Median, 41.0 years (IQR: 31.0, 46.0; Range, 22.0-71.0); Gender: 79.6% Female; Subtype: RRMS; MS duration: Median, 4.6 years (IQR: 1.0, 11.4; Range, 0.2-36.4); EDSS: NR	Prospective/ MS clinic data-base	FTY	

Notes: Unless otherwise stated, IFNβ-1a includes both intramuscular and subcutaneous administration. All studies are observational unless otherwise stated. Sample sizes included are reported statistics, not total sample, unless specified. Only baseline and preintervention data are reported for intervention studies. Where required, means and standard deviations were combined excluding IV medications data, using sample group statistics through an online calculator: https:// www.statstodo.com/CombineMeansSDs_Pgm.php.

AH = adherence; CIS = clinically isolated syndrome; DC = discontinuation; DMF = dimethyl fumarate; EDSS = expanded disability status scale; FTY = fingolimod; GA = glatiramer acetate; IFNβ-1a = interferon beta-1a; IFNβ-1a i.m = interferon beta-1a intramuscular; IFNβ-1a s.c = interferon beta-1a subcutaneous; IFNβ-1b = interferon beta-1b; IQR = interquartile range; MPR = medication possession ratio; NR = not reported; pwRRMS = people with relapse remitting multiple sclerosis; PPMS = primary progressive multiple sclerosis; PDC = proportion of days covered; PEG = pegylated interferon; PM = propensity matched; RRMS = relapse remitting multiple sclerosis; SPMS = secondary progressive multiple sclerosis; TFN = teriflunomide.

adherence of 82.0%, and another study reported MPR adherence of 53.0%. There was only one comparative binary oral DMT study with a MPR adherence of 74.0%.
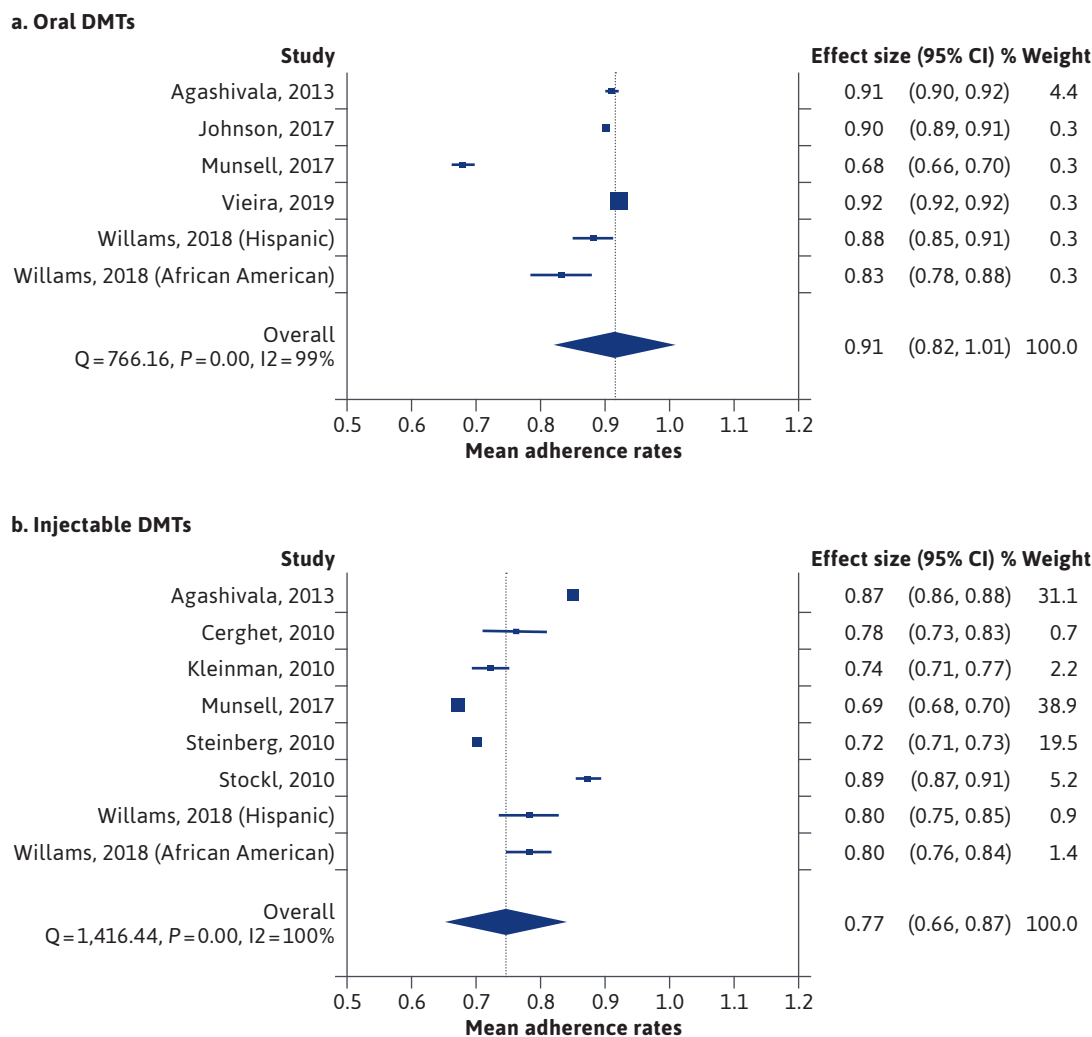
For 12-month observation studies, MPR adherence for injectable DMTs (N=7) and PDC (N=6) ranged, respectively, between 47.0% and 77.4% and 46.0% to 90.0%. Whereas MPR adherence for oral DMTs (N=7) ranged between 53.0% and 89.2%. PDC adherence (N=6) ranged between 60.4% and 94.0%. Meta-analysis for at least 80% oral and injectable DMT adherence did not find a statistical difference between pooled estimates for MPR (injectable: 62.0%; 95% CI: 51.0%-73.0%; oral: 79.0%; 95% CI: 61.0%-95.0%) or PDC (injectable: 80.0%; 95% CI: 66.0%-92.0%; oral: 80.0%; 95% CI: 52.0%-100.0%) measures (Supplementary Figure 1, available in online article).

