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REVIEW

A Review of the Impact of Platform Therapies (DMTs) on Associated Clinical Symptoms of Multiple Sclerosis

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Abstract: Persons with multiple sclerosis (pwMS) experience varied symptoms, often influencing clinical decisions. Symptoms including cognitive deficits, pain, fatigue, and depression profoundly impact quality of life (QoL). Disease-modifying therapies (DMTs) primarily focus on reducing relapses and delaying progression; however, their ability to alleviate symptoms is less known. This narrative review consolidates the current evidence of the role of platform DMTs (Glatiramer Acetate (GA), Interferon (IFN), Dimethyl Fumarate (DMF), Teriflunomide (TER)) on the associated symptoms of MS and their efficacy in prevention of relapse, and disease progression. A literature search was conducted using the PubMed database for studies assessing the impact of GA and other platform DMTs on associated symptoms and effectiveness in pwMS. Studies using specific validated scales to assess each of the symptoms in pwMS treated with platform therapies were considered. A total of 132 publications were identified, and of which 13 were found appropriate for inclusion in the review. Effectiveness outcomes included annual relapse/exacerbation rates and lesion size. The impact of platform DMTs was evaluated in 13 studies in patients with MS having associated symptoms such as cognitive deficits (n=4), pain and spasticity (n=3), and fatigue, depression and overall QoL (n=6). Additionally, eight studies assessed the overall effectiveness of GA in the treatment and management of pwMS. Although a limited number of studies compared the impact of platform therapies on MS-related symptoms, treatment with GA demonstrated statistically significant improvements in cognition, pain, spasticity and fatigue, which was also clinically meaningful on minimum detectable change parameters. This review offers insights and proposes a hypothesis for conducting a large-scale study to explore the impact of platform therapies on MS symptoms that affect quality of life. It may also aid clinicians in making evidence-based therapeutic decisions for the effective management of PwMS.

Keywords: disease-modifying therapies, glatiramer acetate, interferons, persons with multiple sclerosis, quality of life

Introduction

Multiple sclerosis (MS), an autoimmune disease of the central nervous system (CNS), disrupts nerve signaling due to damage to the myelin sheath and nerve fibers.[1] The global prevalence of MS increased from 2.3 million in 2013 to 2.9 million in 2023.[2] Significant advances have been made in understanding the pathophysiology, epidemiology, and genes involved in MS.[3,4] The MS landscape has evolved with an understanding of its two key components representing a continuum across the disease course—relapses due to inflammation and progression mediated by neurodegeneration.[4] Relapsing-remitting MS (RRMS) comprises nearly 85% of presenting MS diagnoses and is characterized by intermittent attacks or exacerbations of neurologic symptoms followed by a remission period.[5]

Due to the complex nature of the disease, symptoms of MS differ widely among persons with MS (pwMS)[6] and the severity of symptoms can vary depending on the location of the nerve damage and the extent of disease progression. MS-related symptoms include problems with vision, fatigue, pain and spasticity, sexual dysfunction, cognitive dysfunction, and mental health problems such as anxiety and depression[7] Clinical evidence suggests an association between the severity and number of symptoms and declining quality of life (QoL) in pwMS.[8–11] Most pwMS demonstrate reduced

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QoL compared to the general population.[12–14] In clinical practice, the primary focus of treatment is to limit disability by reducing relapses and preventing disease progression. Amelioration of symptoms and improving QoL remain equally important.[1,15]

The last three decades have witnessed a rapid evolution in treatment strategies for MS, with various disease-modifying therapies (DMTs) having the potential to reduce relapses and delay disease progression by interfering with several immunological mechanisms.[16–18] As of 2023, 20 DMTs have been approved by the European Medicines Agency (EMA) and the United States Food and Drug Administration (US FDA) for the treatment of MS.[19] Of the approved DMTs, glatiramer acetate (GA), recombinant beta-interferons (IFNβ), dimethyl fumarate (DMF), and teriflunomide (Teri) have been considered platform treatments for MS.[20,21] In practice, the treatment strategy involves employing the DMT with the most favorable benefit-risk profile considering the type of MS, the level of disease activity, prognostic factors, patient-related factors, and risk of adverse events associated with the DMT.[22] It is not often that the symptoms associated with the disease are considered when selecting the DMT.

Many studies link diminished QOL with specific MS symptoms (fatigue, impaired mobility, spasticity, etc). Even in patients already receiving DMTs, symptoms and QoL play an important role in patient function and ability to perform activities of daily living (ADLs).[23] One of the publication[24] highlighted that certain DMTs have the potential to positively impact QoL of PwMS,[24] and the assessment and reporting of symptoms affecting the QoL is suboptimal with a multitude of diverse instruments.[24] Although few studies demonstrate the impact of DMTs on MS symptoms and QoL improvement in pwMS,[23,24] a further exploration may reveal a unique action of each of the platform DMTs on associated individual symptoms in pwMS. This narrative review examines the current evidence for platform DMTs on their impact on MS-related symptoms such as cognitive deficits, pain, spasticity, fatigue, depression and QoL, sexual dysfunction, bowel and bladder dysfunction, visual acuity problems, and anxiety to inform clinicians of this perspective. This review would help the clinicians by providing an update on the impact of platform DMTs on specific MS symptoms and contribute to evidence-based clinical decisions in MS management.

Literature Search

Using the PICO (participants, intervention, comparisons, and outcomes) framework, an independent search was conducted for a combination of medical subject headings (MeSH) and keywords, including “glatiramer acetate [MeSH]”, “multiple sclerosis [MeSH]”, “interferon”, “dimethyl fumarate”, “teriflunomide”, “cognition”, “quality of life”, OR “QoL”, “muscle weakness”, “stiffness”, “spasticity”, “bowel disease”, “bladder dysfunction”, “physical disability”, “hobbing”, “walking”, “pain” OR “tingling” OR “numbness”, “fatigue”, “depression”, “visual acuity”, “anxiety”, “sexual dysfunction”, in the PubMed database. Computer-based and manual searches were performed using PubMed per the search strategy described in Supplementary Table 1 and articles published until December 2023 were considered. Clinical trials and observational studies evaluating symptom management with GA and other platform DMTs in pwMS were retrieved. To examine the most current effectiveness results for GA a broad search was conducted in PubMed using the term “glatiramer acetate” with filters for clinical trials and observational studies in humans spanning the last 15 years (2009 to 2023). Only full-text articles published in the English language were included.

Most real-world studies examined used the following scales for evaluating fatigue, depression, and overall QoL: Fatigue Impact Scale [FIS], Beck’s Depression Inventory [BDI-II] or Beck Depression Inventory-Short Form [BDI-SF], Short Form-36 [SF-36], and Treatment Satisfaction Questionnaire for Medication [TSQM]. Hence, for these symptoms, only studies using either one of these scales were included in this review. For all other symptoms considered in the review, there were no limitations on the scales used. For each of the symptoms, the outcomes of interest included: (1) the incidence of MS-related symptoms following treatment with platform DMTs; (2) the mean ± standard deviation (SD) scores or the change in score for each of the scales evaluated at baseline and post-treatment. The effectiveness outcomes considered were the annual relapse rate (ARR), annual exacerbation rate (AER), and lesion size measured using magnetic resonance imaging (MRI). As envisaged in the title and primary objective, the scope of the review is limited to the platform DMTs and does not include other DMTs or drugs approved for management of MS.

