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REVIEW

Scoping review of the availability and uptake of disease modifying therapies in children and adolescents with multiple sclerosis

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ABSTRACT

Introduction: Approximately 10% of individuals with multiple sclerosis (MS) have pediatric-onset (<18-years-old). Pediatric-specific barriers to accessing disease modifying therapies (DMT) exist. Issues include few pediatric-based randomized controlled trials (RCT), often required for formal regulatory approval, and resultant challenges with cost/coverage. This review assessed real-world DMT uptake in pediatric-MS to better understand potential barriers.

Areas covered: We performed a scoping review of observational studies examining DMTs in patients with pediatric-MS published between 07/1993 and 06/2024. PRISMA guidelines were used. Databases searched included: Cochrane Library, Ovid MEDLINE/Embase, Scopus, and Web of Science. Studies must include >10 DMT exposed pediatric-MS patients with full-text available in English. RCTs/pharmaceutical-industry funded studies were excluded. Of 2114 abstracts screened, 88 studies were included. A total of 21,591 patients (13,411 females) were included. DMTs were used in 68.7% ($n = 14,833$). Most studies were from Europe (53.4%), North America (22.7%), or the Middle East (10%). Regional variabilities were found in DMT uptake between continents. Only 13 (14.8%) studies included information on DMT funding source.

Expert opinion: Pediatric-MS patients showed low DMT uptake with variability in DMT use based on region. Limited data was found regarding specific barriers to DMT access. Further research is needed to better understand regional barriers to access.

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Disease modifying therapy; pediatric-onset multiple sclerosis; medication access; DMT uptake; scoping review

1. Introduction

Multiple sclerosis (MS) is a chronic inflammatory and degenerative disease of the central nervous system and a leading neurological cause of non-traumatic disability in young individuals. Up to 10% of persons with MS (PwMS) have disease onset in the pediatric years [1]. Pediatric-onset MS (POMS) patients have higher disease burden, higher number of relapses, and more inflammatory disease [2–6]. These individuals are at risk for motor and cognitive disability at a younger age than patients with adult-onset MS [7–10].

Early treatment is crucial for reducing relapse frequency and slowing disability progression [8,9,11–14]. In both adult and pediatric populations, early initiation of high-efficacy disease modifying therapies (DMT) is associated with fewer new or enhancing lesions on magnetic resonance imaging (MRI), lower relapse rates, reduced disease burden, and better health outcomes [11,12,15–18]. As such, first-line use of high-efficacy DMTs has become the mainstay of MS care in adults. However, implementing these strategies in POMS populations is challenging as most DMTs are not approved to be used within pediatrics and therefore use is often off-label or not possible.

In recent years, several high-quality observational studies have evaluated the effectiveness and safety of various DMTs for POMS. A growing body of pediatric data underscores the importance of early use of higher-efficacy therapies, similar to that seen in adults [19–24]. For example, a recent retrospective cohort study from the MSBase and Italian MS Registry, which included 5,224 POMS patients across 151 centers in 41 countries, found that the use of higher-efficacy therapies substantially reduced the risk of reaching key disability milestones. Another study within this population found that natalizumab and fingolimod were associated with significantly lower rates of relapse compared to patients treated with injectable DMTs [24]. Given that this review focuses on access and usage patterns rather than effectiveness, we will not address treatment effectiveness in detail. However, it is important to acknowledge the growing body of recent observational studies examining effectiveness and safety within the area of POMS [13–15,19–21,24–26].

General barriers to DMT access in PwMS relate primarily to cost and coverage. A 2021 international survey of MS experts found that 72% of respondents from countries surveyed reported barriers to DMT access, with the most common

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Article highlights

- This scoping review analyzed real-world DMT use in 88 observational studies involving 21,591 patients with pediatric-onset MS.
- DMTs were used in just over two-thirds of pediatric-onset MS patients.
- The uptake and pattern of DMTs use varied across continents and changed over time.
- Limited information is available regarding DMT funding sources and processes for securing funding across different regions.

barrier cited being cost to the government, healthcare system, or insurance [27]. In addition, respondents from almost half of the countries surveyed reported problems with continuous, uninterrupted usage of DMTs, most commonly due to irregular supply or delays with reimbursement for DMTs during renewals [27]. A United States (US)-based survey of PwMS found that 46% of respondents reported difficulty accessing DMTs, most common reasons reported being authorization requirements by insurance companies and high out-of-pocket costs. About half of PwMS went without DMT while navigating access issues, with nearly half of these individuals reporting relapses during this time [28].

In addition to the general barriers to DMT access for all PwMS, there are additional challenges specific to the pediatric population, mainly due to the limited number of completed randomized controlled trials (RCTs) in POMS. Regulatory approval, which is typically required for government or insurance providers to cover treatments, is harder to obtain for pediatric medications without results from RCTs. Despite the growing body of observational research, these observational studies are often not considered in the regulatory approval process. While over 20 DMTs have been approved for adults with MS, many of which have demonstrated safety and effectiveness in pediatric observational trials, only the three which have been studied in pediatric-specific RCTs – fingolimod, dimethyl fumarate (DMF), and teriflunomide – are approved by the European Medicines Agency (EMA, DMF for patients >13 years, fingolimod and teriflunomide for patients >10 years) [29–33]. Of these, only fingolimod is US Food and Drug Administration (FDA) approved for patients >10 years [34–38]. The lack of regulatory approval limits access to these therapies and exacerbates coverage and cost issues. Even in higher-income settings, most DMTs for children with MS are used off-label, and decisions about coverage are left to individual insurers without standardized guidelines. This makes it more difficult – if not impossible – to secure funding through the same channels available to adult MS patients. Given these regulatory and access challenges, it is not surprising that a recent large-scale insurance database study in the US found that 65.3% of pediatric patients with MS did not receive any DMT in the first year after their MS diagnosis [39].