For studies conducted over 24 months, mean MPR adherence for injectable DMTs (N=7) ranged between 35.0% to 79.0%, and the results from two studies reporting mean PDC were 67.3% and 74.7%. There were two oral DMT adherence studies for 24 months. One study reported an MPR of 64.7%, and the second study classified adherence into four categories using mean PDC, from perfect adherence (100%) to nonadherence (<85.8%). No participants were classified as nonadherent, possibly due to methodological error, given that 22.4% of participants who discontinued treatment during the observation period were excluded from analysis.

Of the seven 36-month binary adherence studies for injectable DMTs, one reported an MPR of 51.7%. PDC adherence (N=2) was reported as 42.4% and 86.0%, and autoinjector adherence studies (N=4) ranged between 82.9% and 95.6%. There were no 36-month binary oral adherence studies.

Continuous Adherence. Twenty-nine studies reported mean adherence on a continuous scale: 21 injectable and eight oral DMTs. Two studies reported a less than eight-month continuous adherence for injectable DMTs. One study measured autoinjector adherence. The other study combined injection count and MPR data with a mean

FIGURE 2 Meta-Analysis of Mean Adherence Rates

a. Oral DMTs

Study	Effect size (95% CI)	% Weight
Agashivala, 2013	0.91 (0.90, 0.92)	4.4
Johnson, 2017	0.90 (0.89, 0.91)	0.3
Munsell, 2017	0.68 (0.66, 0.70)	0.3
Vieira, 2019	0.92 (0.92, 0.92)	0.3
Willams, 2018 (Hispanic)	0.88 (0.85, 0.91)	0.3
Willams, 2018 (African American)	0.83 (0.78, 0.88)	0.3
Overall Q = 766.16, P = 0.00, I2 = 99%	0.91 (0.82, 1.01)	100.0