Results

The systematic search in PubMed database for key MeSH terms yielded 132 articles on the impact of platform DMTs on each of key symptoms, and quality of life (Figure 1). The identified studies were reviewed for their relevance to research question of impact on specific symptom with a minimum of 1 of platform DMTs being assessed in pwMS. Most of studies (119 out of 132) did not meet the defined review criteria to answer the research question.

A total of 13 studies were included in this review. The impact of GA treatment and other platform DMTs on symptoms including cognitive deficits, pain and spasticity, fatigue, depression, and QoL were assessed in 13 studies, and on the effectiveness of GA treatment in pwMS was evaluated in 8 studies. There was a paucity of studies on the impact of platform DMTs for sexual dysfunction, bowel and bladder dysfunction, visual acuity problems, and anxiety; hence, their impact on these symptoms could not be reviewed. Though the search openly considered all the published studies of platform DMTs for impact on MS symptoms, most of studies had assessed either GA and/or IFN for action on MS related symptoms, and only 1 study assessed the impact of DMF and Teri along with GA and IFN.

Cognitive Function

Four studies assessing the impact of platform DMTs on cognitive function showed significant improvement in cognition post-treatment (details outlined in Table 1).[25–28] These studies evaluated cognition by employing various scales,

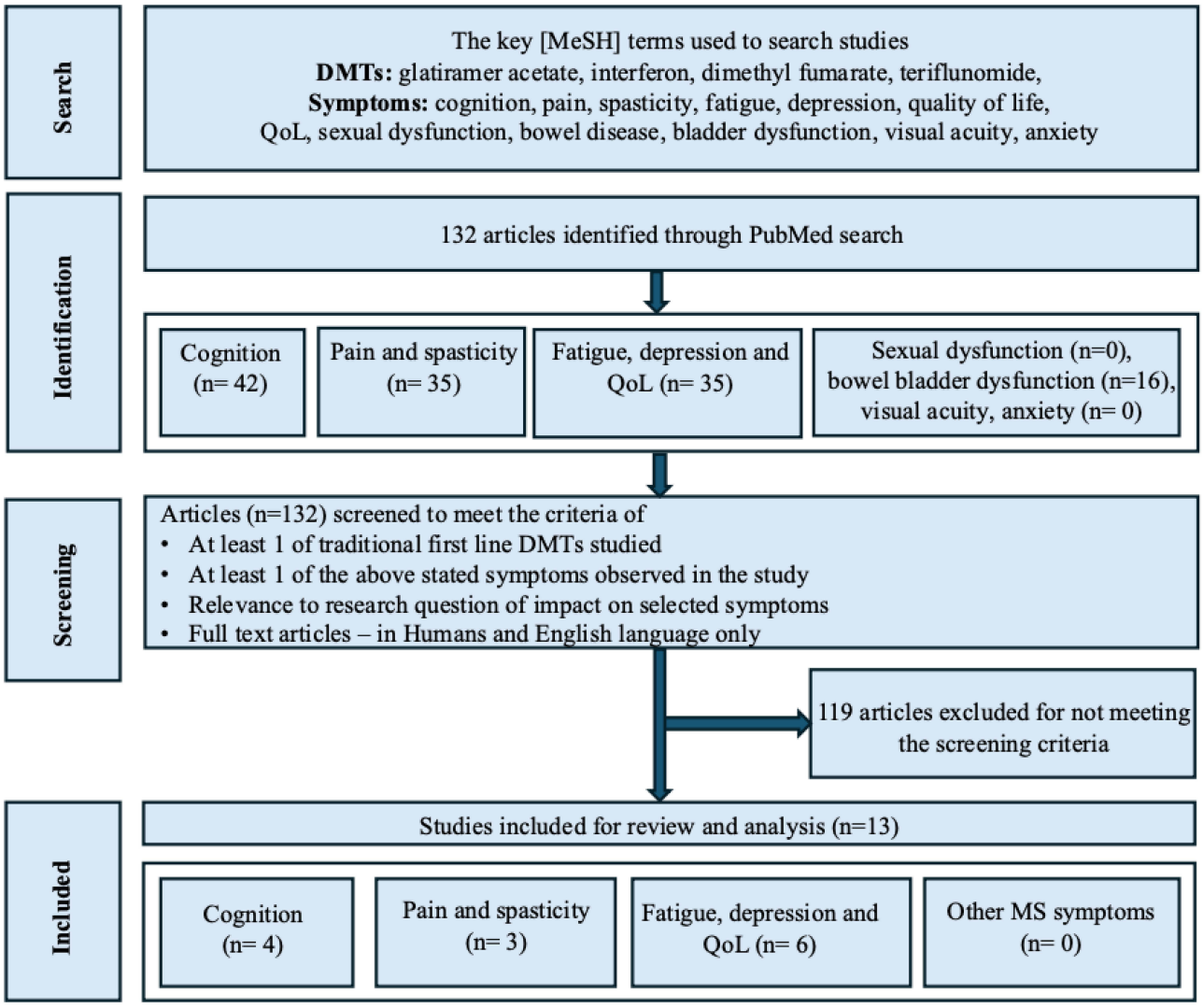

Figure 1 Search strategy for inclusion of studies in review.

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Table 1 Details of Studies Evaluating the Effect of GA and Other Platform DMTs on Cognition in PwMS

