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The UK patient experience of relapse in Multiple Sclerosis treated with first disease modifying therapies

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KEYWORDS
Multiple sclerosis; Disease modifying therapy; Relapse; Patient survey; Patient perspective

Abstract
Background: The fixed, progressive disability associated with late Multiple Sclerosis (MS) is known to have a major impact on patients and their families, but the impact of relapse earlier in the disease course is less well documented, particularly from the patient's perspective. This study aimed to understand the effects of relapse for people with MS (PwMS), focusing on the years immediately after starting disease modifying therapy (DMT) when experience of a relapse may particularly influence a patient's opinions of their disease and its therapy.

Methods: This was a multi-centre, retrospective, observational research study, recruiting patients from 7 UK NHS Hospital Trusts. Consenting patients with relapsing-remitting MS (RRMS), who had started a DMT more than 36 months before screening, were sent a study questionnaire. Data on MS relapses and treatments over 3 years were collected simultaneously from medical records.

Results: One hundred and three patients completed the questionnaires. Relapses were under-reported to health care professionals, with 28% of respondents failing to report their most recent attack and 46% declaring they had failed to report an attack in the past. During their most recent relapse, 67% of those in paid employment reported taking time off sick, 48% reduced working hours temporarily, and 41% worked reduced hours and took time off sick. Sixty-six percent required additional support to undertake routine daily tasks during their most recent relapse. A range of effects of relapse which cannot be measured in financial terms were also reported, including effects on physical abilities, mental health and family roles and relationships.

Conclusion: This contemporary UK-based study provides an insight into the experience of relapse early in the treatment of RRMS from the patient perspective. The comparison of documented
1. Introduction

Multiple Sclerosis (MS), with an onset typically between the ages of 20 and 40, has a major impact on the physical wellbeing and social role not only of the person directly affected, but also of their relatives. The cost of late disability is the main driver in economic impact models (Hakim et al., 2000). A UK cost-of-illness analysis showed that employment rates reduce from 82% in early disease to 6% at an Expanded Disability Status Scale (EDSS) score of 7 (Kobelt et al., 2006).

However, a focus on the health economics of progressive disease may underestimate the impact of relapse on patients, carers and healthcare providers. Some effects, such as the strong emotional reactions elicited in patients and loved ones (Kalb, 2007), may not routinely be measured. In clinical trials of existing DMTs, reduction in disability appears to be driven by reduction in the clinical relapse rate. The occurrence of relapse remains the principal determinant for starting or escalating Disease Modifying Therapies (DMTs) under current UK DMT guidance (Association of British Neurologists, 2001; National Institute for health and Care Excellence, 2007, 2012).

This report describes the impact of relapse in a cohort of patients recruited to study the experience of the first 3 years of de novo DMT treatment. We focus here on the wider burden of relapse, including the change in patient contact with health care professionals, the financial impact of a relapse on People with Multiple Sclerosis (PwMS) and the impact of a relapse on patients’ attitudes to DMT. Discrepancies between clinician-documented and patient-reported relapse symptoms were also explored.

2. Methods

This was a multi-centre, retrospective survey of patients recruited from 7 UK NHS Hospital Trusts, selected to give a geographical spread across England and Wales. The study received a favourable ethical opinion from the London-Bromley Research Ethics Committee (ref. 12/LO/0248).

2.1. Study subjects

Data were obtained from participant self-completed questionnaires. Demographic details and information on relapses reported to the clinician within the first 3 years following DMT initiation were obtained from hospital medical records and, where possible, compared with patient-reported details. Inclusion criteria were: (1) RRMS diagnosis by 2005 MacDonald criteria (Polman et al., 2005); (2) first DMT after 1st July 2007 and at least 36 months before screening inclusion date; (3) ability to complete study questionnaires (by carer or self); and (4) consent to complete study questionnaires and for a researcher to review medical records.

To characterise the cohort, patients were also asked to complete an EQ5D, Beck’s Depression Inventory scale and the Patient Determined Disease Steps score (PDDS) (Learmonth et al., 2013).

Written consent was sought from eligible patients by post by their clinician. Patients were approached in consecutive date order of DMT initiation, until all eligible or 40 study participants per site had been recruited.

2.2. Data collection, quality control and analysis.

Patient questionnaires were completed between July 2012 and March 2013. Some patients did not fully complete the questionnaire, therefore the number of respondents (n) varied by question. Where self-evident from subsequent answers, blank yes/no questions were completed by an investigator.