Mean adherence rates

b. Injectable DMTs

Study	Effect size (95% CI)	% Weight
Agashivala, 2013	0.87 (0.86, 0.88)	31.1
Cerghet, 2010	0.78 (0.73, 0.83)	0.7
Kleinman, 2010	0.74 (0.71, 0.77)	2.2
Munsell, 2017	0.69 (0.68, 0.70)	38.9
Steinberg, 2010	0.72 (0.71, 0.73)	19.5
Stockl, 2010	0.89 (0.87, 0.91)	5.2
Willams, 2018 (Hispanic)	0.80 (0.75, 0.85)	0.9
Willams, 2018 (African American)	0.80 (0.76, 0.84)	1.4
Overall Q = 1,416.44, P = 0.00, I2 = 100%	0.77 (0.66, 0.87)	100.0

Mean adherence rates

Notes: Pooled subgroup results are presented (overall pooled estimates not available). Weights are from Doi's IVHet Model.
Effect = mean adherence ratios.

adherence, respectively, of 89.0% and 95.0%. One small study (25 participants) reported oral DMT adherence using PC (91.0%) and compared it to MEMS cap results (90.0%).

Ten injectable and eight oral DMT studies reported a mean 12-month adherence. For injectable DMTs, MPR (N = 8) and PDC (N = 3) adherence ranged, respectively, between 69.0% to 92.0%, and 67.0% to 86.0%. For two autoinjector studies, reported adherence was 97.0% and 98.0%. For oral DMTs, MPR adherence (N = 5) ranged between 68.0% and 92.0%, PDC adherence (N = 5) ranged between 73.0% and

83.0%, and two studies measuring PC reported adherence as 89.0% and 99.0%. One oral DMT adherence study utilizing MEMS cap reported 84.0% adherence.

Pooled MPR adherence for 12-month oral and injectable DMTs was, respectively, 91.0% (95% CI: 82.0%-101.0%) and 77.0% (95% CI: 66.0%-87.0%; Figure 2). Given the heterogeneity between studies (Cochran's Q: 766.16, df = 5, P < 0.001; I2: 99.3%), we substantiated meta-analysis results using meta-regression (Table 2), which showed significantly higher mean adherence for oral compared to injectable DMTs (β = −0.146; 95% CI: −0.263 to −0.029). The doi plot points

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TABLE 2	Results from IVhet Meta-Regression Model Showing the Difference in Mean MPR Across Different Groups of Studies					
	Coef.	**Robust std. err.**	**T**	**P>t**	**LCL**	**UCL**
Group 2	−0.14	0.049	−2.91	0.013	−0.25	−0.03
_cons (Group-1)	0.91	0.008	103.76	0.000	0.89	0.93

Group-1, n = 6; Group-2, n = 8.

toward major asymmetry across studies (LFK index: −5.18; Supplementary Figure 2, available in online article), proposing study heterogeneity.

Over 24 months, injectable MPR adherence (N=5) ranged between 55.0% and 90.0%, at 36 months injectable MPR (N=1) was 76.0%, and autoinjector adherence (N=4) ranged from 91.0 to 95.0%. There were no comparable oral DMT studies at 24 or 36 months.

DISCONTINUATION RATES

Discontinuation studies were defined by length: longer than a 30-day gap (N=3), at least a 60-day gap (N=4), and longer than a 90-day gap (N=10). One study used temporary (<6 months) and definitive discontinuation (>12 months). Eight studies did not provide a discontinuation definition (Supplementary Table 3).

There were four injectable studies with an observation period of less than 12 months, ranging between 5.0% and 26.2% discontinuation. One oral DMT study reported 28.0% discontinuation.

For 12-month injectable (N=10) and oral (N=7) DMT studies, overall mean discontinuation ranged, respectively, between 15.2% to 50.8% and 10.5% to 33.3%. Meta-analysis for 12-month studies (N=10 injectable and N=7 oral DMTs) highlighted the presence of significant heterogeneity (I2 injectable: 99.5%; I2 oral: 93.1%) between studies, including within subgroups. There was no appreciable difference in 12-month mean discontinuation

rates across groups (Figure 3, injectable: 27.0%; 95% CI: 19.0%-34.0%; oral: 24.0%; 95% CI: 17.0%-31.0%).

