Multiple Sclerosis patients' understanding and preferences for risks and benefits of disease-modifying drugs: A systematic review

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Abstract

Background: Multiple Sclerosis (MS) patients are faced with complex risk-benefit profiles of disease-modifying drugs (DMDs) when making treatment decisions. For effective shared decision-making, MS patients should understand the risks and benefits of DMDs and make treatment decisions based on personal preferences.

Methods: This is an inclusive systematic review to primarily assess current understanding of MS patients for information about DMDs provided during the standard healthcare system. The secondary aim assesses MS patients' preferences for specific risks and benefits of treatments. A systematic search was conducted using PubMed, Embase and Google Scholar. A total of 22 studies were reviewed across both aims. Relevant quantitative and qualitative data was extracted by two authors. A narrative synthesis was conducted due to heterogeneity of research findings.

Results: There was a trend for DMD risks to be generally underestimated and DMD benefits to be generally overestimated by MS patients. Treatments that could potentially offer substantial symptom improvement, delay in disease progression, or reduction in relapses were preferred even at the expense of higher risks.

Conclusions: Many patients' experience of information during the standard healthcare system does not provide satisfactory understanding of the risks and benefits of DMDs. Effective ways to communicate risk and benefit DMD information when making shared treatment decisions needs to be identified. Patient preferences of DMD risks and benefits should also be taken into account.

Keywords

Multiple Sclerosis, disease-modifying drugs, understanding, preferences, systematic review, shared decision-making

1. Introduction

Multiple sclerosis (MS) is a chronic immunological disease of the central nervous system which progresses at different rates between individuals [1,2]. Disease-modifying drugs (DMDs) are treatments which can delay the progression of MS, but often present complex profiles of risks and benefits [3]. DMDs typically provided at the earlier stages of MS are selected for their long-term safety profiles and minimal monitoring requirements, and are generally referred to as first-line treatments [4]. The efficacy of these therapies are modest [5]. More aggressive DMDs may be considered when initial therapies are not effective. These DMDs generally offer superior efficacy but also higher probabilities of adverse effects, which can range from flu-like symptoms to fatal conditions such as leukemia or progressive multifocal leukoencephalopathy (PML) [3,6–9]. MS patients are thus faced with complex risk-benefit profiles when deciding on the best course of treatment.

A shared decision-making approach is particularly suited for a chronic condition such as MS, where there is great complexity and uncertainty about suitable treatments for an individual [10,11]. This approach is defined as the shared and proactive exchange of information between health professionals and patients, when making treatment decisions during consultations [12–14]. Effective shared decision-making in MS should improve patients' understanding of the risks and benefits of DMDs and allow patients to make treatment decisions in accordance with their personal values, which will likely improve patient engagement in the decision-making process [15,16].

Evidence-based information about DMDs should be effectively communicated during consultations based on the shared decision-making approach, since many MS patients seek autonomy during treatment decisions [17,18]. Autonomous patients desire accurate information about treatments, which includes current research findings about DMD risks and benefits [19,20]. If accurate information is not provided during consultations, it is likely that autonomous patients will seek information beyond the health care system that may be inaccurate or outdated. The benefits of providing clear and accurate treatment information to patients is also evident beyond initial treatment decision. One such benefit is improvement in treatment adherence, as patients with accurate understanding of treatment risk-benefit profiles are less likely to discontinue treatment due to unrealistic optimistic expectations [21,22]. Hence, it is important to determine whether MS patients sufficiently understand the complex risk-benefit profiles of DMDs when information is provided during the standard healthcare system.

It is also important to elicit patient values and preferences in order for shared decision-making to work effectively [16]. Patient preference in the shared decision-making context is generally defined as patient's choice of treatment based on available treatment options [14,23]. Preference for certain risks and benefits that treatments offer may be a sensitive predictor of patient's preferred choice of treatment. For instance, patients are likely to choose a treatment compatible with the level of risks they are willing to take [24,25] and may be more likely to forgo the benefits of long-term survival for the benefits of an improved quality of life [26]. In a recent review, MS patients' perception of treatment risks was also found to greatly impact patients' treatment decisions with their neurologists during the shared decision-making process [27]. For this reason, it is important to identify the extent to which patient preferences for both the risks and benefits that DMDs typically offer can influence MS patients' treatment decision.

