A Targeted Literature Search and Phenomenological Review of Perspectives of People with Multiple Sclerosis and Healthcare Professionals of the Immunology of Disease-Modifying Therapies

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ABSTRACT

Introduction: The mechanisms of action of disease-modifying therapies (DMTs) for multiple sclerosis (MS) are complex and involve an interplay of immune system components. People with MS (PwMS) may lack a clear understanding of the immunological pathways involved in MS and its treatment; effective communication between healthcare professionals (HCPs) and PwMS is needed to facilitate shared decision-making when discussing the disease and selecting DMTs and is particularly important in the coronavirus disease 2019 (COVID-19) era.

Methods: In this patient-authored two-part review, we performed a targeted literature search to assess the need for better communication between HCPs and PwMS regarding treatment selection, and also conducted a

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qualitative survey of four patient and care-partner authors to obtain insights regarding their understanding of and preferences for the treatment and management of MS.

Results: Following a search of the Embase and MEDLINE databases using Ovid in June 2020, an analysis of 40 journal articles and conference abstracts relating to patient empowerment and decision-making in DMT selection for MS showed a preference for safety and efficacy of treatments, followed by autonomy and convenience of administration. A need for better communication between HCPs and PwMS during treatment selection to improve patient satisfaction was also identified. The open survey responses from the patient authors revealed a need for greater involvement in decision-making processes and desire for improved communication and information tools.

Conclusions: This targeted literature search and phenomenological review confirms PwMS preferences for empowered decision-making in disease management and treatment selection, to optimize independence, safety, and efficacy. It also identifies an unmet need for improved communication and information tools that convey MS information in a relatable manner. Furthermore, this review seeks to address this unmet need by providing plain language figures and descriptions of MS immune mechanisms that can be used to facilitate discussions between HCPs and PwMS.

PLAIN LANGUAGE SUMMARY

In multiple sclerosis (MS), there are different cells in the immune system that contribute to the disease. The main cells in the immune system are T and B cells. People with MS (PwMS) might not be familiar with details about the immune system, and healthcare professionals might not always communicate details about how treatments work clearly to PwMS when choosing treatments with them. It is important for PwMS to have all the information they need to help make decisions about treatments. This information needs to be given in a way they can understand. This is especially important during the coronavirus disease 2019 (COVID-19) pandemic. In this paper, we first looked at what research has already been published about what is most important to PwMS when making treatment decisions. The existing research says that safety and effectiveness are the most important things and that PwMS prefer treatments that they can take themselves. PwMS also need better communication and information from doctors to make decisions and to help explain how MS treatments work in the body. Next, we gave a survey to the patients who are authors of this paper to ask about what is important to them when making treatment decisions. Their answers were very similar to the existing research. Overall, PwMS need better communication from healthcare professionals about the immune system. This paper also includes plain language descriptions and figures to help healthcare professionals explain and discuss the importance of the immune system in MS with PwMS.

Key Summary Points
Why carry out this study?
The mechanisms of action of disease-modifying therapies (DMTs) for multiple sclerosis (MS) are complex and involve an interplay of T cells, B cells, and other immune system components.
Informed, shared decision-making empowers people with MS (PwMS) and results in improved care, but many PwMS may not be familiar with or fully understand the immunological concepts involved, and healthcare professionals (HCPs) may not be able to communicate the concepts clearly.
What was learned from the study?
This study involved a targeted literature search to establish PwMS preferences for safety and efficacy of DMTs through routes that optimize independence, and to identify unmet needs for improved communication between HCPs and PwMS.
A qualitative survey of the patient authors of this work confirmed these findings and provided phenomenological insights into the decision-making process.
This review involving patient and care-partner authors further seeks to counter the identified unmet need for better communication by providing plain language explanations and figures of immune mechanisms in MS to serve as information tools for HCPs to use when communicating and discussing immune concepts with patients.

INTERACTIVE INFOGRAPHIC

This article contains an interactive infographic of the immune system in MS. To view it, click here: https://sn.pub/BOTxix.

INTRODUCTION

Multiple sclerosis (MS) is a chronic, progressive, immune-mediated disease characterized by demyelination of the central nervous system leading to neurological and physical disability [1, 2]. It is estimated that MS affects over 2.8 million individuals worldwide [3], and the prevalence in the USA has been estimated to be as high as 1 million people [4]. Owing to the complexity of the disease, theories of MS immunopathogenesis have evolved over the years, with current models focusing on the interplay of T and B cells, evidenced by the overlap of effects on these cell subsets by disease-modifying therapies (DMTs) [5].

Many people with MS (PwMS) may not be familiar or comfortable with MS terminology, including immunology and drug mode/mechanism of action (MoA) terms [6]. However, given that healthcare professionals (HCPs) and PwMS consider many factors when selecting a DMT, such as efficacy, safety, administration route, and frequency, broader comprehension of MS immunology and terminology would be useful. A better understanding of potential treatment effects may lead to more informed decision-making when choosing DMTs. However, the importance and relevance to PwMS of comprehending these concepts in informing choices when selecting new DMTs is not currently known. Moreover, PwMS' understanding of how DMTs can affect B and T cells, and interpretations of risk and administration preferences for therapies, may have been influenced by the coronavirus disease 2019 (COVID-19) pandemic. While safety and efficacy may be expected to take precedence over MoA knowledge in PwMS' considerations of DMTs, understanding treatment MoAs can meaningfully inform safety and efficacy, and there is a clear need for such information to be more clearly and consistently accessible, in terms of both

content and methods of communication. These concepts were initially identified and explored in a poster presented at the MS Virtual 8th Joint ACTRIMS-ECTRIMS Meeting 2020 [7].

The Immune System in MS

While MS pathogenesis is highly complex and not fully elucidated, it is understood to be mediated in part by the interplay and balance of B and T cells [5]. In MS, multiple immunological and inflammatory processes, including axonal damage and demyelination, gliosis, cortical neurodegeneration, and neuronal loss, result in atrophic lesions in the brain [8, 9]. These processes are largely driven by: (1) effector B cells and B-cell lineage plasmablasts and plasma cells generating autoreactive oligoclonal antibodies, (2) circulatory cytotoxic T cells that have migrated across the blood–brain barrier, and (3) complement elements and other innate components of the immune system such as microglia and inflammatory mediators such as cytokines [8, 9]. Furthermore, there is an imbalance in the regulatory T and B cells that usually keep these inflammatory and cytotoxic processes in check and maintain immunological homeostasis, resulting in unregulated immune-mediated tissue damage (Fig. 1) [10]. See "Box 1" for a lay language explanation of MS immunology.