Author (Year); Study Type	Population	Treatment	Scale(s)	Results	Inference
Lanzillo (2020);[26] Observational, cross-sectional study	PwMS (n=280) on platform DMT for ≥1 year and no clinical relapse 6 months before study initiation	• GA (inj, n=37) • IFN (inj, n=156) • DMF (oral, n=62) • Teri (oral, n=25) *No doses mentioned*	• SDMT	• SDMT scores: mean ± SD • All: 40.3 ± 13.1; GA: 36.4 ± 9.5; IFN: 40.6 ± 13.3; DMF: 44.7 ± 14.7; Teri: 34.7 ± 9.1; **p=0.001.**	Compared with INF, PwMS on Teri were the oldest, with higher disability, worst depression at BDI, worst cognitive performances at SDMT, **p=0.001**; and authors suggested to be careful in evaluating these results.
Cinar (2017);[25] Controlled multi-center, examiner-blinded, prospective study	PwMS (n=161);healthy controls (n=102)	• IFNβ-1a (SC, n=53) • IFNβ-1b (n=52) • GA (n=56) • for 12 months	• BICAMS battery (SDMT, CVLT-II, BVMT-R)	• The number of cognitively impaired patients decreased from 28.5% to 20.5% based on SDMT, **p=0.009**; 31.7% to 21.7% based on CVLT-II, **p=0.024**; and 26.1% to 18.6% based on BVMT-R, p value not provided.	In this study, a significant difference was determined in terms of cognitive status between MS patients using IFNβ or GA and the healthy control group. There is no significant difference between IFNβ and GA in terms of cognitive protection.
Ziemssen (2016);[28] Observational, non-interventional, open-label study, 170 sites from Germany	PwMS (n=754); (n=709 [95.6%] had RRMS) Treatment naive (de novo) or previously treated with immunomodulatory drugs or mitoxantrone	• GA 20 mg/mL subcutaneously once daily for 2 years	• MUSIC • PASAT	MUSIC-Cognition • Difference in scores before and after treatment • Previously treated (n=131): 1.39 ± 4.21, **p<0.001.** • De novo (n=301): 1.67 ± 4.37, **p<0.001**; Between baseline and final evaluation, scores improved in 274 patients (60.5%), deteriorated in 125 (27.6%), and remained unchanged in 54 (11.9%); there were no data for • 301 patients. PASAT • Previously treated (n=103): 41.63 points at baseline, 45.76 points at end of study, **p<0.001.** • De novo (n=246): 43.11 points at baseline, 46.76 points at end of study, **p<0.001.**	Findings from the PASAT (n = 370) showed improvements in cognition, **p=0.001**; which was observed among 103 previously treated patients (41.63 points at baseline, 45.76 points at end of study, **p=0.001**) and among the 246 de novo patients (43.11 points at baseline, 46.76 points at end of study, **p=0.001**).
Ziemssen (2015);[27] Observational study	PwMS (n=668) on another DMT from Latin America, Canada/ Western Europe, and Eastern Europe	• Switched to GA 20 mg/d for 24 months	• PASAT	• Patients from all regions showed an improvement in mean PASAT (cognition) scores. • Latin America 6.3 ± 9.1, **p=0.003.** • Canada/Western Europe 3.8 ± 9.6, **p=0.0024.** • Eastern Europe 0.8 ± 5.3, not significant.	Paced Auditory Serial Addition Test and Multiple Sclerosis Inventory Cognition scale scores showed a statical improvement in both GA treated cohorts, **p<0.05**; of Latin America (n=20) and Canada/ Western Europe (n=47). However clinically meaningful improvement in cognition in GA treated MS cohorts over 2 years in Latin America (6.25 points change), whereas the change was not so clinically in cohorts from Canada and western Europe (3.83 points change).

Notes: Bold text indicates significant p-values.

Abbreviations: BICAMS, Brief International Cognitive Assessment for Multiple Sclerosis; BVMT-R, Brief Visuospatial Memory Test Revised; CVLT-II, California Verbal Learning Test, second edition; DMF, Dimethyl fumarate; DMT, Disease-modifying treatment; GA, Glatiramer acetate; IFN, Interferon; IFNβ, Interferon beta; inj, Injectable; MUSIC, Multiple Sclerosis Inventory Cognition; PASAT, Paced Auditory Serial Addition Test; PwMS, Persons with multiple sclerosis; SC, Subcutaneous; SDMT, Symbol Digit Modalities Test; Teri, Teriflunomide.

including Symbol Digit Modalities Test (SDMT), the Multiple Sclerosis Inventory of Cognition (MUSIC), Paced Auditory Serial Addition Test (PASAT), and the Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS) battery, which included SDMT, the Brief Visuospatial Memory Test-Revised (BVMT-R) for visual-spatial memory, and the California Verbal Learning Test, second edition (CVLT-II) for verbal memory.

Lanzillo et al[26] assessed the effect of four platform DMTs (GA [n=37], IFNs [n=156], DMF [n=62], and Teri [n=25]) on cognitive function in 280 persons with RRMS (pwMS) who were on platform DMT treatment for ≥1 year and did not have a clinical relapse six months before study initiation. Regarding clinical and demographic characteristics, pwMS on INF constituted more than half of total study subjects, and were younger with long therapy duration, while those on Teri hardly constituted less than one-tenths of total subjects and were the older with higher disability at the start of study. A slowing of information processing is often seen in MS journey, and SDMT is considered as sensitive to measure this cognitive aspect. The two different groups of researchers in MS field suggest the reliability and validity of SDMT test and support a responder definition of SDMT change of 4 points or 10% in magnitude.[29] Lanzillo et al[26] group found no major change (less than 10%) in cognitive function on SDMT score in MS patients on GA and IFNs, whereas an improvement of more than 10% on SDMT score was seen on DMF and deterioration of 10% on Teri, respectively, in MS patients. On statistical analysis, there was a significant difference (p=0.001) in SDMT scores among all four treatment groups: GA: 36.4 ± 9.5, IFN: 40.6 ± 13.3, DMF: 44.7 ± 14.7, and Teri: 34.7 ± 9.1. A sensitivity analysis considering SDMT scores was performed to avoid outlier-related bias. Compared with INF, pwMS on Teri were the oldest, with higher disability, worst depression at BDI, worst cognitive performances at SDMT (p = 0.001). Although clinically meaningful change of 4 points or more was observed in IFN and Teri group with a statistical significance difference of impact, the authors concluded to be careful in evaluating these results considering the demographic and sample characteristics in the groups (Table 1).

In a multi-center, controlled study, Cinar et al[25] were the first to use the BICAMS battery to monitor cognitive status in pwMS (n=161) treated with GA (n=56), subcutaneous IFNβ-1a (n=53), or IFNβ-1b (n=52) over 12 months. There were significant improvements in the SDMT, BVMT-R, and CVLT-II scores following treatment with GA or IFNβ (p<0.001) as compared to healthy volunteers. This corresponded with a significant decrease in the number of cognitively impaired patients after treatment with GA and IFNs at the end of one-year study period (SDMT: from 28.5% to 20.5%; p=0.009, CVLT-II: from 31.7% to 21.7%; p=0.024, and BVMT-R: from 26.1% to 18.6%; p value not provided). Difference between treatment groups of IFN and GA was not observed in terms of minimal detectable change in SDMT score, as it was less than 10% variation, and it shows that GA and IFNs appear to have similar effect on the cognition. The authors acknowledged the limitation of not being able to include placebo arm of untreated MS cohort in this one-year study.

The QualiCOP study evaluated cognition in pwMS (n=754; 95.6% pwMS) who were previously treated (n=237) or treatment-naive (n=481).[28] Following 2-years of treatment with GA (20 mg/mL), significant improvements (p<0.001) were observed in MUSIC-Cognition and PASAT scores, in both, those previously treated and treatment-naive patients. Paced Auditory Serial Addition Test and Multiple Sclerosis Inventory Cognition scale scores showed robust improvement in cognitive function among previously treated MS cohorts, who switched to GA treatment. In another 2-year observational study consisting of 668 pwMS who switched to GA (20 mg/d) from another DMT, significant improvements in PASAT scores were observed following GA treatment in patients from Latin America (6.3 ± 9.1; p=0.0030), and Canada/Western Europe (3.8 ± 9.6; p=0.0024), but not Eastern Europe (0.8 ± 5.3; not significant).[27] The relevance of considering a change of 4 points in PASAT and SDMT score in evaluating the impact of DMTs on cognition has been acknowledged by different group of researchers.[30] Paced Auditory Serial Addition Test and Multiple Sclerosis Inventory Cognition scale scores showed a statistical improvement in both GA treated cohorts (p<0.05) of Latin America (n=20) and Canada/Western Europe (n=47). A clinically meaningful improvement in cognition in GA treated MS cohorts over 2 years was seen in Latin America cohort (6.25 points change), whereas the change was not so clinically meaningful in cohorts from Canada and western Europe (3.83 points change).

