The impact of disease-modifying therapy access barriers on multiple sclerosis patients: A mixed methods study

Abstract

**Background:** In the United States, relapsing-remitting multiple sclerosis (RRMS) patients can face difficulty accessing disease-modifying therapies (DMTs) due to insurance, pharmacy, or provider policies. These barriers have been associated with poor adherence and negative health outcomes.

**Objectives:** The goals of the current study were to describe the overall occurrence of difficulties and delays associated with gaining access to DMTs among patients with RRMS, to assess DMT adherence during periods of reduced access, and to contextualize the patient journey from receipt of a prescription for DMT to obtaining and taking their medication when faced with access barriers.
**Methods:** U.S.-based adult patients self-reporting RRMS were recruited from an online health data-sharing social network, PatientsLikeMe. Patients were invited to complete a web-based survey if they reported a diagnosis of RRMS and were prescribed a DMT for MS. Follow-up phone interviews were conducted with 10 respondents who reported experiencing a MS-related relapse during the time they had experienced challenges accessing DMTs.

**Results:** Among 507 survey completers, nearly half were either currently experiencing an issue related to DMT assess or had difficulty accessing a DMT in the past (233/507, 46.0%). The most frequently reported reasons related to access difficulty were authorization requirements by insurance (78/182, 42.9% for past issues and 9/42, 21% for current issues) and high out-of-pocket costs (54/182, 29.7% for past issues and 13/42, 31% for current issues). About half (51%) of patients with current access issues and over a third (38%) of those with past issues went without their medication until they could access their prescribed DMT. Relapses were reported during periods of reduced DMT access for nearly a third (56/118, 29.8%) of those with past issues and nearly half (22/45, 49%) of those with current issues. Resolving access issues involved multiple stakeholder agents often coordinated in a patient-led effort. Among those who had resolved issues, about half (57/119, 47.9%) reported that doctors/office staff were involved, under half (48/119, 40.3%) were involved themselves, and about a third (39/119, 32.8%) reported the drug manufacturer was involved in resolving the issue. Follow-up interviews revealed that the financial burden associated with obtaining a prescribed DMT led to non-adherence. Additionally, patients felt that DMT treatment delays and stress associated with obtaining the DMT triggered relapses or worsened their MS.

**Conclusions:** This study expands current research by using a patient-centered, mixed-methods approach to describe the patient perspective on barriers to MS treatment, process to resolve barriers, and the perceived impact of treatment barriers on outcomes. Issues related to DMT access occur frequently, with patients often serving as their own agents when navigating access difficulties to obtain their medication(s). Patient support for resolution of DMT access is needed to prevent undue stress and nonadherence.

**Keywords**

Multiple sclerosis; self report; surveys and questionnaires; patient adherence; out-of-pocket costs; cost sharing; mixed-methods; insurance, pharmaceutical services
Introduction

Multiple sclerosis (MS) is a chronic autoimmune disease of the central nervous system, affecting an estimated 450,000 to 550,000 people in the United States [1,2]. The financial burden accompanying MS is a central component of the disease experience, ranking second among all chronic conditions in direct costs behind congestive heart failure [3]. In addition to the impact of decreased productivity and unemployment [4-6], patients often shoulder the burden of high out-of-pocket costs for medications, tests, MRIs, medical equipment, and inpatient/outpatient visits [3,7,8].

Disease-modifying therapies (DMTs) slow disease progression and related disability and are the prevailing treatment for patients with MS [9]. Responding to rising costs of DMTs [10,11], insurers have adopted strategies to optimize utilization of specialty medications through management, including requiring prior authorization, step therapy (where a patient must fail a preferred medication first), or tiered formularies that increase cost-sharing for patients [12,13]. Falling into the “specialty drug” tier of most benefits plans, DMTs are subject to higher patient out-of-pocket costs (i.e. tiers that require high co-insurance or co-payment) than non-specialty drugs [14]. Due to the clinical benefits of specialty drugs like DMTs, use remains relatively insensitive to such cost-sharing programs [14,15]. For MS patients, high out-of-pocket costs for DMTs have been associated with lower adherence and inappropriate disease management, which leaves patients at increased risk of relapse and payers vulnerable to increased associated resource use [16,17].

A growing body of research has explored the impact of current insurance coverage and related barriers of DMT access on MS patients. An estimated 25% of MS patients taking DMTs receive these drugs at little to no cost through pharmaceutical company financial aid programs, and such programs have been shown to increase adherence [18,19]. Discounted drug programs can be essential in mitigating prohibitive financial barriers for patients; however, regulations may prevent those with government-based insurance coverage from using these programs [20], so they may not be an ideal solution for all patients.

One understudied aspect of patient access to MS DMTs is the patient experience in navigating the treatment acquisition landscape. Although prior research has focused on the number of patients receiving DMTs, how they paid for their treatment, and insurance-related access barriers [19], it is not yet clear how patients perceive and navigate the current health care
system to obtain their medication and how they perceive this impacts their health outcomes and self-reported quality of life.