Relapse symptoms were grouped into domains to compare clinician and patient reports. In clinician notes, relapse severity was defined as:

- Severe: if documented as ‘severe’ or ‘disabling’, required hospitalisation or steroid therapy.
- Moderate: if neither criteria for ‘severe’ nor ‘mild’ were applicable.
- Mild: if documented as ‘mild’ or equivalent.

The term ‘relapse’ was defined for patients in the questionnaire as: either the appearance of new symptoms related to MS or very definite worsening of old symptoms, which lasted for at least 24 h and occurred after the patient had been stable for at least a month (with the absence of raised temperature, infection, or any other health problem).

Patients were asked to comment in detail on their most recent relapse. For some patients (n=27), the relapse described was outside the 3-year period following drug initiation, so for these patients no comparison with a relapse documented in the medical record was possible. Patients were also asked to record details of all MS-related visits they made to Health Care Professionals (HCPs) during their most recent relapse.

Responses to questions with multiple-choice options were analysed quantitatively and summarised as percentages. The responses to the open ‘comments’ question were analysed qualitatively, by thematic analysis. This was conducted by two researchers separately, with a third researcher arbitrating between any differences in the themes identified.
3. Results

3.1. Study sample: patients, disease and treatment history

One hundred and forty one (37%) of the 378 MS patients identified as eligible consented to take part in the study and 103 (73%) of those who consented or 27% of those eligible) returned questionnaires (‘the respondents’) although not all answered every question; number of respondents is reported with each result. In one case, due to a move to another area, hospital notes for the study period were incomplete, reducing the analysable cohort to 102 where medical record data was needed. Mean (SD) age was 40.2 (10.1) years at DMT initiation and 44.9 (10.0) years at questionnaire completion. Seventy seven percent of participants were female, (n=79/103). Fifty nine percent of the study sample (n=58/98 evaluable patients) started DMTs within 1 year of RRMS diagnosis with a median time from MS diagnosis to first DMT of 34 weeks (Interquartile range (IQR) 15 to 84).

There was a wide range of MS severity as described by PDSS, with 32% of 100 respondents reporting only mild impairment or normal functioning and 10% requiring bilateral support/a wheelchair or buggy/bedridden. Median PDSS score was 3, indicating gait disability (IQR 1 to 4), which equates approximately to EDSS (Kurtzke, 1983) grades 4-5.5.

Quality of life (EQ5D) mean score was 0.60 (SD 0.21) and EQSD VAS mean score was 63 (SD 22) (Szende and Williams, 2004). Forty-one percent of patients had a Beck’s Depression Inventory (BDI) score ≥ 19, indicating moderate or severe depression, with a median score of 15 (IQR 9 to 23).

During the 3 years following first DMT initiation, 59% (60/102) of patients experienced at least one relapse. The median number of documented relapses per patient was 1 (range 0-6). The mean annualised relapse rate (ARR) was 0.36 (n=102), with 63%, 49% and 41% of patients remaining relapse-free for 1, 2 and 3 years respectively. The 60 patients who relapsed during the first 3 years had a total of 109 relapses recorded in the medical record. Of these, 27 (25%) were mild, 42 (39%) moderate, 39 (36%) severe and 1 (1%) not known. 30/102 (29%) patients experienced at least one severe relapse.

Interferon was the initial DMT for 82/102 (80%) patients, with 58 (57%) receiving interferon as their only treatment. Other first line DMTs were glatiramer acetate for 19 (19%) patients and natalizumab for 1 patient.

Fifty nine (58%) patients remained on their initial DMT for at least 3 years, 39 (38%) changed drug at least once, with 8 of these patients subsequently discontinuing all DMTs, and 4 (4%) discontinuing treatment after only one DMT.

3.2. Data from patient-completed questionnaire

3.2.1. Reporting of relapses

Twenty nine (28%) of 102 patients responded that they did not report their most recent relapse to the MS specialist team. The most common reasons recorded were ‘mild relapse/not necessary’ (n=5) and ‘made contact with GP’ (n=4).}

Forty-six (46%) of 101 respondents reported that they had experienced a relapse in the past but not contacted a healthcare professional. The main reasons were: ‘considered symptoms too mild’ (18 patients) and ‘did not feel there was anything staff could do’ (8 patients).

In 40/103 (39%) instances the most recent relapse described by the patient in their questionnaire response fell within the retrospective data collection period and was confirmed by the patient as having been reported to a clinician. When the information provided in the questionnaires was compared with the data from the retrospective review of the medical records, in 27/40 (68%) instances the relapse described by the patient could be identified. Exact concordance between the symptoms reported by the patient and the medical record was found in 10/27 (37%) relapses. More symptoms were reported by patients than clinicians in 11/27 (41%) relapses and in 5/27 (19%) more symptoms were recorded by clinicians than reported by patients (for one patient the same number but different symptoms were recorded). Four episodes reported by the patients as relapses were not felt to be relapses in the opinion of the clinician, with valid reasons recorded.