Pain and Spasticity

GA was assessed for pain and spasticity symptoms in three studies using various scales, including the Penn Spasm Frequency Scale (PSFS), Modified Ashworth Scale (MAS), Adductor Tone Rating Scale (ATRS), and Global Pain Score (GPS) (details outlined in Table 2).[31–33]

Spasticity of varying severity affects up to 80% of patients with multiple sclerosis (MS), which is often overlooked and undertreated.[34] Meca-Lallana et al[31] conducted a study to assess the effects of GA on spasticity in patients with relapsing-remitting MS who had been previously treated with IFNβ or were treatment naive in a small cohort (n=28). After 18 months of GA treatment in patients who were previously treated with IFNβ (n=13), statistically significant reductions were observed in PSFS (p=0.002), MAS right hemibody (p=0.002), MAS left hemibody (p=0.045), and GPS (p=0.002) scores. Although clinically meaningful thresholds for changes in muscle tone and muscle spasms have not been formally established in the MS population, a change of 20% from baseline is considered as clinically meaningful.[35] While the ATRS score decreased from 1.15 ± 0.55 to 0.64 ± 0.81, the improvement was not significant. In contrast, in treatment-naive patients (n=15), 12 months of GA treatment decreased PSFS, ATRS, and GPS scores; however, none were statistically significant. The study concluded with the results suggest that GA may reduce spasticity in patients previously treated with IFNβ, which supports the need to conduct large trials for a more precise understanding of the effects of GA on spasticity.

Meca-Lallana et al[32] then assessed pain and spasticity in a larger cohort of pwMS (n=68) who switched from IFNβ (subcutaneous IFNβ-1a [42.6%], intramuscular IFNβ-1a [41.2%], and IFNβ-1b [32.4%]) to GA. The primary end points of the study were to measure the impact of GA at 3, 6 months on pain and spasticity using the scales such as PSFS, MAS, and ATRS. Following the switch to GA, significant reductions ($p<0.01$) in mean scores on all spasticity measurements (PSFS, MAS, and ATRS) were observed at 3- and 6-months post-treatment vs baseline. Likewise, statistically significant reductions from month 3 to month 6 were also observed in MAS scores. A 20% improvement in pain recognized as the MCID in correlation with 18% change on spasticity scales.[36] Similarly, the GPS score for pain reduced from 29.4 ± 22.1 at baseline to 24.7 ± 19.4 at 3 months ($p<0.01$) and 19.1 ± 14.8 at 6 months ($p<0.01$). The researchers of the group endured a study limitation of being of observational and a lack of a comparator group.

In an observational study, Pöllmann et al[33] retrospectively assessed headache frequency, intensity, and duration in MS patients following ≥6 months of treatment with GA (n=49) or IFNβ (n=53). In patients with pre-existing headaches, a more significant proportion of IFNβ-treated patients reported increased headache frequency by >50% (34% vs 6% for GA; p=0.001), increased headache duration by >50% (21% vs 2% for GA; p=0.01). Headache intensity increased by >3 based on the Visual Analogue Scale in 13% of IFNβ-treated patients but in none of the GA-treated patients (p=0.01). New headaches post-treatment was reported by 17% of IFNβ-treated patients vs 2% of GA-treated patients (p=0.001). In another cohort where IFNβ treatment was prospectively assessed (n=65), headache frequency and duration increased by >50% in 18% of patients within the first 6 months of treatment, and new headaches were reported within 24 hours of the first IFNβ injection in 12% of patients. The study concluded that as compared to GA, the IFN therapy could increase the frequency and duration of headache in pwMS to a considerable extent, and another group of researchers found a similar correlation of higher prevalence of headache with IFN therapy in 109 pwMS.[37] The insights from these studies appear to be meaningful and warrant for large clinical trial to address the current limitation of fewer studies with small sample sizes.

Fatigue, Depression, and QoL

A UK MS Register-based study found that the fatigue impacts between 69% and 83% of people with MS (pwMS) and has been graded as a "severe" symptom by 74% of pwMS.[38] In this review, six studies using at least one of the scales to assess fatigue (FIS), depression (BDI-II or BDI-SF), QoL (SF-36), and treatment satisfaction (TSQM) were considered (details outlined in Table 3).

Among pwMS (n=428) treated with GA for more than a year, Fricska-Nagy et al[41] reported that the prevalence of fatigue and depression was 62.4% and 13.4%, respectively. The 62.4% prevalence of fatigue after a mean disease

Table 2 Details of Studies Evaluating the Effect of GA and Other Platform DMTs on Spasticity and Pain in pwMS

Author (Year); Study Type	Population	Treatment	Scale(s)	Results
Meca-Lallana (2012);[32] Observational multi-center study	PwMS (n=68) switched from IFNβ to GA and received GA for at least 24 weeks	• GA (dose as per Summary of Product Characteristics) for 6 months	• PSFS • MAS • ATRS • GPS	• Statistically significant (**p<0.01**) reductions in mean scores on all spasticity measurements (PSFS, MAS, highest MAS score, ATRS, GPS) were observed from baseline to Month 3 and Month 6. • MAS, highest MAS score, and GPS improved further at 6 months vs 3 months. • Patients who did not receive baseline spasmolytic treatment reported statistically significant lower mean (SD) GPS and MAS scores at baseline, Month 3, and Month 6.
Meca-Lallana (2010);[31] Prospective, nonrandomized, open-label, uncontrolled, observational study	PwMS (n=28) who are treatment-naive or switched from IFNβ to GA	• GA 20 mg/d - switched treatment (n=13): 18-month treatment- treatment-naive (n=15): 12-month treatment	• PSFS • MAS • ATRS • GPS	• In patients who switched from IFNβ to GA, statistically significant reductions in MAS right hemibody, **p=0.002**; MAS left hemibody, **p=0.045**; PSFS, **p=0.002**; GPS, **p=0.002** was seen. Improvement in ATRS not significant. • In treatment-naive patients, statistically significant reductions were not observed in any of the above-mentioned parameters. • GA may reduce spasticity in patients previously treated with IFNβ, a finding which was statistically significant, and clinically meaningful (with more the 20% improvement).
Pöllmann (2002);[33] Observational study	PwMS (n=167) on immunomodulatory therapy	• IFNβ prospective (n=65) for 6 months • IFNβ retrospective (n=53) for 1 year • GA retrospective (n=49) for 2 years	• HA frequency and duration • 10-step VAS - HA intensity	• Among the retrospective study groups, in patients with pre-existing HA, HA frequency and duration increased by >50% with IFNβ but not GA; **p=0.001** and **p=0.01**, respectively. HA intensity increased by >3 VAS in IFNβ-treated patients, 13% vs 0%, **p=0.01**. New HA was also significantly higher in IFNβ-treated patients, 17% vs 2% with GA, **p=0.001**. • Among the IFNβ prospective group, HA frequency and duration increased by >50% in 18% of patients and in 35% with pre-existing HA within first 6 months; 12% developed new HA within 24 hours of the first injection.