The goals of the current study were to describe the overall occurrence of difficulties and delays associated with gaining access to DMTs among patients with MS, to assess the impact of access barriers on DMT medication adherence and MS outcomes, and to contextualize the patient experience in obtaining a DMT after the receipt of a prescription.

**Methods**

**Study design**

This mixed-methods study included a population of patients with MS who were members of PatientsLikeMe® as of February 2016. PatientsLikeMe is a real-time data-sharing and research platform of patient communities devoted to a variety of life-changing health conditions. As of August 1, 2016, PatientsLikeMe had over 400,000 members with over 2,500 different health conditions, including about 50,000 members with MS, most (56%) of whom reported having relapsing-remitting MS (RRMS.) Participants were not compensated. This study was exempt from review by the New England Independent Review Board (NEIRB) on February 26, 2016 (Study #16-082).

The study was designed into two distinct phases, consisting of a web-based survey and qualitative interviews following survey completion with a subset of patients who had experienced a relapse during their access issue.

**Phase 1: Web-based Survey**

A sample of patients with RRMS from the PatientsLikeMe community participated in a cross-sectional, web-based questionnaire fielded by PatientsLikeMe [21]. A closed design was used, meaning only members of PatientsLikeMe who were invited to take part and who had logged in with their personal password could see the survey. An informed consent document was displayed prior to starting the survey, and a waiver of documentation of informed consent was
obtained from NEIRB. The survey was administered electronically for four weeks in February and March 2016.

**Survey Development**

The survey included demographics and a series of questions concerning experiences with access to DMTs. Three mutually exclusive branching options were used to segment respondents who 1) were currently experiencing a DMT access barrier 2) had past (but not current) barrier accessing DMTs, and 3) never experienced an access barrier with their DMTs. Preliminary survey items were derived from targeted literature review and consultation with MS experts; a PatientsLikeMe patient member (DM) provided feedback on items, survey length, and patient interpretability. Prior to fielding the survey, it went through a series of reviews among investigators and was electronically pre-tested for design elements, question ordering, and flow. See Supplementary Appendix 1 for survey questions.

**Survey Population**

Eligible participants were aged 18 years or older, who self-reported residence within the United States, reported a physician diagnosis of RRMS, and had recent (90-day) activity on the PatientsLikeMe website. Eligible participants were sent a private survey invitation through the PatientsLikeMe website. Participants were screened out if they did not confirm the above eligibility criteria, or reported never being prescribed a DMT for RRMS.

**Measures**

**DMT access barriers** included any of the following: lack of insurance; insurance not covering the DMT; prior authorization documentation requirement; high out-of-pocket costs; requirement to take another DMT before the prescribed DMT (i.e., step through), inability to obtain the DMT at their desired pharmacy or infusion center, or other difficulties.

**Adherence** was measured by asking participants how often they take their medication as prescribed. Responses could be given in 10% increments from 0% (none of the time) to 100% (always).

**Health literacy** was measured by the respondent’s level of confidence filling out medical forms by themselves [22-23]. A dichotomous variable was created to classify those who were
“quite a bit” or “extremely” confident as having high health literacy; those who responded “somewhat,” “a little,” or “not at all” as having low health literacy.

**Stress** was measured on a 10-point numeric scale. Respondents who had experienced an access barrier were asked how stressful their most recent DMT access issue was from 0 (not at all) to 10 (greatly). Those who had not experienced an access issue were instead asked about their stress level in the last seven days.

In addition to survey responses, most recent Patient Determined Disease Steps (PDDS) score [24-27] was obtained from participants' PatientsLikeMe profiles. PDDS is measured on a 9-point scale from 0 (Normal) to 8 (Bedridden).

**Analyses**

Subgroups (current, past, or never had DMT issue) were defined by the following two (2) questions: “Which option best describes your experience with accessing or receiving your DMT medication for MS?” (current DMT access difficulty, a past difficulty, or never had a difficulty), and “Have you ever had any of the following difficulties accessing or receiving DMT medications for MS? (select-all-that-apply list including items such as: covered by insurance plan and it required authorizing documentation).

During analysis, it was discovered that some participants reported they had never experienced a DMT access issue, however, when queried about specific access issues, they selected a specific DMT access barrier (e.g., authorizing documentation, high out-of-pocket costs, medications not covered by insurance). For clarification, a 2-question follow-up survey was fielded in June and July 2016 to 108 respondents who fell into this category.

The first question was closed-ended: “Were any of the following situations burdensome enough to delay or prevent you from getting your DMT medication? (check all that apply).” Answer options included 1) having to fill out paperwork or get other documentation for DMT access, or 2) DMT out-of-pocket costs too high. The second question was open-ended: “Please tell us a little bit more about this difficulty and the effect it had on you (if any).”

Variables with closed-ended response options were analyzed using descriptive and summary statistics. Wilcoxon rank-sum tests were used to compare groups with non-normally distributed values. T-tests were used to compare groups with normally distributed values. An alpha value of 0.05 or less was considered significant. Statistical analyses were performed using
SAS software, version 9.4 (Cary, NC). Open-ended questions were coded for themes using conventional content analysis in ATLAS.ti software (version 5.0) [28-29].