To the best of our knowledge, the present systematic review is the first to gather evidence on MS patients' understanding and preferences for risks and benefits of treatments. The primary aim will evaluate MS patients' understanding of risk and benefit information for DMDs acquired during their journey through standard healthcare systems, preceding any interventions or decision aids that may be provided beyond regular consultations. The secondary aim will identify MS patients' preferences for treatment risks and benefits across studies, and assess whether these preferences can have an impact on patient's treatment decisions.

2. Method

2.1. Systematic literature search

The systematic literature search was conducted in February 2016 through PubMed, Embase and Google Scholar using specific search terms for both study aims (see Table 1). After removing duplicate entries, a total of 889 records were identified (see figure 1).

Studies were eligible for inclusion if they were: in English, with human adults and of any study design. Studies with patients of any MS disease subtype were included. No date restriction was applied. For both aims, studies were included if they had some evaluation of disease-modifying drugs and when the evaluations focused on patients with MS.

Studies were excluded if they discussed medications for MS symptom management or complementary medicines. Studies with evaluation of patients' understanding of disease-modifying drugs post educational intervention was not included. However, baseline measures prior to any educational intervention were eligible for inclusion in the present review. Studies that assessed MS patients' understanding for other areas in MS, including diagnosis and prognosis, were excluded. Studies focusing only on patients' adherence to DMDs were also excluded.

Following screening of titles and abstracts, 835 records were excluded. Full texts were subsequently accessed. Studies that were considered relevant from screening references were also identified. Thus, data was extracted for a total of 58 full-texts, and studies were included into the final review if inclusion and exclusion criteria were met (see figure 1).

2.2. Data extraction

Data extraction was carried out by one reviewer (GR) using data extraction forms specifically designed for the current review, and was verified by another (DL). Any discrepancies were resolved by discussion. After extraction of full texts, a total of 22 studies were included into the final review across both study aims. One study had relevant findings for both the primary aim and secondary aim. Thus, 14 studies were included into the primary aim and 9 studies were included into the secondary aim.

Baseline characteristics of MS patients were extracted from all 22 studies, which covered age, the type of MS and current DMD status. Since very few studies exclusively assessed understanding or preferences of treatment risks and benefits in MS, studies with any evaluation of either aims were retained.

For the primary aim, any data available on understanding of treatment risks or benefits, or understanding of the treatment overall, was retained. Only understanding of information about real DMDs was incorporated into this aim. This information sometimes existed as baseline measures in intervention studies. Both self-report and objective measures were included for review, in addition to themes from qualitative studies.

For the secondary aim, patients' preferences for treatment risks only, treatment benefits only and a combined trade-off between treatment risks and benefits were considered. Preferences for treatment risks and benefits were defined as patients' attitudes towards risks and benefits, the levels of risks and benefits MS patients were willing to

accept, or MS patients' perception of their current DMD. Preferences for risks and benefits of both real DMDs and hypothetical treatment scenarios were included in this aim, providing that hypothetical risk-benefit scenarios were relevant to MS. Similar to the primary aim, information from self-report and objective measures were discussed.

Relevant data was obtained from numerical information in texts, tables, graphs, and relevant statistical analysis. For qualitative studies, relevant themes were extracted and discussed. Medication names are given as reported in each study. Due to the heterogeneity of the studies in the present review, a narrative synthesis was conducted.

2.3. Quality assessment

All studies in this review were examined independently for quality by two reviewers (GR and DL) using the Effective Public Health Practice Project (EPHPP) quality assessment tool for quantitative studies [28]. This particular tool was chosen because it is often used to evaluate different types of quantitative studies in the health care setting [29], it has high inter-rater reliability [29] and is considered ideal for use in systematic reviews [30]. As per the tool, the final quality rating was derived from the rating of 6 measures (see tables 2 and 4).