Box 1. The Immune System in MS

In multiple sclerosis (MS), there is destruction of the protective coating of the nerves. This protective coating is called the myelin sheath, and it is made up of individual myelin cells. This process of destruction is called "demyelination" and referred to as "lesions" or areas of brain damage. There is also more general inflammation and destruction of the brain cells, particularly the neurons. This is sometimes referred to as "atrophy." Some of the demyelination and atrophy is caused by signals from the immune system that kill or damage the myelin cells, neurons, and other brain cells. These immune signals normally protect the body from infections, but in autoimmune diseases such as MS, they lead to the immune system's mistakenly attacking the body's own cells. Immune cells that target the body's own cells are known as "autoreactive."

There are several types of immune signals, and they come from different cells of the immune system. The two main types of immune cells that are involved in MS are called "B cells" and "cytotoxic T cells." "Cytotoxic" means that something is toxic to cells. Other immune cells also play a role, such as "regulatory T and B cells," which are important for stopping other cells from sending too many damage signals. This helps create a balance between immune responses that are too strong or too weak (Fig. 1a). Usually, B cells produce types of molecules called "antibodies" that travel in the blood and help fight infections. Cytotoxic T cells deliver the damage signal directly to infected cells using molecules on the surface of the T cell (Fig. 1b). In MS, B cells, antibodies, and cytotoxic T cells can mistakenly kill or damage myelin cells, neurons, and other brain cells. "Complement" and "cytokines" are other types of damaging molecules made by other cells of the immune system that can also cause general inflammation, atrophy, and demyelination. In MS, the overall balance between damaging cells and regulating cells is lost (Fig. 1c).

Disease-Modifying Therapies and Their Mechanisms of Action

DMTs are immunomodulatory therapies that can change or alter the MS disease course by reducing the number of relapses, reducing the appearance of new lesions on magnetic resonance imaging, and slowing progression and atrophy [11, 12]. Recent evidence has shown that there is significant interplay and an overlap of the effects of DMTs between lymphocyte subsets [5, 13]. The relationship between B and T cells is highly complex, and introducing immune modulation into this system can have clear impacts on the balance of these cell populations. At the time of publication, there are 22

◄**Fig. 1** The balance of the adaptive immune system and MS. **a** The resting immune system. On one side, inflammatory and reactive mechanisms limit infections and respond to foreign antigen. On the other side, regulatory mechanisms keep the adaptive response in check and maintain a homeostatic balance. **b** The immune system during an infection. The infection has already shifted the balance towards tolerance, so inflammatory and reactive mechanisms are upregulated to fight the infection and restore homeostasis. Regulatory mechanisms are downregulated. **c** The immune system in MS. The balance is shifted towards autoimmunity and autoreactivity, but the regulatory homeostatic mechanisms are not sufficient to curb the immune responses. Autoreactive lymphocytes migrate into the central nervous system and through a number of pathogenic mechanisms cause widespread demyelination, gliosis, and neurodegeneration, forming lesions of atrophic brain tissue. *MS* multiple sclerosis

branded or generic variations of DMTs approved by the US food and Drug Administration for the treatment of relapsing MS, which can be summarized into five overall drug categories based on their immunomodulatory effects (Table 1) [14].

The majority of DMTs have direct impacts on most lymphocytes, but some can target specific populations. The small-molecule modulators of the sphingosine-1-phosphate receptor prevent egression of autoreactive T cells from the lymph nodes and downregulate inflammatory mechanisms. However, non-lymphatically sequestered cells such as circulatory effector B cells are known to be unaffected by this MoA [15–17]. Anti-α4-integrin monoclonal antibodies prevent endothelial migration of lymphocytes across the blood–brain barrier into the central nervous system. Anti-CD52 monoclonal and DNA synthesis and repair inhibitors are immunosuppressive and immunoablative agents that mediate lymphocyte depletion of both B and T cells [15]. However, there are also B-cell-specific depletion therapies, anti-CD20 monoclonal antibodies, that act mostly on B lineage cells; Bruton's tyrosine kinase inhibitors are also being investigated as potential B-cell-

Table 1 Categories of FDA-approved disease-modifying therapies for MS [14]

Immunomodulatory effect	General mechanism of action	Route of administration
Prevention of lymphocyte egression from lymph nodes, i.e., retention of lymphoid cells in the lymph nodes	S1P receptor downregulation	Oral
Prevention of lymphocytic endothelial migration	Anti-α4-integrin monoclonal antibody	Infusion
Lymphocyte depletion	Anti-CD52 monoclonal antibody	Infusion
	DNA synthesis and repair inhibition	Oral and infusion
B-cell-specific depletion	Anti-CD20 monoclonal antibody	Infusion and injection
Suppression of inflammatory processes	Myelin basic protein mimicry	Injection
	Nrf2 pathway downregulation	Oral
	Interferon receptor activation	Injection