**Data Exclusion**

A validated sample of survey respondents excluded 121 respondents from the analyzed sample who gave conflicting responses on the survey branches. The total number of respondents in the “never” category reduced from the full sample of 507 respondents to 386.

**Phase 2: Qualitative Interviews**

Interview methods are described using the consolidated criteria for reporting qualitative research (COREQ) [30]. During the second phase of this study, 10 respondents who completed the questionnaire were selected to participate in a single, 60-minute follow-up interview between April and June 2016. Interviews were conducted at the participants’ convenience via phone or video conference by researchers (KS, BK). The interviewers had no prior relationship with interviewees. Interviews were audio-recorded and transcribed. Participants were not given transcripts or findings for review.

**Interview Sample Population**

Participants were selected for interviews based on survey response reporting either a current or past issue with DMT access, at least one MS relapse during the period of their DMT access difficulty, and consent to a follow-up interview in the first survey.

**Interview Guide Development**

The goal of the interview was to supplement information collected in the questionnaire, among participants who had experienced DMT access barriers and a negative health event (e.g., MS relapse) during the assess issue, using qualitative data (See Supplementary Appendix 2 for Interview Guide). Four research questions directed the interview guide: 1) How did patients resolve their DMT access issues?; 2) What are the clinical consequences of DMT access barriers?; 3) What are the impacts of DMT access issues on quality of life?; and 4) Who are the agents involved in helping patients access their DMT?
**Analyses**

Interviews were analyzed for themes by researchers using a constant comparative method [31-32]. To represent interactions between study participants and the agents or organizations involved in resolving their access to DMTs, an aggregate egocentric social network map was created based on the interviews [33-34]. To create the map, an iterative process was used to draw connections between each interviewee and others involved in DMT access resolution. Each subsequent interviewee was compared to the previous ones until all connections mentioned in the interviews were placed on the generalized map, with the “ego” (patient) in the center.

**Results**

**Survey results**

**Survey sample**

Of 5239 patients invited to the survey, 947 viewed the invitation and 584 participated in the survey for a participation rate of 61.6%. A total of 507 patients completed the survey, for a completion rate of 86.8% (507/584). A subset of 40 patients (out of 108 who were invited) completed the follow-up survey for a participation rate of 85%. Among survey completers (n=507), most were female (78.3%, 397/507), White (89.6%, 441/507), and on average, 49 years old (Table 1). The majority (66%, 234/507) had high health literacy; however, the percentage of those with high health literacy was lowest among those currently experiencing access issues (56% of those with a current issue, 25/45, vs 73.4% of those with a past issue, 138/188, and 83.0% who never issues, 127/153, had high health literacy). This difference was statistically significant ($\chi^2=14.61$, d.f. =1, $P<0.001$). Median PDDS score was 4 (range 1-8, IQR 3.0), indicating some gait disability. Of those in the validated sample (n=386), the majority (233/386, 60.4%) had experienced difficulty accessing a DMT in the past (188/386, 48.7%) or were currently experiencing an issue related to DMTs access (45/386, 11.7%). Average time to receive the originally prescribed DMT after experiencing an access barrier was 8.3 weeks (SD 16.5).