The Critical Appraisal Skills Programme (CASP) tool was used to appraise the quality of qualitative studies in this review (see table 3). This tool was chosen as it has often been recommended for reviewers [31] and was previously used in other systematic reviews [32]

3. Results

3.1. Results: Primary aim

3.1.1. Patient and study characteristics

A total of 14 studies were included in the primary aim (see table 5 and 6). With the exception of three qualitative studies [33–35], the studies mostly consisted of surveys and questionnaires. Data from some studies was derived from baseline measures of randomised-controlled trials [36–38]. Two quantitative studies were found to have the strongest quality rating [36,39].

Across the 14 studies, a total 8032 patients were included with a range of MS disease subtypes, which comprised: 27 (0.3%) patients with Clinically Isolated Syndrome (CIS), 2,532 (31.5%) Relapsing-remitting MS (RRMS) patients, 349

(4.3%) Primary Progressive MS (PPMS) patients and 870 (10.8%) Secondary Progressive MS (SPMS) patients. Of the remaining, 251(3.1%) patients were reported as having benign MS, with unclear or unreported MS disease subtype for all other MS patients (49.8%). The mean age of patients was 42 (range: 34 – 50). The mean value excludes MS patients in studies that only stated the median values of age [40], the range of ages [34,35] and those studies that did not specify age of MS patients [36,41].

Of the studies which recorded patient's current DMD, the majority of patients were taking first-line treatments, including interferons in seven studies [34,36,38,41–44] and Glatiramer acetate in four studies [35,38,41,42]. MS patients taking aggressive medications were also recorded, including Natalizumab (Miller et al., 2012), Fingolimod [37] and Mitoxantrone [41,45]. Eight studies focused primarily on MS patients taking a single DMD [33–37,43–45]

3.1.2. Study outcomes

Understanding of overall treatment information

MS patients' understanding of overall DMD information during the routine healthcare system was assessed using questionnaires and surveys by seven studies.

Self-report measures in one study indicated that 44% of MS patients considered themselves extremely well-informed about their current DMD [43]. Using a visual analogue scale in another study, just under 20% of patients reported being fully informed about current DMDs [37]. Using retrospective surveys, 28% of patients reported being well-informed about DMDs at time of diagnosis, with just over 50% patients stating that they did not receive any information about DMDs at diagnosis [46]. On the other hand, between 75% to 84% of MS patients reported being partly or totally informed about current DMDs [40,42], and 85% of MS patients felt they were aware about other DMD treatment options based on one question from a 12-item questionnaire [41]. Of those patients who felt informed about DMDs, 71% of MS patients felt the information received was of a sufficient standard [46].

Objective measurements were used by two studies within the present review to establish MS patients' understanding of overall treatment information. Abolfazli and colleagues [44] administered a 25-item questionnaire to MS patients, nine questions of which assessed understanding of the first-line treatments in general, and three questions each focused on understanding of the five specific DMDs that fell within this category. Only 30% of MS

patients were able to correctly answer seven of the nine questions that assessed understanding of the drugs generally, with the remaining two questions answered correctly by just over 60% of MS patients. The authors concluded that understanding of overall information about first-line DMDs was low for the assessed MS patients [44]. Another study also employed an objective questionnaire, which was presented to patients as part of a baseline measure before intervention [37]. MS patients in this study answered a median of six questions correctly about overall understanding of their current DMD from a maximum score of 18 [37]. Both studies also analysed factors which were associated with greater understanding by MS patients for overall information about DMDs. A common significant patient factor associated with better understanding across both studies was gender, since females displayed greater understanding of overall information about first-line DMDs [44] and the more aggressive treatment Fingolimod [37]. Greater understanding of overall DMD information was also related to: a high level of education [44], the delay between onset of symptoms and diagnosis of MS [44], increased mobility [44], younger age [44], ability to self-inject for some first-line treatments [44] and patients who were in a relationship as opposed to being single [37].