CD cluster of differentiation, *FDA* Food and Drug Administration, *MS* multiple sclerosis, *Nrf2* nuclear factor erythroid 2-related factor 2, *S1P* sphingosine-1-phosphate
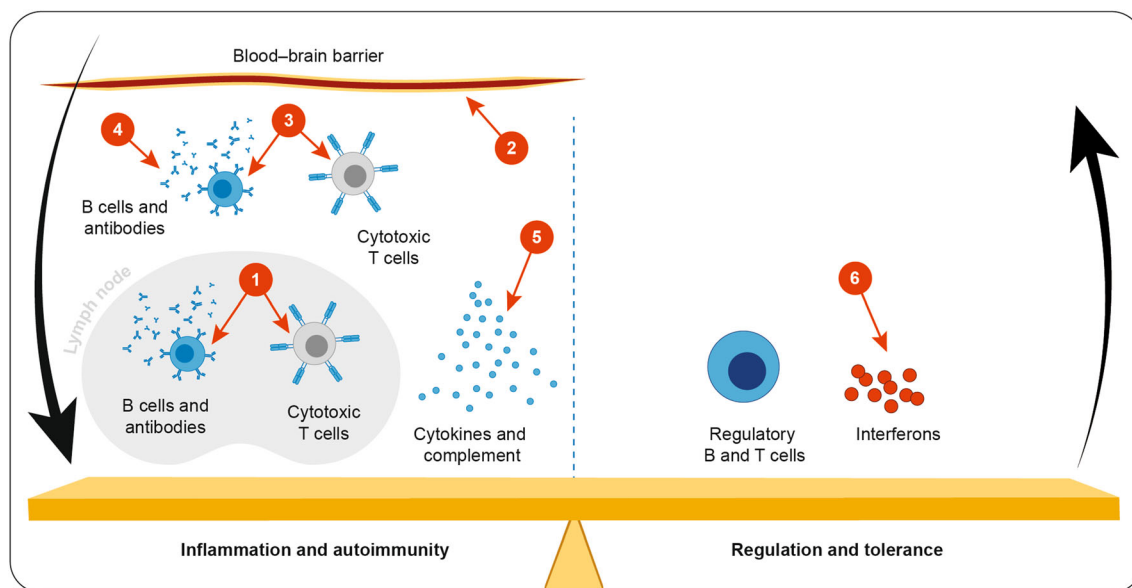
Fig. 2 The effect of DMTs on the immune system in MS. (1) S1P receptor modulators prevent autoreactive lymphocytes from egressing from the lymph nodes via S1P receptor downregulation. (2) Endothelial migration of autoreactive lymphocytes across the blood–brain barrier is blocked by anti-α4-integrin activity. (3) Immunosuppression and lymphocyte cell death to varying degrees are driven via inhibition of DNA synthesis and repair mechanisms and anti-CD52 activity. (4) B-cell depletion and death via B-cell-specific anti-CD20 activity. (5) Glatiramer acetate mimics myelin basic protein to redirect inflammatory responses; fumarate therapies downregulate the Nrf2 pathway to slow inflammation. (6) Interferon therapies mimic interferons to upregulate inherent immunosuppressive mechanisms of the regulatory immune system. *CD* cluster of differentiation, *DMT* disease-modifying therapy, *Nrf2* nuclear factor erythroid 2-related factor 2, *S1P* sphingosine-1-phosphate

specific therapies [18]. Finally, fumarate therapies, interferon therapies, and glatiramer acetate all act to suppress and mitigate inflammatory processes via nuclear factor erythroid 2-related factor 2 pathway downregulation, interferon receptor activation, and myelin basic protein mimicry, respectively (Fig. 2). See "Box 2" for a lay language explanation of DMT MoAs.

Box 2. How DMTs Work

Disease-modifying therapies (DMTs) work by acting on different cells or molecules of the immune system to affect the balance of "reactive" immune cells versus "regulating" immune cells. Immune cells that react to the body's own cells are known as "autoreactive." Most DMTs work by reducing the ability of autoreactive immune cells to kill or damage myelin cells, neurons, and other brain cells. Others work by improving the ability of regulating cells to control the immune system. Some DMTs can be designed to target specific cells of the immune system. But, because the immune system is very complex, some studies show that DMTs can also affect other cells as well as the overall balance of the immune system (Fig. 2).

In MS, B and T cells leave the lymph nodes and move from the blood into the brain and spinal cord to cause damage. This is known as crossing the "blood–brain barrier." Some DMTs work by preventing the autoreactive B and T cells from leaving the lymph nodes (1). Other DMTs work by stopping the autoreactive B and T cells from crossing the blood–brain barrier (2). These DMTs prevent B and T cells that are autoreactive from traveling around the body, but still let other cells that

(MeSH) to help narrow the results. These are scientific terms for different medical problems used by healthcare professionals. You can read more about MeSH terms at the National Library of Medicine website: https://meshb.nlm.nih.gov/search.

Survey and Correspondence Insights

The specific methods of data collection for the questionnaire have been presented elsewhere [7]. In brief, a qualitative questionnaire was designed by two authors (A.R. and J.L.W.) in December 2018 based on preliminary discussions with the patient authors. This was designed to explore factors most important to PwMS when considering potential DMTs following a phenomenological PwMS narrative approach. This included PwMS' understanding of the immunological processes of MS and the MoAs of MS treatments, and preferences regarding route of administration and provision of MS clinical information. The questionnaire was distributed via email to three PwMS (J.B., D.C., and T.S.) and one care partner (J.C.) based on their advocacy expertise and involvement in the patient-authored literature, all of whom are authors of this work. General insights were gathered from the HCP authors (two neurologists [J.G. and A.Z.O.], a pediatric neurologist [M.L.S.], and a physician assistant [J.K.]) via personal correspondence, based on their professional expertise and established relationships. Ethics committee approval was not required for this survey, which was performed in accordance with the Helsinki Declaration of 1964 and its later amendments. All survey respondents who are also authors of this publication provided informed consent to participate in the survey and for their responses to be included in this publication. This was a noninterventional qualitative survey conducted by Novartis in the USA to assess PwMS and HCP opinion. The research followed General Data Protection Regulation guidance. Survey respondents did not receive any incentive payment for completion of the survey, and all participated as authors in the development of this manuscript, in compliance with the International Committee of Medical Journal Editors authorship requirements and Good Publication Practice.
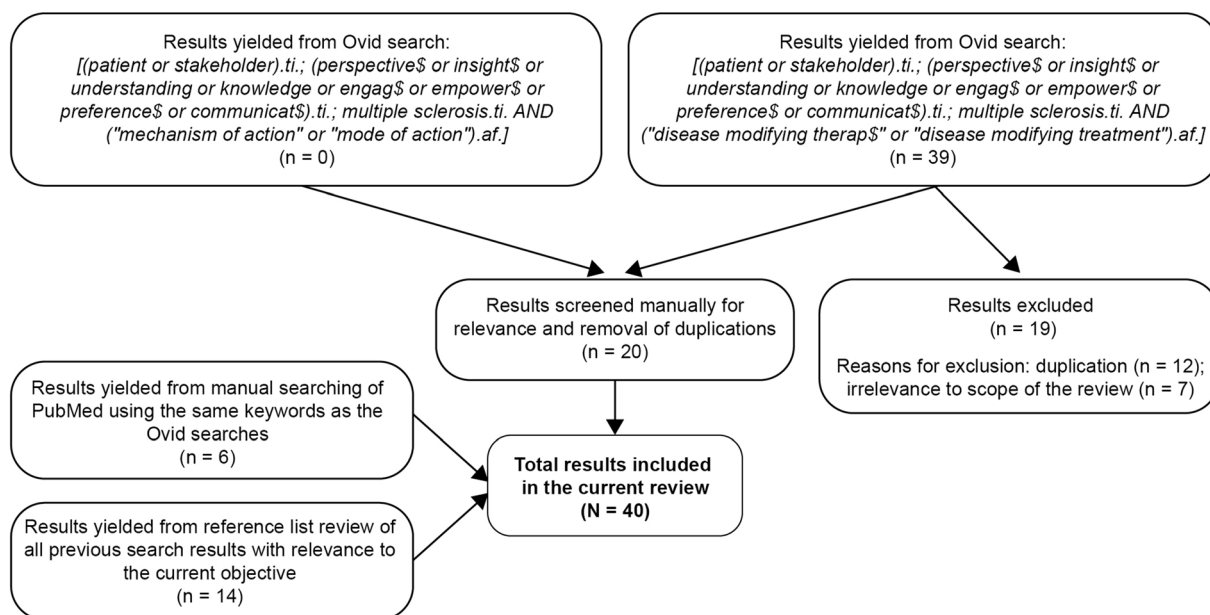
RESULTS