Table 1. Participant Characteristics
<table>
<thead>
<tr>
<th></th>
<th>Total Completed, N=507</th>
<th>Validated Sample*, N=386</th>
<th>Current Issue, N=45</th>
<th>Past Issue, N=188</th>
<th>Never Issue, N=153</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n (%)</th>
<th>n (%)</th>
<th>n (%)</th>
<th>n (%)</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years), mean (SD)</strong></td>
<td>49.1 (10.4)</td>
<td>49.7 (10.2)</td>
<td>50.2 (9.7)</td>
<td>48.9 (10.8)</td>
<td>50.5 (9.7)</td>
</tr>
<tr>
<td><strong>Female</strong></td>
<td>397 (78.3)</td>
<td>308 (79.8)</td>
<td>39 (86.7)</td>
<td>154 (81.9)</td>
<td>115 (75.2)</td>
</tr>
<tr>
<td><strong>White</strong></td>
<td>441 (89.6)</td>
<td>335 (89.8)</td>
<td>40 (90.9)</td>
<td>161 (88.5)</td>
<td>134 (91.2)</td>
</tr>
<tr>
<td><strong>Ethnicity Not Hispanic</strong></td>
<td>462 (94.7)</td>
<td>357 (95.7)</td>
<td>41 (93.2)</td>
<td>173 (95.6)</td>
<td>143 (96.6)</td>
</tr>
<tr>
<td><strong>Number of Comorbidities, median (range, IQR)</strong></td>
<td>1 (1-27, 1.0)</td>
<td>1 (1-27, 2.0)</td>
<td>1 (1-21, 3.0)</td>
<td>1 (1-27, 1.0)</td>
<td>1 (1-15, 1.0)</td>
</tr>
<tr>
<td><strong>Education</strong></td>
<td>n=320</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High school or Less</td>
<td>53 (12.7)</td>
<td>39 (12.2)</td>
<td>6 (16.2)</td>
<td>21 (13.6)</td>
<td>12 (9.4)</td>
</tr>
<tr>
<td>Some college</td>
<td>165 (39.6)</td>
<td>126 (39.4)</td>
<td>18 (48.6)</td>
<td>56 (36.1)</td>
<td>52 (40.6)</td>
</tr>
<tr>
<td>College degree</td>
<td>131 (31.4)</td>
<td>107 (33.4)</td>
<td>5 (13.5)</td>
<td>57 (36.8)</td>
<td>45 (35.2)</td>
</tr>
<tr>
<td>Post-graduate work</td>
<td>68 (16.3)</td>
<td>48 (15.0)</td>
<td>8 (21.6)</td>
<td>21 (13.6)</td>
<td>19 (14.8)</td>
</tr>
<tr>
<td><strong>High Health Literacy (Quite a bit or extremely)</strong></td>
<td>n=278</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>234 (66.1)</td>
<td>182 (65.5)</td>
<td>25 (55.5)</td>
<td>138 (73.4)</td>
<td>127 (83.0)</td>
</tr>
<tr>
<td><strong>Health Insurance Status</strong></td>
<td>n=345</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Employer based</td>
<td>209 (47.5)</td>
<td>162 (47)</td>
<td>18 (43.9)</td>
<td>76 (45.5)</td>
<td>68 (49.6)</td>
</tr>
<tr>
<td>Direct</td>
<td>34 (7.7)</td>
<td>26 (7.5)</td>
<td>2 (4.9)</td>
<td>14 (8.4)</td>
<td>10 (7.3)</td>
</tr>
<tr>
<td>Medicare</td>
<td>131 (29.8)</td>
<td>103 (29.9)</td>
<td>10 (24.4)</td>
<td>56 (33.5)</td>
<td>37 (27.0)</td>
</tr>
<tr>
<td>Medicaid</td>
<td>38 (8.6)</td>
<td>32 (9.3)</td>
<td>8 (19.5)</td>
<td>11 (6.6)</td>
<td>13 (9.5)</td>
</tr>
<tr>
<td>Military</td>
<td>7 (1.6)</td>
<td>7 (2.0)</td>
<td>1 (2.4)</td>
<td>3 (1.8)</td>
<td>3 (2.2)</td>
</tr>
<tr>
<td>Veterans Affairs</td>
<td>9 (2.1)</td>
<td>8 (2.3)</td>
<td>1 (2.4)</td>
<td>2 (1.2)</td>
<td>5 (3.6)</td>
</tr>
<tr>
<td>None</td>
<td>8 (1.8)</td>
<td>4 (1.2)</td>
<td>1 (2.4)</td>
<td>3 (1.8)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Other</td>
<td>4 (1)</td>
<td>3 (1.0)</td>
<td>0 (0)</td>
<td>2 (1.2)</td>
<td>1 (1)</td>
</tr>
<tr>
<td><strong>PDSD Score Median (Range, IQR)</strong></td>
<td>4 (1-8, 3.0)</td>
<td>4 (1-8, 3.0)</td>
<td>4 (1-8, 3.0)</td>
<td>4 (1-8, 3.0)</td>
<td>4 (1-8, 4.0)</td>
</tr>
<tr>
<td><strong>Had relapse during access issue</strong> (self-reported)</td>
<td>-</td>
<td>-</td>
<td>22 (48.9)</td>
<td>56 (29.8)</td>
<td>-</td>
</tr>
<tr>
<td><strong>Average delay in weeks</strong></td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>(n=64)</td>
<td>-</td>
</tr>
<tr>
<td><strong>Mean (SD)</strong></td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>8 (16.5)</td>
<td>-</td>
</tr>
</tbody>
</table>

Subgroups (current, past, or never had DMT issue) were drawn from a validated sample based on the questions: “Which option best describes your experience with accessing or receiving your DMT medication for MS.” “Never” includes only those selected none of the DMT access issues, and “never” to “Which option best describes your experience with accessing or receiving your DMT medication for MS?”

*Asked only of those who eventually received the originally prescribed DMT.

Reasons for DMT access difficulties
The most frequently reported reasons for DMT-related access difficulties were “insurance required authorizing documentation” (21.4% current, 9/42, and 42.9% past issue, 78/182) and “high out-of-pocket costs” (31.0% current, 13/42, and 29.7% past issue, 54/182) (Table 2). Other reasons included administrative coordination problems between insurance companies, pharmacies, and clinician’s offices.