This paper aims to identify and better understand the barriers and potential knowledge gaps in DMT availability and uptake in the POMS population. To do this, we conducted a scoping review of all studies assessing the current real-world, regionally specific uptake patterns for DMTs within POMS. We then examined these articles to try to identify funding sources for DMTs used and other barriers to access identified in the everyday care of POMS patients. Understanding these general uptake patterns and pediatric-specific DMT access issues serves as a key foundational step in creating standardized, equitable treatment approaches for POMS.

2. Methods

This scoping review included observational studies that describe DMT use in pediatric MS or clinically isolated syndrome (CIS) with symptom onset <18-years-old published between 07/1993 and 06/2024. The protocol was designed as per PRISMA guidelines and registered with the Open Science Framework (reg. 07/2023) [40]. Databases searched included: Ovid EBM Reviews Cochrane Library, Ovid MEDLINE and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily, Ovid Embase Classic+Embase, Elsevier Scopus, Clarivate Web of Science Core Collection. Conference proceedings of the American Academy of Neurology (AAN), European Committee for Treatment and Research in MS (ECTRIMS) and American Committee for Treatment and Research in MS (ACTRIMS) in the last 4 years (2019–2023) were also searched. Search terms are included in appendix A. DMTs included: interferons, glatiramer acetate, teriflunomide, dimethyl fumarate, natalizumab, fingolimod, ofatumumab, siponimod, ocrelizumab, ozanimod, ponesimod, cladribine, alemtuzumab, and rituximab. The reference lists of all included articles were searched, and relevant papers included.

Covidence software was used for article review [41]. All abstracts were independently reviewed for eligibility according to the pre-determined criteria by two reviewers (BC/LS), any conflicts were resolved by a third reviewer (JJ). Data were extracted from articles by one reviewer (BC/JJ/LS). Each article was reviewed for effectiveness according to the Joanna Briggs Institute (JBI) levels of evidence by one reviewer [42].

Articles were included if they: (1) were observational in design (cross-sectional or longitudinal), (2) mentioned DMT use in a POMS/CIS population with over 10 participants ≤18-years-old using a DMT, (3) specified that the DMT was initiated in the pediatric period (≤18-years-old) if patients were followed into the adult years, (4) included original results (reviews were excluded), and (5) had full text available in English. Articles which included both pediatric and adult patients were included only if pediatric information (data for ≤18-years-old) was reported separately. Exclusion criteria were: (1) DMT funded exclusively by the pharmaceutical industry or within an RCT, (2) case reports or case series with under 10 patients, and (3) studies which had no patients on a DMT or did not specify which DMTs were used. To avoid duplication, if >1 article was published using the same population source, then only the most recent publication was included. We extracted studies which reported numerous DMTs from studies which focused on one specific DMT, as these were felt to better represent overall prescribing practices within a cohort. We assessed each article for information on DMT funding source, information on application for DMTs, or other mentioned barriers in DMT access. To achieve this, we systematically reviewed all articles and documented any sources of funding (e.g. private insurance databases, government organizations) referenced in the introduction or methods section of each paper. When a funding source was identified, we

analyzed the text to determine whether it outlined specific procedures for obtaining or securing the funding, as well as any challenges associated with these processes.

For article classification, we grouped studies into registry-based (single center or multiple centers), and population-based (including administrative/insurance claims-based). We further classified as prospective cohort/case-series (including retrospective review of prospectively followed cohorts), retrospective cohort/case-series, cross-sectional, and case-control based on study methodology. For data extraction, data was grouped into ≤2014 or ≥2015 according to the last year of data collection (or year of publication if last year of data collection not provided). We used 2015 as the cutoff as prior studies identified a shift in DMT prescribing in the POMS population around this time, with a reduction in use of the beta-interferons (IFN) as newer DMTs became available [43–45]. We also classified DMTs into moderate-efficacy (IFN, glatiramer acetate, teriflunomide, DMF) and high-efficacy (natalizumab, fingolimod, rituximab/ocrelizumab/ofatumumab, cladribine, alemtuzumab) [46]. Other treatments such as intravenous steroids, plasma exchange or intravenous immunoglobulins, and other non-DMT immunological medications, were not assessed. If sequencing of a DMT (i.e.