Targeted Literature Review

The search string *[(patient or stakeholder).ti.; (perspective$ or insight$ or understanding or knowledge or engag$ or empower$ or preference$ or communicat$).ti.; multiple sclerosis.ti. AND ("disease modifying therap$" or "disease modifying treatment").af.]* yielded 39 results on Ovid. Following screening for relevance to the current objective and the removal of duplicates, this was then narrowed down to 20 articles for review. The search string *[(patient or stakeholder).ti.; (perspective$ or insight$ or understanding or knowledge or engag$ or empower$ or preference$ or communicat$).ti.; multiple sclerosis.ti. AND ("mechanism of action" or "mode of action").af.]* did not yield any results, confirming the unmet need for assessment of PwMS' understanding of MoA. Subsequently, manual searching of the literature on PubMed using the same keywords yielded an additional 6 articles, and full-text review of all search results and the reference lists identified 14 more articles with relevance to the current objective. In all, 40 journal articles and conference abstracts are included in the current review (Fig. 3; Table 2).

Of the 40 journal articles and conference abstracts in the analysis, 5 were review articles [19–23] (including 2 systematic reviews [22, 23]) and 6 were of a qualitative nature, primarily ethnographic and phenomenological studies [24–29]. The remaining 29 publications were quantitative surveys or discrete-choice experiments and conjoint analyses—common statistical methods for ranking attributes within preferences [30–58].

Independence and convenience of administration are recognized as critical factors in selecting DMTs to initiate therapy or to switch therapy; accordingly, 12 of the quantitative items and 3 qualitative items found a preference or perceived suitability for oral administration, ranging from 31% to 93% of surveyed PwMS

Fig. 3 Flow diagram of the results of the targeted literature search. Searches performed in June 2020

cohorts preferring this method [24, 27, 28, 30–41]. Overall, 6 quantitative and 5 qualitative items explored the role of PwMS–HCP communications in shared decision-making and patient satisfaction with the level of engagement [24, 25, 27–29, 42–47]. In the phenomenological studies, the majority of PwMS were actively involved in decision-making, considered their neurologist a useful figure in their MS treatment path, and were the key drivers of DMT decisions. Across the analyses, technology and education were identified as principal factors for optimizing communication within health services and improving overall patient satisfaction. It is widely acknowledged in the literature and in the medical community that patient satisfaction and understanding can lead to improved treatment adherence and better health outcomes.

Patient Survey and HCP Insights

In addition to the literature review, a preliminary qualitative survey was undertaken to obtain perspectives and insights from PwMS and HCPs on the importance of understanding the MoAs of DMTs. The results from the survey may be helpful in informing and designing future studies that will assess these needs more widely. The full responses to the open-response questions are presented in the Supplementary Material. Overall, the PwMS and care-partner respondents were largely in agreement with the current literature, reporting that safety and efficacy are equally the most important attributes to consider when making DMT decisions, and that routes and modes of administration that offer independence are preferable to those that require HCP oversight.

> "A large factor in selecting a medication is how well will it treat my MS and prevent further progression. Next, I want to know the side effects of the medication and how will it affect my body overall. I like to know what are the large concerns [when] taking a medication and short term [concerns]. Another priority is the method in which you deliver the medication. For example, a pill, infusion, or shot. Finally, how often the medication is required to take. For example, daily, weekly, monthly, etc." (Tim Sabutis)
> "If [efficacy] and side effects are all equal then I suppose I wouldn't care too much about how it works. I would like to know what it would be doing to my body, but in the end, if it's all