Over a 24-month observation period, mean discontinuation for injectable DMTs (N=6) ranged between 6.3% and 57.0%, and oral DMTs (N=7) ranged between 1.0% and 34.0%. Only injectable DMT discontinuation data was available for over a 36-month observation period. The seven studies ranged between 9.7% and 53.6%.
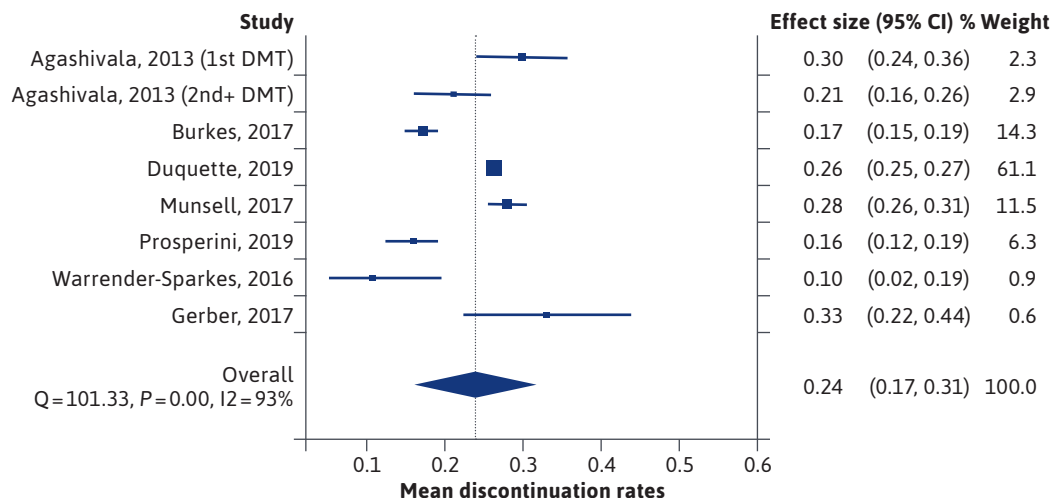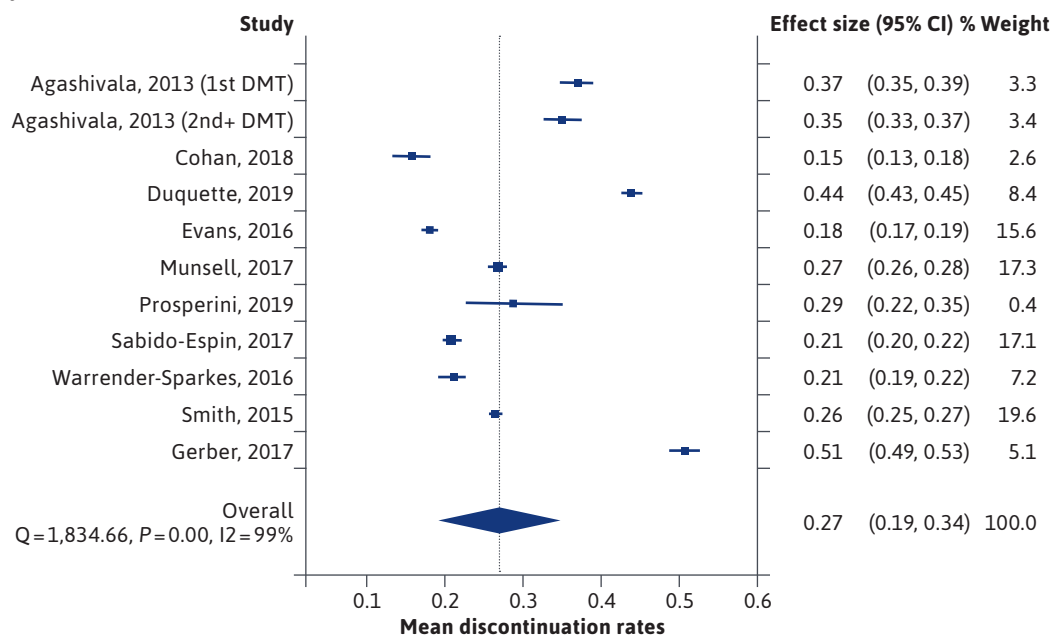
Discussion