**Table 2. Reported reasons for DMT access issue.**

<table>
<thead>
<tr>
<th>Source of Access Issue</th>
<th>Past Issue N=182</th>
<th>Current Issue N=42</th>
<th>Follow-up N=24</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insurance required authorizing documentation</td>
<td>78 (42.9)</td>
<td>9 (21.4)</td>
<td>14 (58.3)</td>
</tr>
<tr>
<td>High out of pocket costs</td>
<td>54 (29.7)</td>
<td>13 (31.0)</td>
<td>8 (33.3)</td>
</tr>
<tr>
<td>Not covered by my insurance plan</td>
<td>20 (11.0)</td>
<td>8 (19.0)</td>
<td>2 (8.3)</td>
</tr>
<tr>
<td>I do not have insurance</td>
<td>17 (9.3)</td>
<td>3 (7.1)</td>
<td>-</td>
</tr>
<tr>
<td>Not at my desired pharmacy/infusion</td>
<td>14 (7.7)</td>
<td>2 (4.8)</td>
<td>-</td>
</tr>
<tr>
<td>Required to take one additional DMT</td>
<td>9 (4.9)</td>
<td>6 (14.3)</td>
<td>-</td>
</tr>
<tr>
<td>Other[b,c]</td>
<td>37 (20.3)</td>
<td>8 (19.0)</td>
<td>-</td>
</tr>
<tr>
<td>I don't know</td>
<td>12 (6.6)</td>
<td>6 (14.3)</td>
<td>-</td>
</tr>
</tbody>
</table>

*Among validated sample of those with past or current difficulties; access reasons were only asked of those who received a DMT prescription from their doctor. Question text for current issue was: What difficulties are you having accessing or retrieving your DMT medication? Check all that apply.; question text for past access issue was: Thinking about your most recent MS DMT access issue, what difficulties did you have accessing or receiving your DMT medication? Check all that apply.

*b* Other past reasons included administrative problems (n=9), provider changed or could not authorize (n=5), insurance/pharmacy denied drug or changed policies (n=5), insurance status change (n=4), appointment or prescription delay by provider (n=4), paperwork issue (n=2), other (n=5).

*c* Other current reasons included insurance policy changes/coverage loss (n=2), doctor/hospital problems (n=2), administrative problems (n=1), switched drug (n=1).

Among the 40 follow-up respondents, a majority (n=24) clarified that the DMT access barrier delayed or prevented them from getting their DMT medication. The reasons for access problems mirrored the results obtained from the full survey, with about half of those who had experienced barriers attributing them to “authorizing documentation” (14/24, 58.3%), a third to “high out-of-pocket costs” (8/24, 33.3%), and several to “not covered by insurance” (2/24, 8.3%). A slight majority of the 40 follow-up respondents (16/24, 66.7%) confirmed that their access difficulty did not delay or prevent them from getting their DMT.
**Adherence to prescribed DMTs during periods of decreased access**

Respondents frequently went without any RRMS medication until they could obtain their prescribed DMT. Nearly half (41.2%, 68/165) of respondents who had experienced a past access issue reported going without their medication(s) until they could access their prescribed DMT, 4.8% (8/165) switched to a different DMT, 1.8% (3/165) continued their old medication, and 1.2% (2/165) received a different DMT until receiving the originally prescribed DMT. Among respondents currently experiencing a DMT access issue, about half (51%, 20/39) responded they were not currently taking any medications for their MS, 23% (13/39) continued their old medication, 13% (5/39) took a newly prescribed DMT, and 3% (1/39) reported they were instead taking a newly prescribed non-DMT medication for MS (Table 3).

**Table 3. Medication status during past and current access issue**

<table>
<thead>
<tr>
<th>Medication Status</th>
<th>Past Issue, N=165</th>
<th>Current Issue, N=39</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not taking any medication/went without medication</td>
<td>68 (41.2)</td>
<td>20 (51.3)</td>
</tr>
<tr>
<td>I received my DMT medication within a reasonable amount of time</td>
<td>56 (33.9)</td>
<td>N/A</td>
</tr>
<tr>
<td>I was prescribed a new DMT instead</td>
<td>8 (4.8)</td>
<td>5 (12.8)</td>
</tr>
<tr>
<td>I continued taking my old medication</td>
<td>3 (1.8)</td>
<td>13 (33.4)</td>
</tr>
<tr>
<td>Received another DMT before receiving my prescribed DMT</td>
<td>2 (1.2)</td>
<td>N/A</td>
</tr>
<tr>
<td>I am taking a newly prescribed other non-DMT medication</td>
<td>N/A</td>
<td>1 (2.6)</td>
</tr>
<tr>
<td>Other</td>
<td>28 (17.0)</td>
<td>N/A</td>
</tr>
</tbody>
</table>

*Asked of respondents who had insurance and/or did not answer that difficulty obtaining DMT at pharmacy/infusion center was their primary DMT access reason. Question text for current access status was: What other MS medication(s) are you taking while your DMT medication access issue is being resolved?; question text for past access issue was Pick the option that best describes how your most recent MS DMT access issue was resolved.