Notes: Bold text indicates significant p-values.

Abbreviations: ATRS, Adductor Tone Rating Scale; GA, Glatiramer acetate; GPS, Global Pain Score; HA, Headache; IFNβ, Interferon beta; MAS, Modified Ashworth Scale; PSFS, Penn Spasm Frequency Scale; PwMS, Persons with multiple sclerosis; PwMS, Persons with multiple sclerosis; VAS, Visual Analogue Scale.

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Table 3 Details of Studies Evaluating the Effect of GA and Other Platform DMTs on Fatigue, Depression, and Quality of Life in pwMS

Author (Year); Study Type	Population	Treatment	Scale(s)	Results
Naser Moghadasi (2023);[39] Observational study (Phase IV)	PwMS (n=368)	• GA 40 mg • Naive (n=191) • Switchers (n=177)	• BDI-II • MusiQoL	• BDI-II score significantly improved (difference: −2.39; 95% CI: −3.74–1.03), **p<0.001.** • MusiQoL Global Index score did not show significant difference (−0.6; 95% CI: −1.34–2.54), **p=0.54**; however, the psychological well-being, **p=0.02**; and rejection, **p=0.04**; dimensions significantly improved post-treatment
Mitsikostas (2022);[40] Prospective, multi-center, observational study	PwMS (n=214)	• IFN naive with IFNβ (n=58) • IFN naive with GA (n=114) • IFN experienced with GA (n=42) for 12 months	• MFIS-5 • HAM-D • SF-36 • MusiQoL	MFIS-5 • Mean scores indicated improvement at 6 months and 12 months vs baseline for all groups HAM-D • At baseline, most patients had no depression or mild depression. Scores did not deteriorate with time SF-36 • Baseline vs 6 months: GA improved vitality by 24.6%, **p<0.001**; social functioning by 16.1%, **p<0.001**; role emotional by 14.4%, **p<0.001**; and mental health by 16.8%, **p<0.001**. • Baseline vs 12 months: the improvements were sustained for vitality (18.8%), role emotional (11.4%), and mental health (16.8%), **p<0.001** for all. • In IFNβ experienced patients, no significant changes were observed in any SF-36 scores in patients treated with IFNß or GA at 6 and 12 months vs baseline. • In treatment-naive patients GA improved vitality (16.6%), social functioning (16.2%), role emotional (17.4%), and mental health (18.1%) scores at 6 months, and at 12 months only the mental health score (18.4%) vs baseline; **p<0.001** for all. MusiQoL • Minor fluctuations in the mean scores during the study
Lanzillo (2020);[26] Observational study	PwMS (n=280)	• GA (inj, n=37) • IFN (inj, n=156) • DMF (oral, n=62) • Teri (oral, n=25) *(No doses mentioned)*	• FSS • BDI-II • SF-36 • TSQM	FSS • Significant differences between groups, **p=0.026**; worst FSS scores from patients using Teri, **p=0.001**. SF-36 • MCS was significantly lower for Teri vs IFN, **p<0.001**. No significant differences were observed for PCS across treatment groups, p = 0.313. BDI-II • Significant difference among treatments, **p=0.011**; with those treated with Teri showing worst depressive symptoms. TSQM • Trend observed for high TSQM (overall satisfaction) for GA, p=0.10, vs other treatments after removing cognitive compromised patients. • Oral treatments, Teri and DMF, showed higher TSQM (convenience) vs IFN, **p<0.001**. • DMF showed a higher TSQM (side effects) vs IFN, **p=0.014**; while Teri showed a lower score vs IFN, **p=0.014**.
Fricska-Nagy (2016);[41] Observational study	PwMS (n=428)	• GA *(No dose mentioned)*	• FIS • BDI-II • MSQoL-54	• Prevalence of fatigue: 62.4% • Prevalence of depression: 13.4% • 35 of 168 patients with fatigue also had depression • Among the 278 patients with depression, all reported having fatigue • Depression and fatigue had a significant negative influence on all MSQoL-54 subscales

Jongen (2014);[42] Prospective, multi-center, observational study	PwMS (n=67, of which n=38 for treatment naive and n=29 for pre-treated)	• GA for 2 years *(No dose mentioned)*	• FIS • BDI-SF • LMSQoL	FIS • Overall, significantly lower at 18, **p=0.0007**; and 24 months, **p=0.0001**; vs baseline. Similar changes observed in treatment-naive and pre-treated cohorts. BDI-SF • No significant change vs baseline at 18 and 24 months for all cohorts LMSQoL • At 18 months it was significantly higher in the total, **p=0.0192**; and pre-treated groups, **p=0.0291**; vs baseline, but not the treatment-naive group (p=0.2638). At 24 months, there was significant improvement in all 3 groups. • Improvements in the first 6 or 12 months correlated significantly with the 2-year level of fatigue and HRQoL and improvements experienced in the first year were preserved up to the end of the 2-year period
Jongen (2010);[43] Prospective, multi-center, observational study	PwMS (n=197, of which n=106 for treatment naive and n=91 for pre-treated)	• GA for 12 months *(No dose mentioned)*	• FIS • BDI-SF • LMSQoL	FIS: • Decreased at 6 and 12 months in the treatment-naive group, **p<0.01**; not in the pre-treated group. BDI-SF • No change LMSQoL • Significant improvements, **p<0.001**; at 6 and 12 months in treatment-naive patients, but not in the pre-treated group. • At 12 months, LMSQoL score change of ≥3 was observed in 43% of treatment-naive patients, **p<0.001**. • In patients who discontinued GA before 12 months (28.4% of patients), the HRQoL score changes were 0 to negative. • Increase in HRQoL was associated with decreased fatigue.

Note: Bold text indicates significant p-values.

Abbreviations: BDI, Beck Depression Inventory; CI, Confidence interval; DMF, Dimethyl fumarate; FIS, Fatigue Impact Scale; FSS, Fatigue Severity Scale; GA, Glatiramer acetate; HAM-D, Hamilton Scale for Depression; HRQoL, Health-related Quality of Life; IFN, Interferon; IFNβ, Interferon beta; LMSQoL, Leeds Multiple Sclerosis Quality of Life; MCS, Mental Composite Score; MFIS-5, Five-Item Modified Fatigue Impact Scale; MSQoL-54, Multiple Sclerosis Quality of Life-54; MusiQoL, Multiple Sclerosis International Quality of Life; PCS, Physical Composite Score; QoL, Quality of life; PwMS, Persons with multiple sclerosis; SF, Short Form; Teri, Teriflunomide; TSQM, Treatment Satisfaction Questionnaire for Medication.

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duration of 11.23 years is in line with the literature data.[44] The authors of the study suggested that the pwMS, who are susceptible to depression could be benefited from the glatiramer acetate treatment, which warrants further research.