The most frequently reported of 10 symptom domains was lower limb weakness/clumsiness/sensory disturbance/mobility; this was recorded by the clinician in 74% of relapses and by the patient in 89%.

3.2.2. Impact of most recent relapse on work and daily living

Of the 101 patients who responded to this question, 67 (66%) reported being in paid employment before their most recent relapse. During the relapse 44/66 (67%) reported taking time off sick, 32 (48%) reduced working hours temporarily, and 27 (41%) reported both working reduced hours and taking time off sick. A permanent change to their working pattern was reported by 11/62 (18%) patients, with 6/62 (10%) giving up work entirely.

Sixty seven (66%) of 102 patients required additional support to undertake routine daily tasks during their most recent relapse. Fifty two (78%) of these reported receiving help from family and friends and 10 (15%) reported incurring costs because of the need for additional help or support.

3.2.3. Financial impact of most recent relapse

Relapses also had a financial impact for some patients; 31% reported a reduction in family income. Where a value was reported (n=22), the reduction per month ranged from £100 to £1000. A change in benefit payments was reported by 7 patients. Where a value was reported, the mean increase was £303 (range, −£40 to +£600) per month (Table 1).

Twenty patients who recorded both a decrease in income and details of whether there had been a change in their benefits, had a mean (SD) monthly reduction in income of £434.00 (£378.53).

Additional one-off costs were reported by 10 patients and these varied; e.g. purchase of a stair lift (1 patient £6000), wheelchair hire (1 patient £60). Twenty five patients reported incurring healthcare attendance associated parking costs, 44 patients incurred additional fuel costs and 13 patients incurred public transport costs.
were either ‘very happy’ or ‘happy’ with their treatment. After their most recent relapse, 59% (41/70) of respondents who were on a DMT were either ‘very happy’ or ‘happy’ with their treatment. Thirty six percent (27/76) reported that they were more likely to be compliant with DMT treatment following their most recent relapse, 36% (27/76) reported that they were more likely to be compliant with DMT treatment following their most recent relapse.

60% (6/10) more contacts with an occupational therapist, and 54% (7/13) more contacts with a physiotherapist during their most recent relapse.

There were 57 responses to the question inviting any other comments the respondent wished to make. The themes identified in these comments are shown in Table 2. The psychological impacts mentioned included stress, fear of the future or the unknown, worry, depression, feeling alone (despite having a spouse), feeling very emotional, frustration at the limitations imposed by the disease and, in one case, mental health issues leading to psychiatric inpatient admission.

### Table 1 Financial costs incurred during most recent relapse.

<table>
<thead>
<tr>
<th>Change in Income/Cost incurred</th>
<th>% Patients responding ‘Yes’</th>
<th>Affected patients mean (SD)</th>
<th>Question respondents mean (SD)</th>
<th>Whole sample mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduction in family income - monthly</td>
<td>31% (28/89)</td>
<td>£549.18 (£376.57)</td>
<td>£145.57 (£309.49)</td>
<td>£117.30 (£283.46)</td>
</tr>
<tr>
<td>Increase in benefit payments - monthly</td>
<td>11% (7/65)</td>
<td>£303.33 (£254.38)</td>
<td>£28.44 (£114.35)</td>
<td>£17.67 (£90.93)</td>
</tr>
<tr>
<td>Additional help and support required - weekly</td>
<td>15% (10/68)</td>
<td>£85.63 (£72.97)</td>
<td>£10.38 (£36.96)</td>
<td>£6.65 (£29.93)</td>
</tr>
</tbody>
</table>

**Healthcare Attendance Associated Costs**

<table>
<thead>
<tr>
<th>Healthcare Attendance Associated Costs</th>
<th>% Patients responding ‘Yes’</th>
<th>Affected patients mean (SD)</th>
<th>Question respondents mean (SD)</th>
<th>Whole sample mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parking cost per relapse</td>
<td>33% (25/76)</td>
<td>£32.80 (£52.21)</td>
<td>£9.88 (£32.01)</td>
<td>£7.00 (£27.27)</td>
</tr>
<tr>
<td>Fuel cost per relapse</td>
<td>57% (44/77)</td>
<td>£37.28 (£62.85)</td>
<td>£19.45 (£48.84)</td>
<td>£13.03 (£40.92)</td>
</tr>
<tr>
<td>Public transport cost per relapse</td>
<td>19% (13/67)</td>
<td>£24.81 (£32.56)</td>
<td>£4.20 (£15.92)</td>
<td>£2.65 (£12.77)</td>
</tr>
</tbody>
</table>

3.2.4. **Visits to healthcare professional during relapse**

Sixty two percent (40/65) of patients reported more contacts than usual with their GP, 67% (8/12) more contacts with a “community therapist” (not further specified), 60% (6/10) more contacts with an occupational therapist, and 54% (7/13) more contacts with a physiotherapist during their most recent relapse.