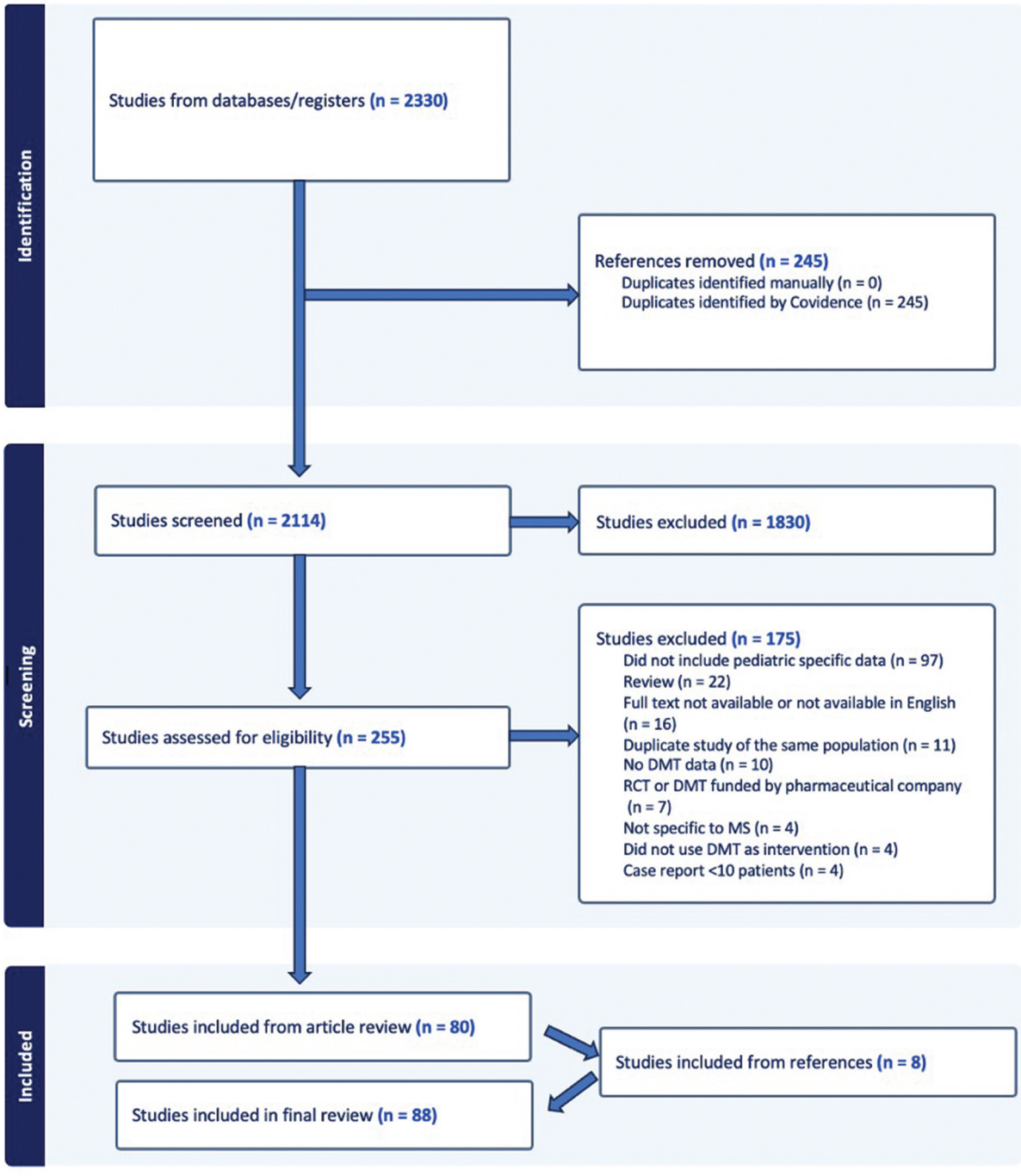

Figure 1. Flow chart of search and article inclusion/exclusion per review criteria for observational studies assessing DMTs in pediatric-onset MS.
DMT = disease modifying therapy, MS = multiple sclerosis, POMS = pediatric-onset MS, RCT = randomized controlled trial.

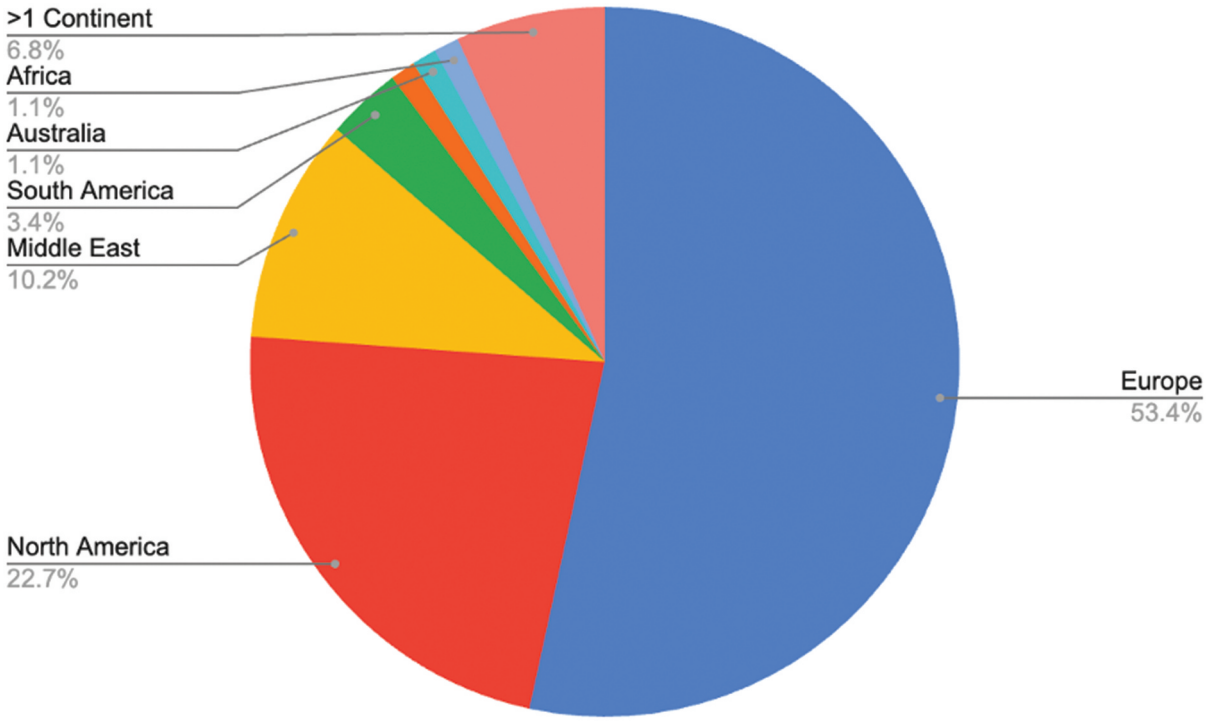

Figure 2. Distribution of articles included in scoping review on observational studies on DMT use in the POMS population per region.
DMT = disease modifying therapy, POMS = pediatric-onset MS.

used first or used second or third) was not specified in the study, it was classified into first used DMT.