MCID estimates indicate that a difference of at least 0.45 points on the FIS constitutes a clinically significant difference in fatigue. Jongen et al[43] observed that GA treatment significantly reduced fatigue ($p<0.01$) at 6- and 12-months post-treatment in treatment-naive pwMS (n=106) but not in those who received treatment previously (n=91). Decreased fatigue correlated with an increase in QoL. In another observational study with a longer study duration of 24 months, compared with baseline scores, FIS was significantly lower at 18 ($p=0.0007$) and 24 months ($p=0.0001$) in both treatment-naive pwMS (n=38) and those who received treatment previously (n=29), and QoL significantly improved among both groups at 24 months[42] and this can be correlated with improvement of 0.52 points on FIS scale, and could be considered as clinically meaningful on benchmark of MCID for FIS. In both studies, there was no significant difference in BDI-SF scores post-treatment with GA.

Naser Moghadasi et al[39] showed that GA treatment (40 mg) alleviated depressive symptoms with a significant improvement in BDI-II scores (−2.39; 95% confidence interval [CI]: −3.74–-1.03; $p<0.001$). While there was no significant difference in the overall Multiple Sclerosis International QoL (MusiQoL) score post-treatment ($p=0.54$), the psychological wellbeing ($p=0.02$) and rejection ($p=0.04$) dimensions improved significantly.

An observational study by Lanzillo et al[26] evaluated the effect of platform DMTs on fatigue, depression, QoL, and treatment satisfaction in pwMS (n=280). Patients on Teri had the worst Fatigue Severity Scale (FSS) (Teri: 42.0 ± 14.0; DMF: 32.4 ± 18.3; GA: 32.5 ± 16.6; IFN: 30.9 ± 16.7; $p<0.001$), BDI-II (Teri: 12; DMF: 7; GA: 7; IFN: 6; $p=0.011$), and SF-36 Mental Composite scores (Teri: 45.2 ± 2.7; DMF: 47.6 ± 3.7; GA: 47 ± 3.3; IFN: 48 ± 3.2; $p<0.001$); however, these patients also had the best TSQM scores, especially with respect to convenience ($p<0.001$) and side effects ($p<0.001$).

Mitsikostas et al[40] evaluated the impact of GA or IFNβ on fatigue, depression, and QoL in pwMS (n=214) who were either IFNβ-naive or IFNβ-experienced over 12 months. The fatigue score improved slightly over 12 months, while the depression scores did not deteriorate over time. Based on the SF-36 scores, following 6 months of treatment, overall, GA significantly improved vitality (24.6%; $p<0.001$), social functioning (16.1%; $p<0.001$), role emotional (14.4%; $p<0.001$), and mental health (16.8%; $p<0.001$) vs baseline. These effects were sustained for vitality (18.8%; $p<0.001$), role emotional (11.4%; $p<0.001$), and mental health (16.8%; $p<0.001$) at 12 months. In IFNβ-naive patients who were treated with GA, significant improvements ($p<0.001$) were observed in vitality, social functioning, role emotional, and mental health scores at 6 months vs baseline. However, no significant improvements were observed with IFNβ treatment or GA treatment in IFNβ-experienced patients at 6- and 12-months vs baseline.

Effectiveness

The effectiveness of GA in MS patients was assessed across eight observational studies (details outlined in Table 4)[27,28,39,45–49] by estimating ARR, AER, and MRI outcomes. In studies where GA was assessed without any comparator, the ARR significantly reduced post-treatment vs baseline[27] in both treatment-naive patients and those who switched from other DMTs.[28,39,49] A long-term 27-year follow-up study comparing early- vs delayed-start in GA treatment in relapsing pwMS (n=251) observed that there was no significant difference in ARR between the groups (early-start: 0.328 vs delayed-start: 0.414; $p=0.1278$) and the proportion of relapse-free patients (early-start: 16.9% vs delayed-start: 11.7%; $p=0.2421$); however, the accumulated ARR over 0–3 years was significantly lower in early-start group ($p=0.0255$).[46] Bovis et al[45] compared the effectiveness of GA vs IFNβ-1a by implementing a previously published statistical method using two independent datasets, a randomized controlled trial and a cohort study. Both studies found that GA was slightly superior to IFNβ-1a with the overall ARR ratios of 0.72 (95% CI: 0.55–0.95; $p=0.018$) and 0.84 (95% CI 0.74–0.95; $p=0.005$), respectively. Patients who were younger at treatment initiation, male, with higher disease activity, longer disease duration, and more significant disability were likely to benefit more from GA than from IFNβ-1a.

Over 5 years, Lebrun-Frenay et al[47] assessed exacerbations in pwMS (n=852) who were treatment-naive or switched to GA from another DMT. The AER decreased from 0.64 exacerbations/year (95% CI: 0.59–0.70) in the 1st year to 0.28 exacerbations/year (95% CI: 0.24–0.32) in the 5th year, and 316 (37.2%) patients remained exacerbation-free throughout the follow-up period. One-third of patients continued GA treatment throughout the 5-year study period, of which 127

Table 4 Studies Evaluating the Effectiveness of GA and Other Platform DMTs in pwMS