Table 2 Results from the targeted and manual literature searches

Author(s)	Title	Publication details	Source	Summary of paper
Adlard et al. [30]	Patient preferences for different modes and frequency of administration of multiple sclerosis disease modifying therapies	*Value Health.* Conference: ISPOR Europe 2018: New perspectives for improving twenty-first century health systems. 2018;21(3):S351. https://doi.org/10.1016/j.jval.2018.09/.2096	Embase	A quantitative discrete choice experiment/conjoint analysis of 140 PwMS on administration variables, showing a preference for oral administration
Agashivala et al. [48]	Compliance to fingolimod and other disease modifying treatment in multiple sclerosis patients, a retrospective cohort study	*BMC Neurol.* 2013;13:138. https://doi.org/10.1186/1471-2377-13-138	References	A quantitative retrospective claims analysis of 1891 claims on DMTs adherence, showing improved adherence to orally administered treatments
Bayas and Mäurer [19]	Teriflunomide for the treatment of relapsing–remitting multiple sclerosis: patient preference and adherence	*Patient Prefer Adher.* 2015;9:265–274. https://doi.org/10.2147/PPA.S61651	Embase	A review of teriflunomide adherence
Bergmann et al. [31]	Patient preferences in the choice of disease modifying drugs for multiple sclerosis	*Neurology.* Conference: 66th American Academy of Neurology Annual Meeting, AAN. 2014;82(10.1). P3.137	Embase	A quantitative discrete choice experiment/conjoint analysis of 1628 PwMS on DMT preferences, showing a 63% preference for oral administration
Bergvall et al. [49]	Persistence with and adherence to fingolimod compared with other disease-modifying therapies for the treatment of multiple sclerosis: a retrospective US claims database analysis	*J Med Econ.* 2014;17(10):696–707. https://doi.org/10.3111/13696998.2014.940422	References	A quantitative retrospective claims analysis of 3750 claims on DMT adherence, showing improved adherence to orally administered treatments

Table 2 continued

Author(s)	Title	Publication details	Source	Summary of paper
Bottomley et al. [36]	A discrete choice experiment to determine UK patient preference for attributes of disease modifying treatments in multiple sclerosis	*J Med Econ.* 2017 Aug;20(8):863–870. https://doi.org/10.1080/13696998.2017.1336099	PubMed	A quantitative discrete choice experiment/conjoint analysis of 250 PwMS on significant risks associated with DMTs, showing a 31% preference for oral administration
Carlin, Higuera, and Anderson [32]	Improving patient-centred care by assessing patient preference for multiple sclerosis disease-modifying agents: a stated-choice experiment	*Perm J.* 2017;21:16–102. https://doi.org/10.7812/TPP/16/102	Embase	A quantitative discrete choice experiment/conjoint analysis of 537 PwMS on DMT preferences, showing a preference for oral administration
Clark et al. [40]	Understanding disease-modifying therapy administration route suitability in different multiple sclerosis patient segments in the 5EU and US	*Value Health.* Conference: ISPOR 2019. 2019;22(2):S378. https://doi.org/10.1016/j.jval.2019.04.1845	Embase	A quantitative survey of 2734 neurologists on suitability of different routes of administration for PwMS, showing a preference for oral administration
Colligan, Metzler, and Tiryaki [20]	Shared decision-making in multiple sclerosis	*Mult Scler.* 2017 Feb;23(2):185–190. https://doi.org/10.1177/1352458516671204	PubMed	A review of shared decision-making processes
De Ceunick Van Capelle et al. [24]	A qualitative study assessing patient perspectives in the process of decision-making on disease modifying therapies (DMT's) in multiple sclerosis (MS)	*PLoS ONE.* 2017;12(8):e0182806. https://doi.org/10.1371/journal.pone.0182806	Embase	A qualitative phenomenology of 10 PwMS on DMT decision-making, showing a preference for oral administration and active engagement in decision-making
De Seze, Borgel, and Brudon [42]	Patient perceptions of multiple sclerosis and its treatment	*Patient Prefer Adher.* 2012;6:263–73. https://doi.org/10.2147/PPA.S27038	PubMed	A quantitative survey of 202 PwMS on perceptions and experiences of MS, showing a desire for increased HCP communication

Table 2 continued

Author(s)	Title	Publication details	Source	Summary of paper
Falet et al. [25]	A qualitative study of patient perspectives regarding the role of the neurologist in advanced multiple sclerosis	*Can J Neurol Sci.* Conference: 53rd Annual Congress of the Canadian Neurological Sciences Federation. 2018;45(2):S24. https://doi.org/10.1017/cjn.2018.133	Embase	A qualitative phenomenology of 18 PwMS on perceptions of the role of neurologists, showing that neurologists are perceived as useful figures in healthcare
Garcia-Dominguez et al. [33]	Patient preferences for treatment of multiple sclerosis with disease-modifying therapies: a discrete choice experiment	*Patient Prefer Adher.* 2016;10:1945–56. https://doi.org/10.2147/PPA.S114619	Embase	A quantitative discrete choice experiment/conjoint analysis of 125 PwMS on risk acceptability, showing a preference for oral administration
Glusman et al. [43]	Patient-provider communication and perceived autonomy support among multiple sclerosis patients who discontinue disease modifying therapy against medical advice	*Mult Scler.* Conference: 31st Congress of the European Committee for Treatment and Research in Multiple Sclerosis, ECTRIMS. 2015;23(11):278. ECTRIMS Online Library: 116267;2025	Embase	A quantitative survey of 104 PwMS on perceived autonomy, showing improved communication and autonomy in PwMS who were treatment-adherent
Heesen et al. [50]	Risk perception in natalizumab-treated multiple sclerosis patients and their neurologists	*Mult Scler.* 2010;16(12):1507–12. https://doi.org/10.1177/1352458510379819	References	A quantitative survey of 69 PwMS and 66 neurologists on risk perceptions of natalizumab, showing PwMS were more accepting of natalizumab-associated risks than HCPs
Heesen et al. [21]	Decisions on multiple sclerosis immunotherapy: new treatment complexities urge patient engagement	*J Neurol Sci.* 2011;306:192–7. https://doi.org/10.1016/j.jns.2010.09.12	References	A review of DMT decision-making processes