3. Results

A total of 2330 studies were screened for inclusion. Eighty-eight studies were eligible, including 8 additional articles identified from review of references in the collected papers [4,6,13,15,16,18–21,23–26,39,43,45,47–118]. All were published between August 2001 and May 2024 (see Figure 1).

Of the studies reviewed, 77 were registry-based (87.5%, 33=single center, 44 = multiple centers), 4 (4.5%) were population-based, and 7 (8.0%) were administrative. Thirty-one (35.2%) studies were classified as prospective, 50 (56.8%) as retrospective, 6 (6.8%) as cross-sectional and 1 (1.1%) as case-control. Twenty-eight studies (31.8%) specifically collected information on one DMT only, whereas 60 (68.2%) collected information on multiple DMTs.

Overall, the majority of publications were from Europe (53.4%), followed by North America (22.7%), Middle East (10%), and South America (3.4%), with the remainder (6.8%) being international (defined as including multiple countries from different continents). Only 1 (1.1%) article was found from each of Africa, Australia, and Asia (see Figure 2 and Table 1). The individual country with the highest number of publications was the US ($n = 15$).

3.1. Funding of DMTs

Only a minority (14.8%, $n = 13$) of articles specified the source of funding for DMT, including government funded ($n = 6$), private insurance ($n = 6$), or self-pay ($n = 1$). Of note, 4/6

Table 1. Summary of studies included in scoping review of observational studies assessing DMT use in pediatric-onset MS.

	Data collected or study published 2014 or earlier	Data collected or study published 2015 or later	Total
Total number of studies	**23**	**65**	**88**
Continent (number of studies)			
Europe	7	40	47
North America	9	11	20
Middle East	1	8	9
South America	1	2	3
Asia	1	0	1
Australia	1	0	1
Africa	0	1	1
International	3	3	6
Total participants	2013	19578	21591
Participants ever used a DMT to treat POMS (%)	1533 (76.2%)	13300 (67.9%)	14833 (68.7%)
Female – number (%)	995 (49.4%)	12446 (63.6%)	13441 (62.3%)
Articles with DMT funding source specified – number of studies (%)	5 (21.7%)	7 (10.8%)	12 (13.6%)

DMT = disease modifying therapy, POMS = pediatric-onset MS.

Table 2. Scoping review of observational studies of DMT use in POMS: Summary of papers which provided sources for funding.

Article	Ref	Country	DMT Funding Source	Number of patients included	Number of patients on DMTs	DMTs Used
Asia						
Yang et al.	[112]	China	Self-Pay	25	15	IFN
Europe						
Frahm et al.	[59]	Germany	German Statutory Health Insurance	613	335	IFN, GA, Nat, Fing
Ivanova et al.	[71]	Bulgaria	Government funded, compassionate care	11	11	IFN
Krajnc et al.	[76]	Slovenia	Government funded (with approval by regional committee for Treatment of MS)	38	24	IFN, GA, DMF, Nat
Saponaro et al.	[32]	France	IFN covered, some in RCTs, others not specified	78	78	IFN, GA, Teri, DMF, Nat, Fing, Alem, Ritux
Von Wyl et al.	[109]	Switzerland	Health Insurance	236	236	IFN,GA, DMF, Nat
Middle East						
Amirov et al.	[39]	Turkey	Applied for special access	75	75	IFN, Ocre
Ismail et al.	[70]	UAE	Government funded	31	20	IFN, GA, Nat, Fing
North America						
Greenberg et al.	[63]	USA	Private insurance	288	100	IFN, GA, DMF, Fing, Nat
Henderson et al.	[65]	USA	Private insurance	488	488	IFN, GA, Teri, DMF, Nat, Fing
Oleen-Burkey et al.	[86]	USA	Private insurance	212	85	GA
Reynolds et al.	[92]	USA	Private insurance	28	28	IFN, GA, Nat
Vollmer et al.	[108]	USA	Private insurance	10	10	DMF, Fing

Alem = alemtuzumab, cyclo= cyclophosphamide, DMF = dimethyl fumarate, DMT = disease modifying therapy, Fing = fingolimod, GA= glatiramer acetate, IFN = interferon, Nat = natalizumab, Ocre = ocrelizumab, RCT = randomized controlled trial, Ritux = rituximab, Teri= teriflunomide, UAE = United Arab Emirates, U.S.A. = United States of America.

articles which reported government funded/special access were from Europe, where 5/6 articles that reported private insurance were from the U.S.A.. The article which reported self-pay was from China (see Table 2). No studies specified the process or steps for applying for or securing funding. See appendixes B-D for full data and DMT information of articles included.

3.2. DMT prescribing patterns

Data on DMT use was reported for 21,591 children/youth with MS, with approximately 2/3 ($n = 14,833$, 68.7%) of POMS patients included treated with a DMT and approximately 1/3 ($n = 6,758$, 31.3%) not on DMTs (see Table 1). The IFNs were the most commonly reported, accounting for nearly half of all DMTs use (see Table 3). When examining only studies that assessed numerous (>1) drugs, moderate efficacy DMTs were reported most frequently, representing 79% of first used DMTs and 68.8% of all DMTs reported (see Table 3). When examining trends over time, moderate efficacy DMTs became used less frequently and high-efficacy DMTs were used more frequently when comparing from prior to 2015 to after 2015 (see Table 4).

3.3. Geographic differences in DMT use

Natalizumab was the most common high-efficacy DMT reported in papers from Europe, while fingolimod was the most common in papers from the Middle East and South America. As for B-cell therapies, rituximab was described at a rate two times higher in papers from North America than in those from other regions, whereas ocrelizumab use was reported twice as frequently in papers from the Middle East than in other regions. Glatiramer acetate was reported more commonly in papers from North and South America than Europe, Middle East, or elsewhere. It was reported as first-line therapy almost five times more often in papers from North America than in papers from Europe (see Table 5).