Author (Year); Study type	Population	Treatment	Measurement(s)	Results
Naser Moghadasi (2023);[39] Observational study (Phase IV)	Patients with RRMS (n=368)	• GA 40 mg • Naive (n=191) • Switchers (n=177)	• ARR • MRI	• ARR significantly reduced (RR: 0.65; 95% CI: 0.43–0.98), **p<0.04.** • The number of gadolinium-enhancing lesions significantly decreased (Difference: −0.38; 95% CI: −0.64–-0.12), **p=0.004**. • No significant reduction in the number of T2 lesions (Difference: −0.32; 95% CI: −0.94–-0.29), p=0.3.
Ford (2022);[46] Open-label extension study	Patients with relapsing MS (n=251)	• GA early start (ES; n=125) • GA delayed start up to 3 years (DS; n=126) • GA at 20 mg/mL subcutaneously once-daily (QD), with an option to switch to 40 mg/mL subcutaneously three times weekly (TIW) when available	• ARR	• No difference in ARR (ES: 0.328 vs DS: 0.414), p=0.1278. • Accumulated ARR over 0–3 years was significantly lower in the ES group, **p=0.0255**. • No difference in proportion of relapse-free participants (ES: 16.9% vs DS: 11.7%), p=0.2421.
Bovis (2021);[45] Observational study	Training - CombiRx RCT (IFNβ-1a + GA with IFNβ-1a or GA + matched placebo used as monotherapy Validation - MSBase cohort	• GA (20 mg/d, n=255) • IFNβ-1a (30 mg once weekly, n=248) • Combination treatment • For 84 months	• ARR	• In the CombiRx trial, patients with the lowest treatment response score (25% of the total cohort), ARR was 60% lower among those treated with GA vs IFNβ-1a (ARR ratio=0.40; 95% CI: 0.25–0.63). Those with the highest treatment response score (25%), ARR was 14% lower among those treated with IFNβ-1a vs GA (ARR ratio=1.14: 95% CI: 0.59–2.18). In the 50% of patients with intermediate treatment response score, ARR was 10% lower among those treated with GA vs IFNβ-1a (ARR ratio=0.90: 95% CI: 0.61–1.34). Overall, treatment with GA reduced the ARR compared to IFNβ-1a by 28% (ARR ratio=0.72; 95% CI: 0.55–0.95), **p=0.018**. • In the MSBase cohort, the overall ARR ratio between GA vs IFNβ-1a was 0.84 (95% CI: 0.74–0.95), **p=0.005**; indicating a slight superiority of the effectiveness of GA over IFNβ-1a.
Lebrun-Frenay (2019);[47] Observational study	Patients with RRMS (n=852, treatment naive and those switching from other DMTs)	• GA (20 mg/d, n=269) for 5 years	• AER	• Median treatment duration: 3.4 years • 5-year AER=0.41 (95% CI: 0.39–0.44) exacerbations/year; decreased from 1st year (0.64; 95% CI: 0.59–0.70) to 5th year (0.28; 95% CI: 0.24–0.32) exacerbations/year. • 316 (37.2%) patients remained exacerbation-free throughout; 80 (9.4%) presented ≥5 exacerbations. • Of 269 treated with GA continuously for 5 years, 127 (47.5%) remained exacerbation-free throughout. • Exacerbation rate was higher among on-treatment patients who discontinued GA, **p<0.0001**.
Zecca (2019);[49] Prospective, multi-center, observational study	Patients with MS (n=194, treatment naive and those switching from other DMTs)	• GA dose not mentioned • Naive (n=64) • Switchers (n=130)	• ARR	• Proportion of patients still on GA after 12 months: naive (n=89, 68.5%); switcher (n=43, 67.2%). • ARR in the previous 24 months from baseline naive: 0.5 (0.5–1.0) vs switchers: 0.5 (0.0–0.5), **p=0.005**. • ARR (12 months - baseline) naive: 0.0 (0.0–0.0), **p=2.9e-10**; switchers: 0.0 (0.0–0.0), **p=0.022**. • Naive patients experiencing relapses 0: 111 (85.4%); 1: 16 (12.3%); 2: 2 (1.5%); 3: 1 (0.8%). • Switcher patients experiencing relapses 0: 51 (79.7%); 1: 11 (17.2%); 2: 1 (1.6%); 3: 1 (1.6%).
Ziemssen (2016);[28] Observational study	Patients with MS (n=754; of which n=709 [95.6%] had RRMS, treatment naive (de novo) or previously treated with immunomodulatory drugs or mitoxantrone)	• GA 20 mg/mL SB once daily for 2 years	• ARR	• ARR significantly reduced 0.87 vs 0.49, **p<0.001**. In previously treated patients ARR reduced 0.98 vs 0.54, **p<0.001**; and de novo patients 0.81 vs 0.48, **p<0.001**. • Relapse-free patients annually increased from 10.7% at baseline to 68.7% post-treatment. Patients with no relapses in the prior 2 years increased from 17.6% and 7.2% to 64.7% and 70.7% in previously treated and de novo patients, respectively.
Meca-Lallana (2016);[48] Observational study	Patients with RRMS (n=54) previously treated with IFNβ	• GA ≥ 6 months	• ARR • MRI	• ARR estimated at 0.14 vs 0.7 in the year prior to switching to GA. • 94.4% without relapse at Month 6 vs 53.7% at baseline. • n=3 had 4 relapses; mild n=3 and moderate n=1. • Active T2-lesions n=16 at baseline vs n=11 at 6 months; number of lesions not significantly different (18.0 ± 14.9 at baseline vs 12.8 ± 9.5 at 6 months), p=0.125. • Gadolinium-enhanced lesions n=16 at baseline vs n=0 at 6 months; number of lesions not significantly different (0.5 ± 0.6 at baseline vs 0.0 at 6 months ± 0.0), p=0.059.
Ziemssen (2015);[27] Observational study	Patients with RRMS (n=668) on another DMT from Latin America, Canada/ Western Europe, and Eastern Europe	• Switched to GA 20 mg/d for 24 months	• ARR - Relapse	• ARR significantly reduced from 0.86 to 0.32, **p<0.001** vs baseline; reduction was observed irrespective of region

Notes: Bold text indicates significant p-values.

Abbreviations: AER, Annualized exacerbation rate; ARR, Annualized relapse rate; CI, Confidence interval; CombiRx, Combination Therapy in Patients With Relapsing-Remitting Multiple Sclerosis; DMT, Disease-modifying treatment; GA, Glatiramer acetate; IFNβ, Interferon beta; MRI, Magnetic resonance imaging; PwMS, Patients with multiple sclerosis; RCT, Randomized clinical trial; RRMS, Relapsing-remitting multiple sclerosis; SB, subcutaneously.

(47.5%) remained exacerbation-free. Interestingly, the on-treatment AER was higher among patients who discontinued GA (p<0.0001).

Lesions were measured at baseline and post-treatment with GA in two studies.[39,48] Naser Moghadasi et al[39] assessed the effectiveness of GA treatment (40 mg) in 368 pwMS through MRI-measured MS activity. After 14 months of GA treatment, the number of gadolinium-enhanced lesions reduced significantly (−0.38; 95% CI: −0.64–-0.12; p=0.004 vs baseline); however, the decrease in the mean number of T2 lesions was not significant. Meca-Lallana et al[48] observed that in pwMS previously treated with IFNβ (n=54), following 6 months of switching to GA treatment, fewer patients had active T2 lesions (11 vs 16 at baseline) and gadolinium-enhancing lesions (0 vs 16 at baseline); however, the difference was not significant.

Discussion

This narrative review is one of the few pragmatic exercises corroborating clinical evidence to help improve our understanding of the impact of platform DMTs in pwMS on associated symptoms of cognitive dysfunction, pain and spasticity, fatigue, depression, and overall QoL. Findings from this review highlight that even after 37 years since the first randomized pilot Phase III trial on MS,[50] the evidence on MS-related symptom management and the effectiveness of therapies in pwMS continues to evolve.

The four studies found a differential impact of platform DMTs on cognitive function on SDMT and PASAT scales.[25–28] Although a statistical difference of the impact on cognition was found by Lanzillo et al[26] group showing superior effect by GA, IFN, and DMF, the MDC change of 4 points on SDMT scale was found in the pwMS cohort treated with DMF and Teri. The different demographic variables and sample characteristics needs to be considered in interpretation of the results. A multicentre study by Cinar et al[25] group found a statistically significant improvement in cognition (on SDMT) with GA treatment as compared to IFN treatment, and similar findings were observed in Qualicop study[28] on PASAT scale of cognition, where the MDC levels were also achieved.

The 2 studies by Meca-Lallana et.[31,32] observed that switching from IFNs to GA treatment in pwMS reduced the pain and spasticity on measurement scales of MAS, PSFS, and ATRS. The improvement levels were statistically significant, and above the MDC on the scales. Considering small sample sizes in both the studies, the authors concluded the need of conducting large trial for generalizability of the finding. At the time of review, there were no studies comparing the impact of other two traditional first line therapies of DMF, and Teri on pain and spasticity. A retrospective assessment by Pollmann et al[33] found that there is an increased frequency, intensity, and duration of headache on VAS scale in pwMS treated with IFNs compared to GA, and a similar observation was found by another group of researchers. Our review findings showed that GA treatment had a considerable effect on fatigue and overall QoL, as observed across three studies.[40,42,43] Two studies using the FIS scale to measure fatigue showed that GA improved symptoms of fatigue within 6 months and the beneficial effects were sustained up to 24 months, especially in treatment-naive patients.[42,43] The study by Mitsikostas et al[40] reported that in treatment-naive pwMS, GA treatment improved some QoL parameters; however, IFNβ treatment did not. Evidence that IFNβ treatment may exacerbate depression in pwMS is mixed.[51,52] GA had a slight impact on depression, with a significant improvement in BDI-II score in one study.[39] Nonetheless, given that fatigue and depression are two primary symptoms that impair QoL in pwMS,[52] identification of at-risk patients and appropriate treatment are crucial in MS care.