In summary, majority of studies which assessed MS patients' understanding of overall DMD information relied heavily on patient self-reports. Although the findings varied both within and across studies, it is clear that not all patients feel sufficiently informed about DMDs during the routine healthcare system. This is also supported by objective measures, albeit in only a few studies. The factors associated with good understanding of overall DMD information were also inconsistent, with only females showing a consistent advantage across two studies.

Understanding of treatment risks.

MS patients' understanding of treatment risks was evaluated by four studies in this review.

Perceived accurate understanding of the risks of unspecified DMDs was reported by 63% of MS patients in one study [18]. A qualitative study interviewing MS patients taking the aggressive treatment Natalizumab showed mixed findings for understanding of the risks associated with this treatment; patients demonstrated both high and low perceived risk [33].

Three studies used objective questionnaires to assess understanding of DMD risks, with two of these studies administering a similar adapted 19-item questionnaire designed for newly diagnosed patients [18,38]. Approximately

30% of MS patients showed 'good risk knowledge' for their DMD based on their scores from this questionnaire [38]. For the other study employing a similar questionnaire, MS patients were only able to answer 34% of the questions correctly on average despite perceiving their risk knowledge as good [18]. Significant correlations were also established between greater understanding of DMD risks and patients who had been recently diagnosed, had the RRMS disease subtype, and were of a younger age [18]. To note, questionnaires employed in both studies primarily measured understanding of the risks associated with MS in general, with only a portion of the questions explicitly focusing on risk understanding of DMDs. In another study employing objective methodology for the understanding of the aggressive DMD Mitoxantrone, 55% of MS patients underestimated the risk of Leukaemia, and up to 82% of MS patients underestimated the risk of cardiotoxicity; both adverse risks associated with this DMD [45]. These findings were based on baseline measures of an interventional study [45].

In summary, although MS patients show mixed perception towards their understanding of DMD risks, objective measures seem to indicate that DMD risks are generally low and underestimated by MS patients during the routine healthcare system.

Understanding of treatment benefits.

MS patients' understanding of the benefits associated with their treatment was evaluated by five studies in the present review.

Over 70% of MS patients taking a range of DMDs believed their current DMD could help their MS [41]. Likewise, a large number of MS patients totally or partially perceived their current medication to have strong benefits: 90% of MS patients perceived that their DMD could reduce the frequency of MS relapses, 86% of MS patients believed that their current medication could delay the progression of disease and just over 70% of MS patients were generally optimistic about their condition as a result of taking their current medication [42]. In two qualitative studies, MS patients taking first-line treatments described their medication as a "saviour" [34] and believed that taking the DMD felt as if they were "doing something progressive" towards their condition [35].

Only one early study employed an objective methodology to measure understanding of DMD benefits. Mohr and colleagues [36] administered a 12-item questionnaire prior to providing an intervention. Only 39% of MS patients

accurately reported the benefits of taking their first-line DMD, and 57% of MS patients were found to optimistically and incorrectly state that MS relapses could be reduced by a half following uptake of their current DMD [36].

Acknowledging the difficulty in comparing studies with self-report and objective measures, and those encompassing MS patients taking a range of DMDs, the limited data in the current review indicates a general trend towards underestimation of treatment risks and overestimation of treatment benefits by MS patients during the routine healthcare system.

3.1. Results: Secondary aim

3.1.1. Patient and study characteristics

The studies in this part of the review consisted mostly of surveys and questionnaires (see table 7). One study that has previously been reviewed in the primary aim also included findings relevant to the secondary aim [44]. Only one study in this section of the review was found to have the strongest quality rating [47].

From the final 9 studies included into the secondary aim, a total of 7427 patients were included with a range of MS disease subtypes, comprising of: 45 (0.6%) CIS patients, 652 (8.4%) RRMS patients, 31 (0.4%) PPMS patients and 59 (0.8%) SPMS patients. Majority of the studies did not clearly report or specify the MS disease subtype (89.8%). The mean age of MS patients was 42 (range: 34 – 52).