3.4. Evidence for effectiveness levels

Of studies included, the vast majority ($n = 58$) we assigned a JBI level of effectiveness score of 3e (observational study without a control group). Three studies were 2e (quasi-experimental design with historic/retrospective control group), 14 were 3c (cohort study with control group), 1 was 3d (case-controlled study), 6 were 4b (cross-sectional) and 6 were 4c (case series) (see appendix B).

4. Discussion

In this scoping review, we aimed to identify POMS DMT uptake patterns, funding sources, and access barriers in different regions around the world as a first step in understanding pediatric-specific issues and barriers to DMT use. In order to do this, we reviewed observational studies with > 10 POMS that had used a DMT published between 1993 and 2024.

In the current review, we found a low uptake of DMTs in POMS with only approximately 2/3 of patients (68.7%) reported in the included studies having ever used or currently on DMTs. We also observed that the specific DMTs used and uptake trends in the included studies varied across different regions and continents. Unfortunately, in our review, little information was found on reasons for this low uptake and regional variability in DMT use within the POMS population. Limited information was reported in studies regarding funding source and the process of securing funding in different regions, with only 14.8% of studies reporting the funding source for DMTs used and no studies discussing the process of application for securing DMT coverage. While the exact cause for the low DMT uptake and regional variabilities is unknown, common barriers to

Table 3. Scoping review of observational studies of DMT use in POMS: summary data for total DMTs used and 1st DMT used for only studies which included multiple DMTs being used.

	IFN	GA	DMF	Teri	Moderate efficacy*	Nat	Fing	Ritux	Ocre	Clad	Alem	Ofat	High efficacy*
1st DMT used	4750 (46.9%)	1134 (11.2%)	400 (3.9%)	131 (1.3%)	8004 (79%)	780 (7.7%)	449 (4.4%)	244 (2.4%)	45 (0.4%)	5 (0.0%)	2 (0.0%)	1 (0.0%)	2127 (21.0%)
Total DMTs	4985 (40.4%)	1192 (9.7%)	562 (4.6%)	155 (1.3%)	8483 (68.8%)	1143 (9.3%)	819 (6.6%)	322 (2.6%)	82 (0.7%)	6 (0.0%)	16 (0.1%)	1 (0.0%)	3846 (31.2%)

All numbers provided in brackets represent percentages of each DMT used from either 1st DMT used or total DMTs used, respectively.
*Data from articles which had DMTs grouped into moderate or high efficacy (see Appendix C) and number of patients on each DMT was not provided were not included in the individual DMT percentages but were included in the total moderate or high-efficacy DMTs within that region. Therefore, individual DMT percentages in the table when added together may not equal total moderate or high efficacy categories.
Alem = alemtuzumab, Clad = cladribine, DMF = dimethyl fumarate, DMT = disease modifying therapy, Fing = fingolimod, GA = glatiramer acetate, IFN = interferon, MS = multiple sclerosis, Nat = natalizumab, Ocre = ocrelizumab, Ofat = ofatumumab, Ritux = rituximab, Teri = teriflunomide.
No articles with pediatric patients on Ozanimod, Siponimod or Ponesimod were found.

Table 4. Scoping review of observational studies of DMT use in POMS: number and percentage of DMTs used by date of data collection completion (or publication if data collection date not specified).

	IFN	GA	DMF	Teri	Moderate efficacy	Nat	Fing	Ritux	Ocre	Clad	Alem	Ofat	High efficacy
≤2014	1313 (80.6%)	259 (15.9%)	8 (0.5%)	0 (0.0%)	1580 (96.9%)	41 (2.5%)	9 (0.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	50 (3.1%)
≥2015	5720 (43.1%)	1068 (8.1)	580 (4.4)	155 (1.2)	9112 (68.7%)	1269 (9.6%)	887 (6.7%)	414 (3.1%)	100 (0.8%)	0 (0.0%)	16 (0.1%)	1 (0.01%)	4150 (31.3%)
Total	7033 (47.2%)	1327 (8.9)	588 (3.9)	155 (1.0)	10692 (71.8%)	1310 (8.8%)	896 (6.0%)	414 (2.8%)	100 (0.7%)	0 (0.0%)	16 (0.1%)	1 (0.01%)	4200 (28.2%)

All numbers provided in number (percentage) of each DMT used from total DMTs within that cohort.
Note: all articles with year of data collection completion not specified were.
Alem = Alemtuzumab, Clad = Cladribine, DMF = Dimethyl Fumarate, Fing = Fingolimod, GA= Glatiramer acetate, IFN = interferon, Nat = Natalizumab, Ocre = Ocrelizumab, Ofat = Ofatumumab, Ritux = Rituximab, Teri= Teriflunomide.
No articles with pediatric patients on Ozanimod, Siponimod or Ponesimod were found.

Table 5. Scoping review of observational studies of DMT use in POMS: number and percentage of total DMTs used and 1st DMT used in POMS patients by continent.