Forty one percent (20/50) of patients attended their MS Specialist Nurse and 35% (19/57) their neurologist more than usual.

### Table 2 Themes in open comments from questionnaire respondents.

<table>
<thead>
<tr>
<th>Theme</th>
<th>Sub-themes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Impact on health and ability</td>
<td>Physical effects, Psychological effects</td>
</tr>
<tr>
<td>Burden on family/friends</td>
<td>Need to take over practical tasks, Emotional burden</td>
</tr>
<tr>
<td>Working life</td>
<td>Negative impact of relapse, Attitude of employers</td>
</tr>
<tr>
<td>Finances</td>
<td>Association with impact on work, Mitigating circumstances reducing the impact</td>
</tr>
<tr>
<td>Factors affecting relapse</td>
<td>Triggers of relapse, Factors affecting an existing relapse</td>
</tr>
<tr>
<td>Health care provision</td>
<td>Positive comments, Inadequate provision</td>
</tr>
<tr>
<td>Treatment effects</td>
<td>Positive effects, Negative effects</td>
</tr>
<tr>
<td>Control</td>
<td>Loss of control over aspects of life, Regaining control</td>
</tr>
<tr>
<td>Coping</td>
<td>Strategies, Mitigating circumstances</td>
</tr>
</tbody>
</table>

3.2.5. **Impact of relapse on attitude to treatment**

Of the patients who were taking a DMT at the time of the most recent relapse, 36% (27/76) reported that they were more likely to be compliant with DMT treatment following their most recent relapse and 54% (41/76) reported no change in compliance.

Before their most recent relapse, 59% (41/70) of respondents who were on a DMT were either ‘very happy’ or ‘happy’ with their treatment. After their most recent relapse, 57% (43/76) of respondents who were on a DMT, were either ‘very happy’ or ‘happy’ with their DMT.

3.2.6. **Open comments**

There were 57 responses to the final question inviting any other comments the respondent wished to make. The themes identified in these comments are shown in Table 2.

3.2.6.1. **Impact on health and ability.** Patients described physical symptoms and impairments associated with a range of effects on their abilities, including loss of mobility, inability to read, write or move independently of carers, needing to lie down every afternoon and inability to take an active role in sexual intercourse. One respondent described their quality of life as ‘reduced to a mere existence’ whilst another described the impact as ‘nothing that affects my day to day living’. Several people voiced concern at not regaining their pre-relapse level of health or function. The psychological impacts mentioned included stress, fear of the future or the unknown, worry, depression, feeling alone (despite having a spouse), feeling very emotional, frustration at the limitations imposed by the disease and, in one case, mental health issues leading to psychiatric inpatient admission.
3.2.6.2. Burden on family/friends. This emerged as a dominant theme, particularly in relation to the spouse/partner and young children. Specifically, the impacts included the practical - for example, needing family to take over household chores and cooking. Childcare was also a big issue with family or friends taking time off work to accompany/transport them to hospital appointments and relatives having children to stay during the acute phase of a relapse. The emotional upset and general ‘burden’ caused to family was a great concern to some. Some respondents expressed regret at the change in interaction with family, including not being able to do what they used to with their young children/grandchildren. One respondent described severe strain on their relationship leading to its break up, which they attributed to MS if not directly to the relapse. Others acknowledged the importance of the support they received from their family.

3.2.6.3. Working life. MS relapses were associated with a range of impacts on respondents’ working lives, which in some cases were clearly described as being of paramount importance, either for mental health or financial reasons. People described their MS relapse as causing them to take time off work, reduce their hours, lose responsibility, retire, resign or be unable to work since their most recent relapse. Some respondents described their employers as being supportive while others described pressure either to return to work or to resign. Some relied on an intermittent pattern of work to avoid having to reduce their working hours or deal with sickness absence sanctions.

3.2.6.4. Finances. Some respondents stressed the importance of the financial impact, due to their being the principal earner in the family. Others mentioned factors that mitigated the financial impact, such as understanding employers giving family time off work to provide transport to hospital (which would otherwise have incurred more cost), and insurance or pensions which provided financial support when they could no longer work.