Of the studies which reported the current DMDs of MS patients, majority reported patients taking first-line treatments, which includes interferons in five studies [44,48–51] and Glatiramer acetate in four studies [48–51]. Patients taking more aggressive DMDs also formed a part of this review, specifically patients taking Natalizumab [49–52], Fingolimod [50,51] and Rituximab [50]. Two studies focused primarily on a single DMD [44,52].

3.1.2. Study outcomes

Preferences for treatment risks.

Four studies, each employing objective methodologies, looked at MS patients' preferences for the risks of taking a treatment.

Tur and colleagues [49] assessed the level of risks that MS patients were willing to accept for hypothetical therapeutic scenarios. The authors also assessed the relationship between accepted levels of hypothetical treatment risks and current DMDs taken by MS patients. A visual analogue scale showed that MS patients on the aggressive treatment Natalizumab were willing to accept higher levels of hypothetical treatment risks in comparison to MS patients on any other DMD [49].

Hypothetical treatment scenarios were employed by two further studies using objective methodologies, which compared MS patients' preferences for different levels of treatment risks [50,51]. Both studies confirmed that DMDs with significant adverse side-effects were less preferred than DMDs with minor side-effects. In fact, both studies revealed that medications with no possibility of death or disability were significantly favoured to a medication with even a very low possibility (0.05% to 1%) of death or disability [50,51]. Mood changes were the only specific side-effect that would decrease the probability of taking a DMD by MS patients [50,51].

Using a standard gamble question task, another study employed a hypothetical treatment scenario which presented information about a treatment that could cure MS, and a real treatment scenario which presented the risk profile of the aggressive DMD Natalizumab [53]. MS patients showed similar preferences for risks in both the hypothetical and real treatment risk scenarios, as adverse risks were accepted when in the range of 1 in 10,000 [53]. For the hypothetical treatment scenario, MS patients that were significantly likely to prefer higher levels of adverse risks were those presenting with the following characteristics: wheelchair bound, male, not responsible for dependents, not currently taking a DMD, taking Natalizumab and not routinely wearing a seatbelt for car travel [53]. With the exception of MS patients who were not taking a DMD, the same characteristics of MS patients preferred higher levels of treatment risks in the real DMD scenario [53].

Despite the comparison of hypothetical and real treatment risk profiles in this section of the review, MS patients showed similar low preferences for treatment risks.

Preferences for treatment benefits.

MS patients' preferences for treatment benefits were assessed by five studies in the present review.

Two studies used subjective measures to assess the preferences of MS patients towards treatment benefits [44,47]. MS patients with a positive outlook towards their current DMD ranged from 20% to 90% within one study [44] and was approximately averaged at 60% in another [47]. Patient factors significantly associated with a positive attitude were patients with: lack of functional problem, no MS family history and knowledge of their current DMDs [44].

Turning to objective measures, Prosser and colleagues [48] utilised a gamble health outcomes task using hypothetical treatment scenarios to assess preferences of MS patients for treatment benefits. During this task, patients were required to choose either a drug offering a particular number of relapse-free days, or a drug offering a 50% chance of ending the MS relapse immediately but with 50% chance of the drug not working at all. On average, patients chose drugs likely to lead to 14.6 MS relapse-free days from the possible 29, implying a preference towards treatments offering moderate but guaranteed benefits. However, the authors did note that approximately 30% of MS patients chose an extreme number of relapse-free days, i.e. either 1 or 29 [48].