Self-reported adherence to DMT medication during an access barrier (Table 4) was significantly lower than self-reported typical DMT adherence (mean 8.97 vs 9.61). A paired t-test showed that this difference was statistically significant ($t_{101}=-2.48$, $P=.015$).
Table 4. Self-reported DMT adherence during DMT access issue and typically

<table>
<thead>
<tr>
<th>Adherence to DMT</th>
<th>N</th>
<th>Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>During DMT access issue</td>
<td>102</td>
<td>8.97 (2.47)</td>
</tr>
<tr>
<td>Typical adherence</td>
<td>102</td>
<td>9.61 (1.0)</td>
</tr>
</tbody>
</table>

*_{t_{101}}=-2.48, P=.015

Outcomes during periods of decreased DMT access: Stress and MS relapse

Among respondents who experienced a DMT access barrier, 49% (22/45) of those with a current access issue reported at least one MS relapse during the time of the barrier; 29.8% (56/188) self-reported at least one MS relapse during a past DMT access issue (Table 1). Wilcoxon rank sum tests showed significantly higher stress levels among those who experienced at least one MS relapse during a past access issue (median=8.5, IQR=7.0-10.0) compared with those who did not relapse (median=7.0, IQR=5-9) (Z=3.228, P=.001); this effect did not reach significance for those with a current issue.

Table 5. Self-reported stress by relapse status during access issue

<table>
<thead>
<tr>
<th>Self-reported relapse status</th>
<th>Past Issuea (N=161)</th>
<th>Current Issueb (N=39)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Median (IQR)</td>
</tr>
<tr>
<td>Relapsed during access issue</td>
<td>48</td>
<td>8.5 (7.0-10.0)</td>
</tr>
<tr>
<td>Did not relapse</td>
<td>113</td>
<td>7.0 (5.0-9.0)</td>
</tr>
</tbody>
</table>

*_{Z=3.228, P=.001}

*b_{Z=-1.835, P=.075}


**Stakeholder agents involved in DMT access**

Among respondents who experienced past difficulties gaining access to DMTs (n=119), about half (47.9%, 57/119) involved doctors/office staff to help resolve the DMT access issue, and under half (40.3%, 48/119) said they were at least partially responsible for resolving the issue themselves (Table 6). The remaining agents involved in resolving the issue were the drug manufacturer (32.8%, 39/119), pharmacy or specialty pharmacy (26.1%, 31/119), insurance companies (21.8%, 26/119), and infusion centers (5.0%, 6/119). Few caregivers were involved in resolving the access barrier (2/119, 1.7%).

**Table 6. Stakeholder agents involved in resolving past DMT access issue. (N=119)**

<table>
<thead>
<tr>
<th>Stakeholder agent</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doctors/office staff</td>
<td>57 (47.9)</td>
</tr>
<tr>
<td>Myself</td>
<td>48 (40.3)</td>
</tr>
<tr>
<td>Drug manufacturer</td>
<td>39 (32.8)</td>
</tr>
<tr>
<td>Pharmacy/specialty pharmacy</td>
<td>31 (26.1)</td>
</tr>
<tr>
<td>Insurance company</td>
<td>26 (21.8)</td>
</tr>
<tr>
<td>Infusion center</td>
<td>6 (5.0)</td>
</tr>
<tr>
<td>Caregiver</td>
<td>2 (1.7)</td>
</tr>
</tbody>
</table>

**Qualitative interviews**

**Interview sample**

Qualitative interviews were conducted among 10 survey respondents who experienced at least one MS relapse during a past or current period of decreased access to DMTs. Participants were predominantly female (9 out of 10), with mean age 54 years (range 42-64 years). Half reported being on Medicaid or Medicare (n=5), three on employer-sponsored insurance, one did not specify insurance type, and one had no insurance. Median duration of MS was 9.5 years (range 2-15 years).

**Themes from Qualitative Interviews**
Several themes were identified in the interviews and detailed examples are shown in Table 7.