	IFN	GA	DMF	Teri	Moderate efficacy*	Nat	Fing	Ritux	Ocre	Clad	Alem	High Efficacy*
TOTAL DMTs USED												
Europe	1971 (30.2%)	313 (4.8%)	132 (2.0%)	78 (1.2%)	4050 (62.1%)	552 (8.5%)	323 (5.0%)	115 (1.8%)	15 (0.2%)	0.00	16 (0.2%)	2468 (37.9%)
North America	1182 (39.8%)	724 (24.4%)	328 (11.0%)	9 (0.3%)	2243 (75.5%)	233 (7.8%)	210 (7.1%)	240 (8.1%)	44 (1.5%)	1 (0.03%)	0.0	728 (24.5%)
Middle East	658 (59.2%)	47 (4.2%)	48 (4.3%)	46 (4.1%)	832 (74.8%)	95 (8.5%)	111 (10.0%)	33 (3.0%)	30 (2.7%)	1 (0.09%)	0.0	280 (25.2%)
South America	74 (66.7%)	20 (18.0%)	0.0	0.0	94 (84.7%)	0.0	17 (15.3%)	0.0	0.0	0.00	0.0	17 (15.3%)
Asia	3 (100.0%)	0.0	0.0	0.0	3 (100.0%)	0.0	0.0	0.0	0.0	0.00	0.0	0.0
Australia	12 (92.3%)	1 (7.7%)	0.0	0.0	13 (100.0%)	0.0	0.0	0.0	0.0	0.00	0.0	0.0
Africa	18 (100.0%)	0.0	0.0	0.0	18 (100.0%)	0.0	0.0	0.0	0.0	0.00	0.0	0.0
Multiple continents	3115 (75.2%)	222 (5.4%)	80 (1.9%)	22 (0.5%)	3439 (83.0%)	430 (10.4%)	235 (5.7%)	26 (0.6%)	11 (0.3%)	4 (0.10%)	0.0	706 (17.0%)
Total	7033 (47.2%)	1327 (8.9%)	588 (3.9%)	155 (1.0%)	10692 (71.8%)	1310 (8.8%)	896 (6.0%)	414 (2.8%)	100 (0.7%)	6 (0.04%)	16 (0.1%)	4199 (28.2%)
FIRST DMT USED												
Europe	1946 (38.6%)	304 (6.0%)	96 (1.9%)	65 (1.3%)	3967 (78.7%)	293 (5.8%)	92 (1.8%)	83 (1.6%)	10 (0.2%)	0.00	2 (0.04%)	1071 (21.3%)
North America	1131 (44.7%)	691 (27.3%)	213 (8.4%)	9 (0.4%)	2044 (80.7%)	136 (5.4%)	154 (6.1%)	172 (6.8%)	25 (1.0%)	1 (0.04%)	0.00	488 (19.3%)
Middle East	638 (72.7%)	30 (3.4%)	22 (2.5%)	35 (4.0%)	758 (86.4%)	35 (4.0%)	39 (4.4%)	28 (3.2%)	7 (0.8%)	0.00	0.00	119 (13.6%)
South America	74 (75.5%)	20 (20.4%)	0.0	0.0	94 (95.9%)	0.0	4 (4.1%)	0.0	0.0	0.00	0.00	4 (4.1%)
Asia	3 (100.0%)	0.0	0.0	0.0	3 (100.0%)	0.0	0.0	0.0	0.0	0.00	0.00	0.0
Australia	12 (92.3%)	1 (7.7%)	0.0	0.0	13 (100.0%)	0.0	0.0	0.0	0.0	0.00	0.00	0.0
Africa	17 (100.0%)	0.0	0.0	0.0	17 (100.0%)	0.0	0.0	0.0	0.0	0.00	0.00	0.0
Multiple continents	2977 (76.3%)	222 (5.7%)	80 (2.0%)	22 (0.6%)	3301 (84.6%)	383 (9.8%)	179 (4.6%)	26 (0.7%)	11 (0.3%)	4 (0.00%)	0.00	603 (15.4%)
Total	6798 (54.5%)	1268 (10.2%)	411 (3.3%)	131 (1.0%)	10197 (81.7%)	847 (6.8%)	468 (3.7%)	309 (2.5%)	53 (0.4%)	5 (0.04%)	2 (0.02%)	2285 (18.3%)

All numbers provided in brackets represent percentages of each DMT used from total DMTs within that continent.

*Data from articles which had DMTs grouped into moderate or high efficacy (see Appendix C) and number of patients on each DMT was not provided were not included in the individual DMT percentages but were included in the total moderate or high-efficacy DMTs within that region. Therefore, individual DMT percentages in the table when added together may not equal total moderate or high efficacy categories.

Alem = alemtuzumab, Clad = cladribine, DMF = dimethyl fumarate, DMT = disease modifying therapy, Fing = fingolimod, GA= glatiramer acetate, IFN = interferon, Nat = natalizumab, Ocre = ocrelizumab, Ofat = ofatumumab, Ritux = rituximab, Teri= teriflunomide.

No articles with pediatric patients on Ozanimod, Siponimod or Ponesimod were found.

consider based on prior studies may include differences in formal government/regulatory approval, regional DMT availability, DMT costs, and funding source (e.g. insurance coverage, government funding, out-of-pocket) [27,115,119]. Other factors may include individual clinicians' perspectives on the effectiveness and safety of specific DMTs, as well as patient preferences.

4.1. Formal government approval

Currently, only 3 DMTs have been evaluated in RCTs for POMS – fingolimod, teriflunomide, and dimethyl fumarate [29–32,47]. This lack of RCT evidence within POMS creates challenges in meeting the criteria often required for formal government or other regulatory body approval for DMTs [120,121]. Variations in regulatory practices and interpretations of study results may also lead to differences in regulatory approval across regions. For instance, while the FDA rejected the application for approval of teriflunomide for POMS after the primary endpoints were not met in the RCT evidence submitted, the EMA accepted a secondary endpoint (MRI) and allowed for approval of this agent in 2021 [36,37]. Interestingly, even though fingolimod is the only FDA and Health Canada approved DMT for POMS, published studies suggest less frequent use of fingolimod in North America compared to natalizumab and rituximab. It is possible that in these regions other factors, such as clinician's preferences/experiences, payor policies, and coverage options for DMTs, may play a more substantial role in influencing DMT choice than formal drug approval.