This systematic review and meta-analysis synthesized and reported, across all measurement durations, on objectively measured self-administered injectable and oral DMT adherence and discontinuation rates in people with MS. To our knowledge, it is the first comparative review of injectable and oral DMT adherence and discontinuation rates. Suboptimal adherence and persistence were present for both injectable and oral DMTs. When compared with injectable DMTs and measured using mean adherence, meta-regression showed a 14% significant improvement in 12-month medication adherence for oral DMTs. The improvement contrasted with a 12-month oral and injectable adherence using a cut-off score of at least 80% to determine adherence, which showed no significant difference. Furthermore, there was no appreciable difference in 12-month

discontinuation rates between oral and injectable DMTs.

While previous systematic reviews have examined injectable adherence or discontinuation[8,15] or oral adherence and discontinuation rates[20,21] in isolation, these results have enabled a comparison of adherence and discontinuation between these two administration modalities. In particular, the significant improvement in oral medication adherence proposes that administration modality may relate to medication adherence. Despite the improvement seen in oral DMT adherence, our review shows that suboptimal medication adherence and discontinuation of DMTs remains present for both injectable and oral DMTs.

MEDICATION ADHERENCE

Medication adherence rates varied vastly across studies. When reported utilizing a binary cut-off score of at least 80%—across different measurement methods and calculations, such as claims, autoinjector and MEMS counts, MPR and PDC calculations—studies reporting 12-month adherence ranged between 46.0% and 90.0% for injectable DMTs and between 53.0% and 94.0% for oral DMTs. While there was no difference in adherence between oral and injectable DMTs when measured by a binary cut-off score of at least 80%, there was a significant improvement in oral compared to injectable adherence for studies reporting 12-month mean adherence (91.0% [P<0.001] vs 77.0% (P=0.013), respectively). The improvement is likely due to reduced power associated with binary measurement.[31] This highlights the importance of studies choosing adherence levels formulated from an appropriate rationale. While the 80% adherence cut-off score is most frequently used in the literature, it is arbitrarily applied. Indeed, adherence across drugs, diseases, and

FIGURE 3 **Meta-Analysis of Discontinuation Rates**

a. Oral DMTs

Study	Effect size (95% CI)	% Weight
Agashivala, 2013 (1st DMT)	0.30 (0.24, 0.36)	2.3
Agashivala, 2013 (2nd+ DMT)	0.21 (0.16, 0.26)	2.9
Burkes, 2017	0.17 (0.15, 0.19)	14.3
Duquette, 2019	0.26 (0.25, 0.27)	61.1
Munsell, 2017	0.28 (0.26, 0.31)	11.5
Prosperini, 2019	0.16 (0.12, 0.19)	6.3
Warrender-Sparkes, 2016	0.10 (0.02, 0.19)	0.9
Gerber, 2017	0.33 (0.22, 0.44)	0.6
Overall $Q=101.33$, $P=0.00$, $I2=93\%$	0.24 (0.17, 0.31)	100.0

Mean discontinuation rates

b. Injectable DMTs

Study	Effect size (95% CI)	% Weight
Agashivala, 2013 (1st DMT)	0.37 (0.35, 0.39)	3.3
Agashivala, 2013 (2nd+ DMT)	0.35 (0.33, 0.37)	3.4
Cohan, 2018	0.15 (0.13, 0.18)	2.6
Duquette, 2019	0.44 (0.43, 0.45)	8.4
Evans, 2016	0.18 (0.17, 0.19)	15.6
Munsell, 2017	0.27 (0.26, 0.28)	17.3
Prosperini, 2019	0.29 (0.22, 0.35)	0.4
Sabido-Espin, 2017	0.21 (0.20, 0.22)	17.1
Warrender-Sparkes, 2016	0.21 (0.19, 0.22)	7.2
Smith, 2015	0.26 (0.25, 0.27)	19.6
Gerber, 2017	0.51 (0.49, 0.53)	5.1
Overall $Q=1,834.66$, $P=0.00$, $I2=99\%$	0.27 (0.19, 0.34)	100.0