Table 2 continued

Author(s)	Title	Publication details	Source	Summary of paper
Hincapie, Penm, and Burns [34]	Factors associated with patient preferences for disease-modifying therapies in multiple sclerosis	*J Manag Care Spec Pharm.* 2017;23(8):822–30. https://doi.org/10.18553/jmcp.2017.23.8.822	Embase	A quantitative discrete choice experiment/conjoint analysis of 129 PwMS on significant treatment risks, showing a preference for oral administration
Johnson et al. [26]	Patient perspective on disease-modifying therapy in multiple sclerosis	*Int J MS Care.* 2006;8(1):11–18. https://doi.org/10.7244/1537-2073-8.1.11	References	A qualitative phenomenology of 18 PwMS on DMT preferences, showing that there are significant barriers to DMT initiation and adherence
Johnson et al. [51]	Multiple sclerosis patients' benefit-risk preferences: serious adverse event risks versus treatment efficacy	*J Neurol.* 2009;256:554–62. https://doi.org/10.1007/s00415-009-0084-2	References	A quantitative discrete choice experiment/conjoint analysis of 651 PwMS on risk acceptability, showing an acceptance of risk in return for efficacy
Jonker et al. [35]	Summarizing patient preferences for the competitive landscape of multiple sclerosis treatment options	*Med Decis Making.* 2020;40(2):198–211. https://doi.org/10.1177/0272989X2987944	Embase	A quantitative discrete choice experiment/conjoint analysis of 1162 PwMS, showing a 41% preference for oral administration
Kasper et al. [52]	Informed shared decision making about immunotherapy for patients with multiple sclerosis (ISDIMS): a randomized controlled trial	*Eur J Neurol.* 2008;15:1345–52. https://doi.org/10.1111/j.1468-1331.2008.02313.x	References	A quantitative randomized controlled trial of 297 PwMS on informational interventions, showing the type of informational intervention did not affect the HCP-PwMS dynamic nor the treatment choices
Köpke et al. [53]	Evidence-based patient information programme in early multiple sclerosis: a randomised controlled trial	*J Neurol Neurosurg Psychiatry.* 2014;85:411–18. https://doi.org/10.1136/jnnp-2013-306441	References	A quantitative randomized controlled trial of 192 PwMS on informational interventions, showing the informational interventions improved informed choice

Table 2 continued

Author(s)	Title	Publication details	Source	Summary of paper
Nazareth et al. [44]	Relapse prevalence, symptoms, and health care engagement: patient insights from the Multiple Sclerosis in America 2017 survey	*Mult Scler Relat Dis.* 2018;26:219–34. https://doi.org/10.1016/j.msard.2018.09.002	Embase	A quantitative survey of 5311 PwMS on HCP engagement during relapses, showing improved satisfaction with increased HCP engagement
Poulos et al. [54]	Patient preferences for injectable treatments for multiple sclerosis in the United States: a discrete-choice experiment	*Patient.* 2016;9:171–80. https://doi.org/10.1007/s40271-015-0136-x	References	A quantitative discrete choice experiment/conjoint analysis of 189 PwMS on variables associated with injectables, showing injection frequency may be as important as safety and efficacy
Poulos et al. [55]	A discrete-choice experiment to determine patient preferences for injectable multiple sclerosis treatments in Germany	*Ther Adv Neurol Disord.* 2016;9(2):95–104. https://doi.org/10.1177/1756285615622736	Embase	A quantitative discrete choice experiment/conjoint analysis of 205 PwMS on variables associated with injectables, showing injection frequency may be as important as safety and efficacy
Reen, Silber, and Langdon [22]	Multiple sclerosis patients' understanding and preferences for risks and benefits of disease-modifying drugs: a systematic review	*J Neurol Sci.* 2017;375:107–22. https://doi.org/10.1016/j.jns.2016.12.038	PubMed	A systematic review of 22 publications on MS understanding, showing HCP–PwMS communications may not be adequate to convey understanding
Rieckmann et al. for the Members of the MS in the 21st Century Steering Group [29]	Unmet needs, burden of treatment, and patient engagement in multiple sclerosis: a combined perspective from the MS in the 21st Century Steering Group	*Mult Scler Relat Disord.*;19:153–60. https://doi.org/10.1016/j.msard.2017.11.013	PubMed	A qualitative steering group workshop insights collection of 11 PwMS and 10 HCPs on PwMS–HCP relationships, showing that technology and education are principal factors for positive impact, and communication maximizes health services

Table 2 continued

Author(s)	Title	Publication details	Source	Summary of paper
Riñon et al. [45]	The MS Choices Survey: findings of a study assessing physician and patient perspectives on living with and managing multiple sclerosis	*Patient Prefer Adher.* 2011:5;629–43. https://doi.org/10.2147/PPA.S26479	References	A quantitative survey of 331 PwMS and 280 neurologists on DMT adherence, showing that communication is needed to improve adherence
Schlegel and Leray [27]	From medical prescription to patient compliance: a qualitative insight into the neurologist-patient relationship in multiple sclerosis	*Int J MS Care.* 2018;20(6):279–86. https://doi.org/10.7224/1537-2073.2017-043	PubMed	A qualitative phenomenology of 29 PwMS on neurologist–PwMS relationships, showing a preference for oral administration, and that over half chose their own treatments
Sempere et al. [46]	Using a multidimensional unfolding approach to assess multiple sclerosis patient preferences for disease-modifying therapy: a pilot study	*Patient Prefer Adher.* 2017;11:995–9. https://doi.org/10.2147/PPA.S129356	Embase	A quantitative discrete choice experiment/conjoint analysis of 37 PwMS, showing involvement in shared decision-making was considered adequate
Serafini, Jones, and Pike [41]	Assessment of patient preferences in the treatment of relapsing–remitting multiple sclerosis in public and private systems in Latin America	*Value Health.* Conference: ISPOR 19th Annual European Congress. 2016;23(2):A435. https://doi.org/10.1016/j.jval.2016.09.513	Embase	A quantitative survey of 417 PwMS on route of administration preferences, showing a preference for oral administration
Tencer et al. [28]	Neurologist and patient preferences in multiple sclerosis: UK and US qualitative research findings	*Value Health.* Conference: ISPOR Europe 2019. 2019;22(3):S757. https://doi.org/10.1016/j.jval/2019/09/1977	Embase	A qualitative phenomenology of 20 PwMS and 20 neurologists on treatment considerations, showing a 60% preference for oral administration and that treatment choice is largely driven by PwMS