The frequency of MS relapses was also used as an outcome measure to assess MS patients' preferences for treatment benefits in the remaining two studies and was compared alongside other benefits that DMDs typically offer [50,51]. The highest preference for MS patients in one study was for substantial symptom improvement in MS, followed by prevention of disease progression over 10 years, mild symptom improvement and a five-year delay in MS relapses [51]. Administration in the form of an IV infusion or oral pill was also significantly preferred by MS patients. In fact, the ability to administer the drug orally was preferred even over a five-year delay in relapse [51]. Likewise, any form of improvement in symptoms and the ability to take the drug orally were also strongly preferred by MS patients in the latter study [50]. However, unlike the previous findings, MS patients in this study showed no significant preference for delay in MS relapses or administration of drugs via IV infusion [50]. Additionally, the ability to prevent MRI progression over the years was used as an indicator only in this study and was significantly preferred by MS patients [50].

Although all studies in this review assess MS patients' preferences for treatment benefits, chiefly for hypothetical treatment scenarios, the results are not directly equivalent as the range and actual treatment benefits offered to patients differed greatly between studies. In general, treatments offering high symptom improvement, a delay in disease progression, reduction in relapses and particular administration methods were preferred.

Preferences for treatment risk-benefit profiles.

Three studies objectively measured the risk-benefit trade-off by offering MS patients the choice of benefits and risks for hypothetical treatments, using the conjoint analysis method [50–52]. Whilst all three studies used a similar objective methodology, the studies employed different treatment risk and benefit scenarios. Johnson and colleagues [52] demonstrated that for a five-year delay of disease progression, a 0.48% risk of death by Leukaemia was acceptable for MS patients; which increased to 1.08% for an eight-year delay of disease progression. For a similar delay of disease progression, the acceptable risk of death by liver failure increased by 0.53%, and acceptable risk of severe disability or death from PML increased by 0.36% [52]. Wilson and colleagues [51] found that patients were willing to accept 0.7% risk of developing PML given a delay in the progression of disease [51]. Up to 1% adverse risks were accepted by MS patients if substantial improvements in symptoms could be demonstrated by the treatment [51]. Patients were willing to accept up to 0.59% of severe adverse effects if drugs could be administered orally [51]. In fact, this level of risk acceptance was higher than for drugs which could delay the progression of MS by four years [51] or could reduce the frequency of MS relapses from four yearly to no relapses within the next five years [52]. Further, a risk of up to 30% of severe adverse effects was acceptable for MS patients given 32 years of delay in progression of MS [50].

The study by Bruce and colleagues also assessed risk and benefit trade-offs of hypothetical treatment scenarios, by using a Medical Decision Making Questionnaire (MDMQ) [54]. Similar to previous studies, the choice of whether to uptake a treatment for all patients differed significantly according to the combination of treatment risks and benefits [54]. Additionally, patients who were adherent to their current unspecified treatment were willing to take medications with significantly higher combinations of risks and benefits than patients who were assessed as non-adherent [54].

In summary, despite using similar measures to objectively assess trade-offs of treatment risks and benefits, the three studies employed very different combinations of risks and benefits, limiting any generalised conclusions that may be based on these findings. However, it was clear from these studies that preferred combinations of treatment risks and benefits play a key role in the choice of treatment.

4. Discussion and Conclusion

4.1. Discussion

This systematic review was carried out to explore MS patient's understanding of DMD risks and benefits acquired through their standard healthcare systems, and MS patients' preferences for these risks and benefits; factors likely to impact shared decision-making. MS patients with different disease subtypes and those taking a range of DMDs were assessed by 22 studies in the present review. Understanding of DMD risks and benefits were mostly addressed as part of a larger project. MS patients' preferences for risks and benefits were generally assessed using treatments offering hypothetical risks and benefits. Studies employed both subjective and objective measures. The majority of studies had methodologies that precluded firm conclusions.

DMDs in MS have complex risk-benefit profiles. All DMDs offer benefits of varying levels, such as reduction in the frequency of MS relapses and delay in progression of the disease. Side-effects of treatments can range from mild symptoms to adverse effects that may lead to severe disability or death [3]. When making decisions about DMDs based on these complex risk-benefits, a shared decision-making approach is ideal.