Mean discontinuation rates

Notes: Pooled subgroup results are presented (overall pooled estimates not available). Weights are from Doi's IVHet Model.
Model Effect = discontinuation rates.

patient characteristics may differ.[32] Given that studies looking at adherence on outcome in MS most often use the 80% cut-off score to determine adherence, it is difficult to appreciate the clinical impact of the 14% statistically significant difference for health and economic outcomes. Across measurement types, 12-month mean adherence ranged between 67.0% to 98.0% for injectable and 68.0% to 99.0% for oral adherence. Beyond a 12-month duration, oral DMT data was

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limited, restricting any sort of valid comparative analysis.

Adherence rates for MEMS and autoinjectors were considerably higher than other measures. Use of autoinjectors may improve adherence, given that they may reduce the impact of injection-related issues, such as needle phobias and injection site reactions.[18] However, higher results may be attributed to study parameters, such as study support or participant awareness of adherence observation, not afforded to participants measured via retrospective claims/pharmacy refill data.[33]

Despite improved 12-month oral DMT adherence, in line with previous reviews, suboptimal adherence remains present for injectable and oral DMTs, illustrating the problematic issue of DMT adherence regardless of administration route.[8,20,21] Thus, DMT adherence remains an issue requiring attention, given poorer adherence is linked to greater healthcare resource utilization and days of work lost.[34]

MEDICATION DISCONTINUATION
As with DMT adherence, our review of discontinuation studies found vast differences in discontinuation rates. For 12-month discontinuation, injectable DMTs ranged between 15.2% and 50.8%, while oral DMTs ranged between 10.5% and 33.3%, yet there was no significant difference (pooled 12-month discontinuation: 27.0% and 24.0%, respectively). For 24-months, injectable discontinuation ranged between 6.3% and 57.0%, while oral studies ranged between 1.0% and 39.0%.

Discontinuation rates varied depending on discontinuation definition. Shorter discontinuation definitions (ie, >30-day) resulted in higher discontinuation rates than longer discontinuation definitions (ie, >90-day), pointing to the incorrect categorization of 'having ceased their DMT' when people, may in fact, take 'medication holidays.' The error is highlighted by a long-term study (N=721; M=7.2 years) that showed 57.4% of people with MS who discontinued a DMT recommenced at some point.[35] The investigators reported that, when using a 90-day discontinuation definition, 62.6% of participants discontinued, compared with 26.4% of participants defined by a 12-month discontinuation.[35] Reasons for treatment discontinuation and recommencement are not addressed in the study. Thus, varying discontinuation definitions and observation durations across studies may result in overestimating or underestimating rates of discontinuation, which presents issues with generalizability. This underscores the need for consistent study protocol use in DMT adherence and discontinuation studies, enabling comparative analysis.

Our findings are broadly comparable with a previous discontinuation review for injectable DMTs that found mean discontinuation rates ranged between 16-27%,[15] and the 12-month pooled oral discontinuation was similar to a recent review of 25.4%.[21] Thus, the need remains to provide people with MS ongoing support, encouraging medication continuation regardless of DMT administration route. While this study focused on adherence differences between oral and injectable administration routes, it is acknowledged that DMTs will have different tolerability profiles that may impact adherence. Indeed, medication side effects are known to impact medication adherence and persistence.[18] The current review excluded studies if they did not clearly account for switching to minimize the impact of methodological study bias on reported results. Despite the exclusion, discontinuation studies varied substantially in methodology.

CLINICAL IMPLICATIONS
The improvement in adherence of oral DMTs compared with injectable DMTs highlights a benefit of oral DMT administration that will translate into improved clinical outcomes for people with MS yet does not solve the problem of suboptimal medication adherence and persistent. Thus, people with MS continue to require support to develop strategies to take their medication as prescribed. This is underscored by an absence of improved medication persistence rates for oral DMTs, emphasizing the complexity surrounding medication adherence and persistence beyond self-injection administration issues.