One major obstacle in obtaining the RCT studies necessary for formal regulatory approval is the rarity of POMS, rendering completion of RCTs challenging to complete. Prior research has found that RCTs that assess DMTs within the POMS population take longer to recruit, have lower enrollment numbers, and may be underpowered for the efficacy endpoints chosen [119,121]. Recently POMS specialists have discussed potential strategies to advance the field of POMS given these issues with obtaining RCT data, with a focus on the use of real-world effectiveness data [119,121]. The current review may contribute to mitigating this issue as it is one of the largest reviews to date of observational, real-world studies assessing DMTs within the POMS population.

This review did find that most of the DMT agents currently being used in adults with MS, have been reported to be in use in the pediatric population (see appendix C), and typically with similar safety and efficacy profiles as those reported in adults. However, this was not the primary objective of the current review and, therefore, was not formally assessed. While the current study focused on observational trials, we classified most of the included studies as JBI level 3e evidence (cohorts without a control group). Given the challenges of conducting RCTs in this population, future research should aim to strengthen the evidence base, potentially by incorporating appropriate control groups in observational cohort studies or utilizing quasi-experimental designs.

4.2. DMT coverage and insurance concerns

The lack of formal regulatory approval for the majority of DMTs means that many DMTs are not able to be used or are being used off-label in pediatrics. This is often not standardized and DMT coverage options may vary depending on the specific insurance or government payor. In this review, we found limited information on funding source and the process of securing funding in different regions. Only 13 studies (14.8%) reported their source for funding of DMT and of these none discussed the process of securing or applying for funding. Of studies which did report funding source, most with government-funded DMTs were from Europe or the Middle East whereas most with private-insurance funded DMTs were from North America (specifically the US) – this may speak to a larger trend of how DMTs are funded in these regions.

Trends in insurance coverage are also changing over time as DMTs continue to become more expensive. One study based in the US found that DMT costs increased annually at rates 5–7 times higher than typical prescription drug inflation [122]. Where US Medicare provided almost 100% coverage for DMTs for PwMS in 2007; coverage dropped to 54–89% by 2016 [123]. Many insurance companies have implemented tiered formularies or restrictions on DMT prescribing practices to help mitigate these high costs, which may hinder timely DMT initiation or renewal [122,124]. Given that cost and coverage for DMTs have been well-identified in prior research as a key limitation in DMT access in PwMS [27,28], further research is essential to build on the current findings and more thoroughly examine regional DMT funding options and the processes for securing coverage in pediatric populations. While the current study analyzed published observational trials for commentary on funding sources and access issues, such information may be more likely to be contained in other types of documents (e.g. country-specific or insurance-specific policy statements). Therefore, we would recommend for future research to focus on accessing and analyzing additional sources where this information may be available.

4.3. DMT cost and regional availability

Regional differences in the availability and pricing of DMTs may contribute to variations in uptake patterns. DMT pricing varies between countries and regions. For example, one study found that drug prices for US Medicaid were 2–4 times higher than the price for the same DMT in Canada, Australia, or the United Kingdom (UK) [e.g. glatiramer acetate was $47,253 US Dollars (USD) per year in the US Medicaid system, while $14,779USD in Canada, $13,107USD in Australia, and $11,124USD in the UK] [122]. In 2017, 4 weekly doses of rituximab cost $8,346USD in the US, while only $2,290USD in the UK or $2,076USD in South Africa [125]. Given the differences in healthcare systems and drug coverage between these regions, it is unclear how these cost differences affect actual uptake. Future research should examine DMT costs on an international scale to assess if and how cost variations impact the region-specific uptake patterns observed in the current review.

Over 85% of studies within this review were from Europe, North America, or Middle East, with very limited published information found about prescribing practices or DMT use in countries within regions like Asia and Africa. More information on DMT use in these areas is needed to better understand global barriers to DMT, particularly as several low-to-middle income countries are represented in these regions and these countries may face unique obstacles compared to high-income countries. For instance, the 2021 Atlas of MS international survey found that 70% of MS experts in low-income countries reported no DMT with regulatory approval was available for PwMS, compared to 14% in all countries surveyed [27]. Further, where one quarter of countries worldwide reported issues with use of high-efficacy licensed DMTs, this increased to 50% in low-middle income countries and 100% in low-income countries [27]. Further studies in these regions are needed to better understand their current DMT use and unique obstacles in access.

4.4. DMT trends in POMS

Given the above issues with DMT access, it is important to understand how these barriers might impact the care of pediatric patients. This review found that only about 2/3 of POMS patients reported in the included studies had ever used or were currently on a DMT. This is likely an overestimate as the current review only included studies which had >10 patients on DMTs and papers with no or fewer patients on DMTs were excluded. This statistic is concerning as prior research has well-established that early treatment with DMT therapy is crucial to minimizing the long-term sequalae of MS [7,9,11,14,126]. Of those treated with DMTs, the majority were managed on moderate-efficacy therapies, with interferons being the most commonly used DMT. Much prior research has shown that higher-efficacy DMTs – particularly if used early – are associated with reduced rate of disability worsening, greater time to first relapse, less MRI progression, and overall improved disease prognosis in POMS [7,9,11,12,15,16,18,21,24,59,72,100]. Our current review identified changes in practice over time, with a notable increase in the use of higher-efficacy DMT therapy in recent years (post-2015). However, even recent studies indicate that the majority of first-line treatments remain moderate-efficacy therapies. As high-efficacy DMTs become more widely prescribed, access to these therapies may increasingly be hindered by rising cost disparities. Consequently, the shift toward higher-efficacy, often more expensive treatments, and more aggressive, early treatment is likely to worsen existing access issues, highlighting the need for further research and interventions to address these challenges.