Table 2 continued

Author(s)	Title	Publication details	Source	Summary of paper
Thakur, Manuel, and Tomlinson [56]	Autoinjectors for administration of interferon beta-1b in multiple sclerosis: patient preferences and the ExtaviPro TM 30G and Betacomfort R devices	*Pragmat Obs Res.* 2013;4:19–26. https://doi.org/10.2147/POR.S51838	MEDLINE	A quantitative survey of 201 PwMS on autoinjectable preferences, showing PwMS value reliability and convenience of administration
Tintoré et al. [47]	The state of multiple sclerosis: current insight into the patient/health care provider relationship, treatment challenges, and satisfaction	*Patient Prefer Adher.* 2017;11:33–45. https://doi.org/10.2147/PPA.S115090	Embase	A quantitative survey of 982 PwMS and 900 neurologists on satisfaction with DMTs and the decision-making process, showing that PwMS who were more satisfied with their DMTs were more comfortable having open dialogue with their HCPs
Utz et al. [37]	Patient preferences for disease-modifying drugs in multiple sclerosis therapy: a choice-based conjoint analysis	*Ther Adv Neurol Disord.* 2014;7(6):263–75. https://doi.org/10.1177/1756285614555335	References	A quantitative discrete choice experiment/conjoint analysis of 319 PwMS on oral versus parenteral administration variables, showing a 93% preference for oral administration
Visser et al. [23]	Patient needs and preferences in relapsing–remitting multiple sclerosis: a systematic review	*Mult Scler Relat Dis.* 2020;39:101929. https://doi.org/10.1016/j.msard.2020.101929	Embase	A systematic review of 24 publications on DMT preferences, showing that HCP understanding of PwMS' values is needed to improve adherence
Wicks et al. [57]	US patient perspectives on the multiple sclerosis treatment experience: results of a US web-based survey	*Mult Scler.* Conference: 31st Congress of the European Committee for Treatment and Research in Multiple Sclerosis, ECTRIMS. 2015;23(11.1);278. ECTRIMS Online Library: 115368;173	Embase	A quantitative survey of 943 PwMS on DMT initiation and discontinuation factors, showing that treatment decisions are multifactorial

Table 2 continued

Author(s)	Title	Publication details	Source	Summary of paper
Wicks et al. [58]	Preferred features of oral treatments and predictors of non-adherence: two web-based choice experiments in multiple sclerosis patients	*Interact J Med Res.* 2015;4(1):e6. https://doi.org/10.2196/ijmr.3776	References	A quantitative discrete choice experiment/conjoint analysis of 319 PwMS on oral administration variables, showing that HCPs need to understand PwMS values to address treatment concerns
Wilson et al. [38]	Patient centred decision making: use of conjoint analysis to determine risk–benefit trade-offs for preference sensitive treatment choices	*J Neurol Sci.* 2014;344:80–7. https://doi.org/10.1016/j.jns.2014.06.030	References	A quantitative discrete choice experiment/conjoint analysis of 291 PwMS on risk acceptability, showing a preference for oral administration
Wilson et al. [39]	Patient preferences for attributes of multiple sclerosis disease-modifying therapies: development and results of a ratings-based conjoint analysis	*Int J MS Care.* 2015;17(2):74–82. https://doi.org/10.7224/1537-2073.2103-053	References	A quantitative discrete choice experiment/conjoint analysis of 50 PwMS, showing a preference for oral administration

DMT disease-modifying therapy, *HCP* healthcare professional, *MS* multiple sclerosis, *PwMS* people with multiple sclerosis

equally safe and effective, how it works would not matter much." (Daisy Clemmons)

"I remember before there was a pill form of treatment for MS and the MS community was begging to know when it would be available. The answer was always "in 5 years". I don't know anyone who would choose an injection or infusion over a pill. It seems like there is less risk involved during administration to only swallow a pill. I'd rather be at home and take the pill myself." (Jeri Burtchell)

With regard to immunological terms and drug MoAs, PwMS and care-partner respondents felt they had a better understanding of overall processes (e.g., of the overarching role of the immune system in MS) than they did of specific mechanisms (such as the interplay of T cells and

B cells and their role in MS pathophysiology). It was recognized that MoA knowledge among the patient respondents is currently lacking but represents an area of interest in which to build communication and develop educational material.

"I feel like I have a strong grasp of demyelination vs inflammation in MS. I have done a lot of research on MS and the disease-modifying drugs. The role of B cells vs T cells is something I have not done much research on, however, but am very eager to learn more as B cells become more of a target in emerging therapies. I have some idea of what biologics are and how they work but not a solid understanding…I've always been curious about the mechanism of action with any drug I take,

whether it's for a migraine or for MS. I feel like knowing how drugs work allows me to make better informed choices when it comes to selecting treatments. Understanding the MoA can also shed more light on why certain side effects may be likely to occur. Knowledge is power and when you have a chronic illness like MS it's important to learn all you can about every aspect of the disease and how it's treated… While I feel like I know a lot about MS and about the various treatment options, I know little about their MoAs and what makes B cells or T cells the best targets for treatments. I would love to learn more, especially when it comes to targeted therapies and knowing what works best for an individual based on their type of MS and unique set of symptoms or circumstances." (Jeri Burtchell)

Patient and HCP respondents all reported that face-to-face discussions, supplemented with visual aids such as animations, were preferable to noninteractive materials such as leaflets and websites; one patient further identified the environmental impacts of paper distribution as a negative factor. Crucially, the survey and subsequent correspondence identified the necessity for information delivery to be tailored to the needs of individuals.

"Having information about how the treatment works explained to me by a medical professional using patient-friendly language would be the best option. This allows me to ask questions and get immediate clarification. Websites and videos can also provide FAQ-type answers and be a resource that is readily accessible 24/7 when I may not be able to contact my doctor. Everyone has their own learning style and others may feel having a leaflet is important. I am more visual and would like to have an explainer video that walks me through how a treatment works. I am also trying to become more environmentally conscious and would probably not take a leaflet if I can avoid it. I prefer digital over paper when possible." (Jeri Burtchell)
"I think it is important to use the mode of learning that is effective for the patient. For me, watching and seeing a video is the most effective strategy for me to learn. It is

important for the care professional to meet the client where they best learn to communicate about the disease-modifying treatments." (Tim Sabutis)
"I would prefer a medical professional in case I have questions. They would be able to give an explanation tailored for my needs when trying to understand." (Daisy Clemmons)

In addition, HCP respondents identified the need for increased face-to-face time in the clinic to allow for such conversations to take place.