3.2.6.5. Health care provision. Several respondents mentioned with appreciation the support received from health care professionals including GPs, MS nurses and doctors. However some respondents reported difficulties in accessing appropriate professional help, including delay in obtaining an appointment, the appointment being too short, poor communication between GP and hospital and delays in organising appropriate treatment.

3.2.6.6. Treatment effects. Both positive and negative responses were included. Some respondents reported a lack of relapses since starting a DMT, not getting any worse, milder relapse than prior to starting a DMT and even an improvement in health;

‘…my [DMT] treatment… has really given me my quality of life back’.

Conversely, some respondents focussed on side effects of treatment, especially where these affected their ability to work;

‘The side effects of [DMT] mean I could not work [the following day]… which limits work options’

‘Having to retire from occupation due to taking DMT’

3.2.6.7. Factors affecting relapse. Some respondents traced their relapse back to a specific precipitant including infections, holidaying in a hot climate, being taken off medication and pregnancy/childbirth; e.g.

‘having my son brought the relapse on’

3.2.6.8. Control. The unpredictability of the disease was volunteered as having contributed to a feeling of loss of control and inability to make plans. One respondent described how they ‘took matters into own hands and restarted meds’ to regain control.

3.2.6.9. Coping. Various strategies were described. These ranged from small practical adjustments such as having shopping delivered and using microwave meals during a relapse or getting a flu jab to avoid viral illness. The benefits of a positive outlook were proposed;

‘I am very up beat and like to live a normal life and not let my MS interfere’

Mitigating circumstances identified included being fortunate that they or their spouse had flexible or part time working patterns or understanding employers.

4. Discussion

As only 27% of all eligible patients took part in the study, there may be doubts as to the representativeness of this sample. There was a slightly higher proportion of female questionnaire respondents than in the eligible population (77% vs. 71% respectively) but the sex distribution is not dissimilar to previous population estimates of sex distribution in RRMS (Alonso et al., 2007). Respondents were perhaps slightly older and more disabled than might have been predicted; the mean age at questionnaire completion (44.9 years) was slightly higher than the mean age of those eligible (43.5 years) on 1st January 2013. Forty-one percent of respondents had a BDI score of >19, indicating moderate or severe depression, with a median score of 15 (IQR 9 to 23). This is higher than a UK general population BDI mean of 7.25 (Van Hemert et al., 2002) but in line with other estimates of depression in the UK MS population (Jones et al., 2012). The quality of life (EQ5D) mean score of 0.60 was lower than the general UK population mean of 0.86 (SD 0.23) (Kind et al., 1999) indicating a worse perceived health state. EQ5D VAS mean score of 63.0 was also lower than the general UK population mean of 0.86 (SD 0.23) (Kind et al., 1999) indicating a worse perceived health state.

The annualised relapse rate of 0.36 per patient year is remarkably similar to that seen in clinical trials of beta-interferon and glatiramer acetate (Roskell et al., 2012). Of the relapses that were documented, 75% were considered to be moderate or severe. The generally good patient satisfaction with first line treatment appears unaffected by the occurrence of relapse. This potentially reflects well-managed expectations of the limited efficacy of the first line therapies, which may also be seen in the fact that only 12% of patients stopped all DMTs within 3 years.

Eighty percent of patients were initiated on interferon treatments
The UK patient experience of relapse in multiple sclerosis

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References


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The occurrence and impact of relapses is vital to ensure sound clinical decision-making, and this study reveals some deficiencies in current practice in this regard, associated with under-reporting by patients. Although cost-effectiveness studies tend to focus on long term disability, the multifactorial impact of individual relapses is highlighted in the patient responses, emphasising relapse reduction as a worthy treatment aim in itself.

5. Conclusion

This contemporary UK-based study provides an insight into the patient experience of relapse early in the treatment course of RRMS. Until there are validated surrogate markers of early treatment response, accurate documentation of the occurrence and impact of relapses is vital to ensure sound clinical decision-making, and this study reveals some deficiencies in current practice in this regard, associated with under-reporting by patients. Although cost-effectiveness studies tend to focus on long term disability, the multifactorial impact of individual relapses is highlighted in the patient responses, emphasising relapse reduction as a worthy treatment aim in itself.

Conflict of interest statement

Martin Duddy: honoraria for lectures and consultancy, expenses and hospitality for educational meetings: Bayer, Biogen Idec, Genzyme, Merck, Novartis, Roche and Teva. Martin Lee: nothing to declare.