The effectiveness data, though our search was limited to the last 15 years, provides an overview of the effectiveness of GA and other DMTs in managing RRMS across eight real-world studies. Overall, GA was effective at reducing ARR in both treatment-naive patients and those switching from other DMTs,[27,28,45,48,49] consistent with a previously published study, which showed that effectiveness was maintained up to 9 years.[53] This reduction in relapses is also consistent with the evidence that RRMS progresses within 15–30 years with limited relapses.[54–56] A long-term 27-year continuous follow-up study showed sustained clinical benefits with early initiation of treatment with GA vs delayed treatment, highlighting the importance of early treatment.[46] These findings reflect the long-term clinical benefit of continued use of GA in reducing relapses.[57–59] Furthermore, Bovis et al[45] showed that GA was likely to be more effective in certain patient subgroups (ie, those who were younger at treatment initiation, male, with higher disease activity, longer disease duration, and more significant disability) than IFNβ-1a. Similar subgroup analyses on the impact of DMTs on MS-related

symptoms could provide a better understanding of DMTs that are effective as well as beneficial for symptom management.

The review has certain limitations of including studies from PubMed database with full-text English articles and considering selective scales for comparing the impact of DMTs on symptoms. The varied study design, methodology and symptom scales used in qualifying studies needs a consideration in interpretation of results. Systematic reviews or meta-analyses were not feasible since there were not many studies using the same scales for symptom assessment. Furthermore, although there are multiple scales for assessing fatigue, depression, and QoL, the review only considered those scales that are most used in everyday clinical practice and contemporary research. However, for other symptoms, there was no limitation on the scales used. While the observations from our review align with previous observations of symptom management in pwMS treated with platform DMTs, one needs to be cautious while making interpretations across studies considering different study populations, sample sizes, geographical locations, baseline disease characteristics, comorbidities, study design, and treatment dose and duration. Limited-to-no evidence was available for anxiety, visual impairment, sexual dysfunction, and bowel and bladder dysfunction, highlighting the need for future research to focus on these symptoms. In addition, although our review findings were consistent regarding the overall improvements in symptoms and effectiveness of GA in pwMS as observed across studies, limiting the effectiveness findings to the last 15 years and analyzing studies with specific scales could impact the generalizability of the findings. Finally, the review focused primarily on the impact of platform DMTs on MS-related symptoms; however, including other DMTs approved for MS could draw more evidence to enable better clinical decisions.

Nonetheless, our findings are one of the few to consolidate recent evidence on symptom management in pwMS using GA and other platform DMTs. To enable targeted therapeutic decisions, there is a need to understand the importance of the impact of DMTs on the associated symptoms of MS, and ultimately identifying the patient population with the most optimal clinical response to DMTs. The cumulative evidence from our review ascertains that the continued use of GAs in pwMS despite other effective DMTs is attributable to its acceptable safety profile with a lack of late adverse events, fewer immunologic complications, and lower level of comorbidities interaction,[60] and that the drug is generally well tolerated for a prolonged period of over 25 years.[46]

Conclusion

A review of the current evidence to improve our understanding on the impact of platform DMTs on MS symptoms was conducted. Most of the studies looked at the impact of glatiramer acetate and interferons on cognition, pain, spasticity, fatigue, and depression, which affect the quality of life in pwMS. Treatment with GA resulted in statistically significant improvement in cognition on PASAT scale in two studies, which surpassed the clinically meaningful minimum detectable change. Changes in SDMT scale though showing statistically superior effect of GA and IFN did not meet the defined minimum detectable change criteria.

The pain and spasticity could reduce in pwMS after switching from IFNs to GA treatment, as observed in 2 studies on MAS, PSFS, and ATRS scales. Level of improvement was not only statistically significant but also had major positive shift on minimum detectable criteria. Although the sample size was small in these studies, the findings call for a larger clinical trial to unravel more insights, and generalizability. Two-thirds of pwMS experience fatigue and four studies assessed the impact of DMTs on FIS scale. GA treatment alleviated fatigue with a sustained beneficial effect, however, no other DMTs were studied in these couple of studies. A comparative study also found a beneficial effect of GA over IFN. Whereas one study comparing all four DMTs found significant improvement in fatigue with GA, IFN, DMF, whereas fatigue worsened in TERI cohort. Interpretation of findings may require careful consideration to different sample sizes, and design of the studies.

Together with its demonstrated real-world effectiveness in reducing ARRs and delaying disease progression, GA may offer better QoL to pwMS through the alleviation of cognitive impairment, pain and spasticity, headache, fatigue, and depression. These findings should be of interest to clinicians globally as they provide the most up-to-date cumulative evidence on the role of GA and other platform DMTs in personalized management in pwMS.

Highlights

- PwMS experience a wide range of symptoms, which ultimately impact QoL.
- DMTs are primarily prescribed to reduce relapses and exacerbations in pwMS.
- The impact of platform DMTs on associated symptoms in pwMS is reviewed.
- Overall, GA improves cognition, pain, spasticity, fatigue, and QoL scores.
- Findings will help physicians make informed treatment decisions for MS management.

Abbreviations

AER, Annual exacerbation rate; ARR, Annual relapse rate; ATRS, Adductor Tone Rating Scale; BDI-II, Beck's Depression Inventory; BDI-SF, Beck Depression Inventory-Short Form; BICAMS, Brief International Cognitive Assessment for Multiple Sclerosis; BVMT-R, Brief Visuospatial Memory Test-Revised; CI, Confidence interval; CNS, Central nervous system; CVLT-II, California Verbal Learning Test, second edition; DMF, Dimethyl fumarate; DMT, Disease-modifying therapy; EMA, European Medicines Agency; FIS, Fatigue Impact Scale; FSS, Fatigue Severity Scale; GA, Glatiramer acetate; GPS, Global Pain Score; HAM-D, Hamilton Depression Rating Scale; IFNβ, Interferon beta; MAS, Modified Ashworth Scale; MFIS-5, Modified Fatigue Impact Scale-5-Item; MRI, Magnetic resonance imaging; MS, Multiple sclerosis; MUSIC, Multiple Sclerosis Inventory of Cognition; MusiQoL, Multiple Sclerosis International QoL; PASAT, Paced Auditory Serial Addition Test; PSFS, Penn Spasm Frequency Scale; PwMS, Persons with multiple sclerosis; QoL, Quality of life; RRMS, Relapsing-remitting multiple sclerosis; SDMT, Symbol Digit Modalities Test; SD, Standard deviation; SF-36, Short Form-36; TSQM, Treatment Satisfaction Questionnaire for Medication; US FDA, United States Food and Drug Administration.

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