Table 7. Themes arising from patient interviews

<table>
<thead>
<tr>
<th>Theme</th>
<th>Example Quotes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Financial burden begins prior access issue and impacts DMT adherence</td>
<td>“I had to declare bankruptcy because of my first doctor’s bill. We accumulated $15,000 in debt through the MRIs because they only cover half of one MRI per year and I had 6 that first year...I went from making $6500 a month to $1400 a month [on disability] with two kids and a vehicle. I got a little part time job that’s 12 hours a week, $10 an hour. That pays for my drugs.” -Male, age 42&lt;br&gt;“Patients are not getting help. We cannot afford insurance. My discretionary income is $10, that’s why I needed a physician who accepted cash. With co-pay, deductible and premium I could not afford that.” -Female, age 45&lt;br&gt;“I couldn’t afford the co pay and just quit taking the DMM [disease modifying medication]. I also quit taking other medications I could not afford to purchase.” -Female, age 64</td>
</tr>
<tr>
<td>2. DMT access problems and related stress leads to MS relapses</td>
<td>“I’ve had a series of bad attacks when the prescription lapsed and when the insurance lapsed. I have some severe damage where it comes to process from the printed page and to spit it back out again. That ability is gone unless it’s in context...I had lesions confirmed. The area with the vocabulary. I’m also a bit slow on the processing. There are things I don’t do so well. It takes me that little extra moment, so there’s this pause in my conversation...Those are the two areas of the brain affected.” -Female, age 58&lt;br&gt;“You spend 45 min fighting on the phone it’s like working 8 hours. I have to take 2-3 hours of the day for a nap to get my energy back...I’ve done nothing but fight with [my insurance company].” -Female, age 51&lt;br&gt;“I had a relapse while waiting to get on [DMT]. My left arm is numb and tingling constantly” (Female, age 54)</td>
</tr>
</tbody>
</table>
| 3. DMT access issues affect Quality of Life | “When I didn’t have the medication - I have depression, and that’s not a surprise when you have MS - and it affected me really bad, especially without the [DMT] and I can’t afford it. I kept thinking I don’t know what’s happening inside of me and are things happening to me that I won’t be able to come back from? Not having the medication really affected me emotionally as well.” -Female, age 59, on Medicare with too high co-pay<br>“My husband has to work 10 hour days and he’s stressed because of me. I worry about him. If I couldn’t get coverage on HC.gov, I could have gotten on my husband’s plan but that would have been more money, more money out of his paycheck. I went for the lesser of two evils but it’s still $352 per month. There’s gotta be an in-between. I look for miracles. Someone that doesn’t qualify
Theme 1: Financial burden begins prior to the DMT access barrier and can impact DMT adherence. Many participants reported that, prior to being prescribed a DMT, they had been in financial distress due to MS diagnostic costs and/or loss of income due to inability to work because of their symptoms (Table 4). For example, one participant said she had spent “all our savings” (Female, age 58) on medical costs related to her MS diagnosis, such as magnetic resonance imaging tests. Another filed for bankruptcy due to bills stemming from his initial MS diagnosis. Most interviewees had stopped or reduced paid work due to MS symptoms, and over half (6 out of 10) sought or received disability pay or subsisted on a fixed monthly income lower than the amount of their monthly co-payment for their DMT medication. Most (8 out of 10) who were interviewed went without DMT medication during their access barrier; the remaining two took a DMT they had been prescribed in the past until the access barrier was resolved.

Theme 2: DMT access barriers are associated with stress and relapses. Many participants felt delays in DMT treatment and the stress associated with the process of obtaining the DMT triggered relapses or worsened their MS. As one participant who experienced a combination of billing errors and finding her DMT out of stock at her infusion center asked, “Why do I have to deal with this crap? You know how they say that stress makes it worse?” (Female, age 56). Several participants experienced worsening fatigue and cognitive problems related to MS and the lack of DMT, making efforts to resolve their access issue more difficult.

Theme 3: DMT access issues affect quality of life. Access difficulties impacted different facets of patient life, and emotional and interpersonal impacts were commonly mentioned. Emotional impacts included situational problems like “frayed nerves” (female, age 58) and an exacerbation of pre-existing mental health comorbidities, such as depression. In addition to the time and effort spent on trying to access a DMT, several participants reported that the uncertainty
of having unstable health due to going without a DMT made it difficult to schedule social events in advance.

**Theme 4: Personal resources enable access to overcome DMT access barriers.** Several participants who succeeded in obtaining their DMT reported that they leveraged knowledge and skills from working in medical billing and other healthcare areas to expedite the process. This high level of health care literacy obtained through work experience facilitated their ability to document the issue and reach the appropriate agents who could help resolve the problem quickly.

**Egocentric Social Network of DMT Access**

Patients contacted numerous stakeholders during the process of obtaining a DMT. The complexity and intensity of work involved in resolving the problem placed a high burden on patients. As one patient described, “I do all of the legwork” (Female, age 58). All interviewees contacted their insurance company, physicians, and specialty pharmacy while trying to obtain their DMT. Additional agents contacted included advocacy groups, pharmaceutical companies, government agencies, and hospitals. A conceptual network visualization of these agents is depicted as a social network diagram in Figure 1.
Insurance-related access problems were attributed to changes in plans (e.g., from an employer-sponsored plan to Medicare), formulary changes by insurance companies’ pharmacy benefit manager (PBM), or co-payment payment policies. For example, a change to the PBM contracted with one woman’s insurance company left her with different coverages, new step therapy requirements, and without access to her DMT for months at a time. In addition, insurance changes led to uncertainty about future access, for example one participant could not find information about whether the Medicaid plan he would enter later in the year would cover his DMT. Finally, some patients could not afford to meet insurance requirements to pay the full price of DMT up front and wait get reimbursed later for the portion covered by the insurer.

Providers facilitated documentation of proof of medical need to advocacy groups or pharmaceutical company programs offering co-payment assistance. For some, physician documentation was easily accomplished, while for others it was a frustrating impediment that required additional calls or visits, and in some cases, delayed treatment access.

Barriers at pharmacies centered around finding a specialty pharmacy to work with their insurance and/or co-payment assistance program. Resolving these issues could involve weeks of phone calls and research into plan coverages at specific pharmacies. Several patients reported that insurance companies were unable to provide accurate information about alternative pharmacies that might cover their DMT, forcing patients to independently seek this information on the Internet or elsewhere.