People with MS may experience a range of risk factors for suboptimal medication adherence and discontinuation, including depression, cognitive impairment, complex medication administration regimes (polypharmacy or administration schedule requirements), and complex medical needs (eg, comorbid chronic illness).[3,18] Awareness of these risk factors enables clinicians to be responsive to the potential impact on suboptimal adherence and, as required, to provide support and/or intervention referral. Appreciating issues of suboptimal adherence is also important to breakthrough disease activity or progression, which may trigger unwarranted DMT switching or escalation due to compliance related reduced efficacy.[4,18]

RESEARCH IMPLICATIONS
An evident outcome of this review, which reduces study comparability, is the inconsistencies between-study protocols, methodology, varying adherence thresholds, and discontinuation definitions. While the majority of studies classified participants as adherent using a binary threshold of at least 80, commonly accepted across adherences studies, some studies used incomparable cut scores, such as at least 85,[36] at least 75,[37] or categorical adherence with no explicit

definition of adherence level.[38] The significant difference between oral and injectable DMTs when assessing 12-month mean adherence, compared with 12-month binary adherence of at least 80%—which was nonsignificant—proposes a loss of power to detect medication adherence levels using binary adherence.[31] Future studies would benefit from reporting mean 12-month adherence instead of, or in addition to, binary adherence results of at least 80%.

The wide disparity across discontinuation definitions, ranging from a gap period of more than 30 days to more than 90 days and studies providing no discontinuation definition, limits confidence in the generalizability of study results. Higher discontinuation rates were reported for studies with shorter discontinuation definitions compared to longer gaps, pointing to a need for consistency of discontinuation definition, with longer discontinuation periods likely to provide greater accuracy. Future research would also benefit from identifying patterns of temporary discontinuations, or 'medication holidays,' to inform medication adherence interventions.

Given that switching to an alternative DMT in the event of breakthrough disease activity or adverse events is common in MS healthcare, and medication discontinuation research must account for this to avoid overestimating DMT discontinuation rates. DMT switch rates are shown to be between 19.7 to 30.0%.[3,39,40] Fifteen studies were excluded from this review, as switching was not sufficiently considered. There is a need for methodological and reporting consistency for future studies to examine adherence and discontinuation behaviour in MS.

STRENGTHS AND LIMITATIONS

This review utilized a rigorous methodology, undertaking a thorough systematic literature search.

Separation of the adherence and discontinuation results by measurement type (ie, MPR and PDC), discontinuation definition (ie, 30-day, 60-day, and 90-day gap periods) and observation lengths (ie, <8 months to 36 months), and removal of studies that did not explicitly account for switching, were employed to reduce the chance of overestimating discontinuation. We utilized PROSPERO registration and PRISMA reporting guidelines to minimize reporting bias. The review contributes novel findings to the existing literature on adherence and discontinuation rates for both injectable and oral DMTs.

Results were limited by the large variation across methodology of the included studies, as discussed previously. Our focus on comparative results of 12-month adherence and discontinuation to identify differences in injectable and oral administration modalities attempts to minimize reporting bias and provide generalizable results. The large heterogeneity in the methodology of included studies meant we were only able to report ranges of individual studies for periods other than 12 months. This review examined between-group adherence and discontinuation rates for oral and injectable DMTs without consideration of within-group variability, which may be present at both the level of the individual person and DMT.[15,20]

Conclusions

In summary, this systematic review and meta-analysis compared adherence and discontinuation of oral and injectable DMTs for people with MS. There was a 14% improvement to 12-month mean oral DMT adherence, compared to injectable adherence, but no improvement to 12-month binary adherence using a cut-off score of at least 80%. There was no difference in discontinuation rates

between oral and injectable DMTs. Both oral and injectable DMTs suffer suboptimal medication adherence and discontinuation issues. Our review highlighted several methodological inconsistencies that limit between-study comparisons, emphasizing the need for future adherence and discontinuation research to use consistent definitions, durations, and measures to improve the generalizability of findings and reliability of translatable implications into clinical practice.

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