Regional differences in access, as discussed above, may contribute to some of the regional variabilities in DMT usage trends noted in the current review. For instance, more patients in studies from Europe were on high-efficacy DMTs as first-used or overall DMT used relative to other areas in the world. In terms of the most commonly first-used high-efficacy DMTs, fingolimod and rituximab more common in studies from North America whereas natalizumab was more common in studies from Europe and multiple continents. These trends should be interpreted with caution as the current study included studies of different types and methodologies (registry-based, population-based, administrative based) – therefore making grouping of data and statistical comparisons between studies challenging. Given this, formal statistical analysis to assess for significant relationships or properly address confounders was not applied. However, as the current review summarized a sizable number of observational studies within the POMS population, these trends are interesting to acknowledge as a starting point to better understand the international patterns of DMTs use in POMS.

4.5. Study limitations

There are limitations to this study. First, this review included studies of different types and methodologies, making data comparison between studies challenging. Secondly, where this review aimed to assess uptake patterns, often the reason for differences in uptake (i.e. specific barriers within that location/article) were not explicitly discussed in the papers. Therefore, it is challenging to delineate which barriers are due to drug access issues versus other issues, such as patient or provider preferences. For instance, the current review is not able to assess how much variability in practice is due to clinician's perceived effectiveness or safety of various options. A recent study of disparities in DMTs in PwMS found that individuals with less education and women were less likely to be on a DMT [127]. The impact of these social or demographic factors on DMT prescribing patterns was not able to be assessed in the current study. Thirdly, while we attempted to identify and avoid duplicate studies by removing studies which repeated populations, it is possible that data from some patients appeared in more than one article thereby impacting the statistical independence of the results. Fourthly, while we excluded studies which reported the DMT to be pharmaceutical-funded, in articles which did not report where DMT funding came from we cannot fully exclude that DMTs may have had external pharmaceutical-company funding. Lastly, the current review did not critically appraise for specific bias within studies and published reports we reviewed may be subject to publication and selection bias. Many of the reports, however, were from multi-site studies and included multiple DMTs which provides some reassurance that practice patterns in particular regions were relatively well represented.

5. Conclusion

In summary, this scoping review demonstrated low overall uptake of DMTs in POMS and marked variability of DMT uptake in different countries and regions. While exact reasons for these uptake patterns remain unclear based on the current literature, this may provide indirect evidence for both overarching and region-specific challenges in achieving standardized access to DMTs in POMS. In addition to the common barriers with DMT access faced by all PwMS (e.g. cost, coverage, availability), pediatric-specific barriers exist as well often stemming from challenges with completing RCTs within POMS given the rarity of the condition [102]. Some potential strategies proposed to advance the field given these issues involve a focus on the use of real-world effectiveness data [119,121].. The current paper hopes to help progress the current knowledge on the management in POMS as it is one of the largest reviews to date of observational real-world DMT use within the POMS population. While this review was a preliminary step in understanding DMT uptake obstacles in

POMS, much further research is needed to clarify the overall and regional-specific barriers in DMT access to enable appropriate, timely, and equitable care for all children and youth with MS.

6. Expert opinion

MS is the same disease in children and adults, albeit with contrasting outcomes due to higher levels of disease activity in pediatric onset MS (POMS) compared to those with adult-onset MS. Many observational studies, some of which were performed prior to widespread use and availability of MS DMTs in POMS patients, demonstrated greater brain atrophy through time and early cognitive decline with a steeper drop-off of cognition in their adult years in POMS compared to adults with comparable disease duration. Almost all DMTs that are available to adults with MS are now being used in pediatric populations. While RCTs have been performed in POMS on only 3 MS DMTs, many observational studies have demonstrated safety and effectiveness of most approved MS DMTs. Importantly, these observational studies have demonstrated that the use of *any* DMT early on – regardless of efficacy profile – associates with better outcomes in POMS. These observations highlight the potential for early recognition of MS and access to DMT in children to improve outcomes in children with MS.

Despite abundant real-world evidence of safety and effectiveness of DMT in POMS, only 1 MS DMT is approved for use in children under 18-years-old with POMS in the US, and 3 have received approval by the European Medicines Agency (EMA). This has implications for access, use and uptake of MS DMT in POMS, as payor support for off-label use of DMT can be challenging, even in high-income countries in which access to these therapies for adults with MS is readily available. There is a need for regulators to consider real-world effectiveness studies in regulatory approvals for medications for populations, such as POMS, in which completion of large clinical trials is untenable due to small numbers.

Use and uptake may relate to region-specific factors beyond regulatory limitations. Specifically, little is known about DMT use and uptake for POMS around the world. We found that most publications documenting MS DMT use come from North America and Europe, suggesting at least some access to DMT in these regions including high efficacy therapies. However, little information from other regions of the world is available, particularly from low- to middle-income countries. These regions may experience many barriers to DMT use that start with lack of access to early and accurate diagnosis and may be compounded by lack of access to therapies due to financial constraints. Given the potential of MS DMTs to dramatically change motor and cognitive outcomes in POMS, more information on use and uptake of therapies in both low-middle income countries and high-income countries is needed.

Over the last two decades, revisions to diagnostic criteria for MS have allowed for earlier and more accurate diagnosis of MS in children. Given the potential for devastating motor and cognitive outcomes if left untreated, with early diagnosis comes the responsibility to treat and provide access to therapies for POMS. We must develop truly global platforms that document and evaluate real-world use and uptake of MS DMT in POMS in order to understand the scope of the problem globally and to improve the outcomes of children with MS around the world.

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Author contributions

L Strasser contributed to conception of work, acquisition, analysis and interpretation of data, drafted and revised manuscript. B Cifti and J Johnstone contributed to conception of work, acquisition and analysis of data, and critical review of manuscript. J Cunningham contributed to design of search for the review, acquisition of data, and critical review of manuscript. H Tremlett and EA Yeh contributed to the conception and design of the work, interpretation of data, and critical review of manuscript. All authors provided final approval for publication.

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