"Increased access to technology, credit for time spent on phone, and more face-to-face time in clinic is always needed." (Michael L Sweeney)
"Providers need more time for education." (Jennifer Graves)
"[It is important to spend] time on discussing a personalized approach in therapy selection and shared decision [making] with [the] patient." (Ahmed Z. Obeidat)

DISCUSSION

The findings from the targeted literature search and qualitative survey employed in this review were largely in agreement, and were consistent with the literature regarding PwMS preferences; the findings from both methods highlight a knowledge gap in the importance of understanding MoA immunology by PwMS when making DMT decisions, which this review aims to address in part. The perspectives from the HCP and PwMS authors were also aligned, demonstrating a need for more resources for communication of such concepts, personalized education, and a desire from PwMS for improved health literacy.

Moreover, the findings from both of the methods confirmed expectations of safety and efficacy taking priority in determining factors of DMT decision-making, followed by methods of administration, with the majority of PwMS reporting a preference for methods that allow for autonomy and independence (e.g., oral administration or treatment that can be administered at home).

This desire for more independence in administration represents a wider shift in

philosophies of medical practice, favoring patient empowerment and shared decision-making over the more traditional, paternalistic approaches to delivering healthcare. Shared decision-making is a critical aspect of enabling patients to make fully informed healthcare choices [59]. This cooperative approach is particularly important and advantageous for preference-sensitive conditions with a wide range of treatment options that vary in their attributes, such as MS [20]. The evidence base for the efficacy of shared decision-making models, patient engagement practices, and health literacy approaches in MS specifically is limited but has been presented in a Cochrane Library systematic review, concluding that information provision in MS leads to improved disease-related knowledge compared with no information provision [60]. In the UK, both the National Health Service and the National Institute for Health and Care Excellence assert that shared decision-making has the potential to lead to improved health outcomes for patients [61, 62]. Regardless, the need for shared decision-making is not solely evidence-based but is also an ethical and moral imperative.

However, successful shared decision-making is dependent both on sufficient health literacy among patients and on satisfactory communication and materials from HCPs. In a recent meeting where multiple stakeholders gathered to identify unmet areas of need in MS care, the Members of the MS in the 21st Century Steering Group highlighted the urgent need for improved patient engagement in MS care and research [29]. Many resources exist to aid the delivery of healthcare centered around shared decision-making, notably the Armstrong 2016 Framework for Shared Decision-Making and Neurology, which presents a stepwise approach to: (1) identify a patient's values and goals, (2) present evidence as it relates to their values and goals, and (3) arrive at a decision with the patient [63]. Many other educational programs, decision support techniques, health literacy tools, and treatment-specific decision aids have also been developed to enable shared decision-making healthcare, to provide language for effectively communicating MS concepts, and

ultimately to empower PwMS to arrive at a fully informed healthcare decision [20, 64].

Furthermore, the COVID-19 pandemic has resulted in significant interruptions to the normal delivery of healthcare across all specialties and has introduced many uncertainties, particularly in the treatment of immunological and autoimmune conditions. Immunomodulatory and immunosuppressive therapies are known to incur risks associated with infectious disease, although the exact interactions of COVID-19 with DMTs for MS are largely unknown. Given the broad repertoire of these therapies, there are significant variations in risk analyses, with many guidelines and opinions largely agreeing that cell-depletion therapies likely present the highest risk [65, 66]. At the same time, the discussion of immunology and immunological terms has become more commonplace as mainstream news sources frequently report on developments in vaccines and antigen and antibody tests; this "infodemic" may in turn influence public interest in understanding immunology and immunological health literacy, and interpretations of risk in other contexts [67, 68]. Evidence of the effects of COVID-19 on DMT selection and risk monitoring in MS is a rapidly evolving knowledge base, and communications with PwMS should reflect this.

"The COVID-19 pandemic forced us to rethink our approach in treating MS patients with DMTs. Our initial concerns are readily obvious: Do the current DMTs used in MS patients cause an increased risk of developing COVID-19? Once infected, do the current DMTs in MS cause patients to have worse outcomes than immunocompetent patients? The short answer is that we don't know the answers to these questions yet … In the absence of robust data, clinicians are forced to have a similar conversation that we had with patients prior to the COVID-19 pandemic: What are the risks/ benefits of starting a DMT or for a patient currently taking a DMT?" (John Kramer)

This review had several limitations owing to its limited scope and qualitative nature. The restricted number of survey respondents allowed for a more in-depth, phenomenological approach to the analysis of the free-text

response questions but may have limited applicability to a wider context and was not fit for quantitative analysis. Additionally, performing a targeted literature search enabled the precise unmet need of insufficient patient communications regarding DMT MoAs to be defined; however, the authors acknowledge that these methods are not as robust as a full systematic review.

It is pertinent in this review to recognize and to acknowledge the shifting paradigms in MS theory—in wider understanding both of immunological pathogenesis and of specific immunological MoAs of DMTs—and to ensure that PwMS communications take this into account. For example, MS has historically been considered a demyelinating disease, but recent narratives have shifted towards a whole-brain disease model that considers wider elements of pathogenesis and neurodegeneration [69, 70]. Additionally, it is becoming increasingly clear that even DMTs traditionally thought of as specifically targeting T and/or B cells or other immune components more likely have widespread holistic effects on the immune system [5, 70]. For the sake of transparency and fully informed shared decision-making, it is prudent to acknowledge how the literature has evolved and where gaps remain in our understanding, particularly in individual responses to the therapy and real-world effects.

CONCLUSIONS

Effective communication regarding the MoAs of DMTs has the potential to empower PwMS to take the lead in their therapeutic choices with guidance from HCPs in a shared decision-making model. In addition, our preliminary survey, introduced here, could be implemented in larger cohorts to gather further insights and to quantify findings in order to establish more specific areas of unmet need and to develop best practices for communicating immunology to PwMS.

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Compliance with Ethics Guidelines. Ethics committee approval was not required for this survey, which was performed in accordance with the Helsinki Declaration of 1964 and its later amendments. All survey respondents who are also authors of this publication provided informed consent to participate in the survey and for their responses to be included in this publication. This was a noninterventional qualitative survey conducted by Novartis in the USA to assess PwMS and HCP opinion. The research followed General Data Protection Regulation guidance.

Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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