Nearly all interview participants had sought financial assistance from an advocacy group or a pharmaceutical company. This process was marked by complexity and logistical challenges requiring substantial investment of time and effort to prove need and coordinate stakeholders. Patients reported a range of experiences with patient advocacy groups, from helpful to challenging. Some reported no problems with obtaining co-payment assistance from advocacy groups, but experienced problems elsewhere in the access process. Most described advocacy group funding assistance as a “grant” distributed for a certain total amount of money, after which point they would need to reapply. However, these organizations sometimes lacked sufficient funds to (re-)distribute. Others described spending dozens of hours on calls and paperwork to
prove eligibility, with one woman reporting her income was deemed $100 too high for assistance, despite living in an expensive area with a relatively modest income.

Pharmaceutical companies provided participants with co-payment assistance or direct access to a DMT. Some patients had difficulty navigating the administrative paperwork necessary to access their co-payment assistance programs, which could require original signatures that some found difficult to obtain. Others reported that pharmaceutical companies’ co-payment assistance programs were helpful facilitators, coordinating co-payment assistance between patients, providers, and pharmacies or in one instance directly sending medication to a patient when the insurance company and the pharmacy failed to work with the pharmaceutical company’s co-payment assistance program.

Two interviewees contacted government agencies to enforce insurance coverage of DMTs that were not being followed. This required additional effort and knowledge to access services to enforce coverage of DMTs.

Finally, patients reported that their families provided emotional and financial support, working to provide insurance, and encouraging patients to keep trying until they obtained their DMT. However, several patients reported they felt they were a burden to their spouse or other family members.

Discussion

Principal Results

In the United States, MS patients can face difficulty accessing disease-modifying therapies (DMTs) because of insurance, pharmacy, or provider policies. The current study demonstrated that issues related DMT access occur frequently, commonly due to the need for authorizing documentation, high out-of-pocket costs, and agency/provider coordination problems. Further, patients reported that the effort to overcome barriers was could be exceptionally time-consuming, complex, and stressful for patients with RRMS. This effort required contacting multiple stakeholders in their care administration, including providers, insurers, patient advocacy groups, and others. Furthermore, due to the lack of DMT, patients may navigate this complex process while experiencing disease progression and worsening symptoms. Some patients reported
experiencing negative health outcomes during this lack of access, including relapse.

**Limitations**

There are several limitations of our study which deserve mention. Generalizability of PatientsLikeMe patient population may not reflect the MS population at large, as users of health-based internet sites are more likely to be female, younger, and more educated than those sampled from a clinic [48]. Results from interviews are not representative of all MS patients on PatientsLikeMe, nor those who completed the survey, as they were selected to include only those who experienced difficulty obtaining a DMT. Patient-reported explanations for DMT access difficulties are subject to errors in recall and errors in the reconstruction of events, especially among patients who reported MS relapse during the access issue. Finally, the interview sample size was likely not sufficient enough to achieve concept saturation, so resultant themes should be interpreted with caution.

**Comparison with Prior Work**

These findings confirm previous research showing that insurance-related access barriers can be associated with adverse outcomes such as suboptimal adherence, which is associated with higher medical costs [35-41]. Similar to other studies with MS patients, patients in this study reported that before the DMT issue, many had to reduce or stop working due to functional cognitive decline related to MS [4-6,44,45]. Noting the burden of cost, paperwork, and benefit changes on MS patients trying to obtain DMT, medication advocacy organizations and provider groups have called for system-wide transparency, lower drug prices for DMTs, and policy reforms to assist MS patients with the cost burden of their care [8,46,47].

While the Affordable Care Act (ACA) of 2010 was implemented to benefit patients by improving overall health insurance access [42], many patients still lack access to DMTs due to their high cost and their specialty status [14]. Cost-sharing efforts on the part of payers has forced many patients to seek financial assistance to defray the costs of DMTs [19,43]. This study showed that even when these programs are available, the logistics of taking part are complex, burdensome, and sometimes unsuccessful, leading to elevated stress levels and, potentially, relapse.

**Conclusions**

This work represents one of the few studies to both detail the frequency of DMT access
issues, as well as highlight the patient perspective throughout the DMT acquisition process and the impact this may have on their health outcomes. Further, this study uses a novel approach, blending quantitative and qualitative methods to illuminate the patient experience with DMT access barriers from their own perspective. This approach offers depth and real-world insight that cannot be observed from administrative sources, such as claims databases. Our results stress the need for future research to incorporate the patient perspective to better understand barriers to MS treatment access. Evaluation of the long-term impact of DMT access barriers on patient and disease outcomes are needed. Formulary decision makers must consider the patient experience when making DMT coverage decisions. Clinicians should be aware of how patients experience DMT access difficulties and help deliver solutions to them when feasible. The MS patient experience with DMT access will continue to evolve with ongoing policy and payer landscape changes. Frequent feedback from MS patients and stakeholders will be of paramount importance to ensure access to DMTs and to measure the associated impact on outcomes.

**Abbreviations**

- DMT: disease modifying therapies
- MS: multiple sclerosis
- RRMS: relapsing remitting multiple sclerosis

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Conflicts of Interest

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