For effective shared decision-making, clear and accurate DMD information should be provided to MS patients in order to facilitate understanding of treatment risks and benefits. Yet, it appears from the present review that MS patients do not sufficiently understand information about DMDs following routine consultations in their standard healthcare system. Despite evaluating their risk knowledge as high [18], MS patients in this review showed poor objective risk understanding [18,38]. There was a trend towards underestimation of treatment risks [41,45]. This is problematic for long-term treatment adherence, as some patients are more likely to initiate a treatment that they perceive has lower risks but then discontinue treatment when the risks are higher than initially expected [19,22]. MS patients in this review were generally optimistic about the benefits of their current DMD [33,34,41,47]. However, many patients overestimated the benefits of their DMD in reducing the frequency of relapses and delaying progression of disease [36,42]. This could mean that patients' optimism towards DMDs may not often accurately reflect the actual benefits of the drugs. This can further impact treatment adherence, since patients who do not accurately understand the benefits of DMDs are more likely to discontinue treatments overtime [22], perhaps as optimism for medications is replaced with the realisation that the medication does not offer expected levels of benefits. In fact, a significant relationship between patients who understand information about their treatments and their adherence to treatments is evident in several studies, including those in the present review [21,22,39,42].

Providing accurate and easily understandable risk and benefit information to MS patients should therefore improve treatment adherence towards their chosen treatment.

The ability to understand overall information about DMDs provided during the standard healthcare system was found to be associated with certain patient factors, for example: age, education and functional status [37,44]. It is also possible that symptoms of MS itself, for example depression [55], anxiety [56], fatigue [57] and cognitive impairments [58,59], may further confound understanding of information about DMDs. However, these symptoms were not explored within the studies in this review. Regardless, it is apparent that some MS patients require further support to comprehend treatment information to a good standard. This may explain what prompts many patients to independently seek treatment data through sources beyond standard healthcare [19,42,43]. This external treatment information may not necessarily be accurate or up-to-date and could lead to further misunderstanding. Thus future studies need to primarily focus on improving the existing methods of providing DMD information for all MS patients, in order to improve shared decision-making.

Effective shared decision-making also requires patients to communicate their preference for a particular treatment. Preferences specifically for risks and benefits of DMDs are likely to influence MS patients' treatment choice [24–26]. The secondary aim of the present review assessed the extent to which preferences towards risks and benefits that DMDs typically offer can impact MS patients' treatment decisions. As anticipated, even very low levels of adverse risks reduced patients' preference to take the treatment, and extremely small variations in risk had a significant impact on hypothetical treatment decisions [50,51,53]. Preference for medications with adverse risks rarely exceeded 1%. Preferences for risks also varied with certain patient factors, as higher risks were generally accepted by males, functionally impaired individuals, or people already taking aggressive treatments such as Natalizumab [49,53]. Similarly, certain benefits that DMDs typically offer were significantly preferred over others and had an impact on the choice of treatment. Remarkably, patients strongly favoured medications that could provide symptom improvement [50,51], which implies limited understanding for MS treatments since DMDs are not able to relieve symptoms of MS. To note, medications presented in both studies [50,51] employed hypothetical treatment scenarios and therefore it is plausible that patients perceived symptom improvement as hypothetical despite accurate understanding of DMD benefits [50,51]. It is nevertheless interesting that patients are likely to take higher risks if DMDs can seemingly aid symptoms of their condition. MS patients in this review also showed a greater

preference for treatments offering large reductions in frequencies of relapses, longer delay in disease progression and drugs that could be administered orally, being prepared to accept a greater likelihood of risk in return [50–52,54]. Overall, MS patient preferences varied according to different combinations of particular risks and benefits, and had a significant impact on their choice of treatment. Thus, it is important to elicit patient preferences for particular risks and benefits of DMDs in order to improve shared decision-making in MS.

A limitation of the present systematic review is the difficulty in drawing robust conclusions or conducting a meta-analysis of the studies as a result of the variety of outcome measures employed. A narrative synthesis was considered to be the most appropriate format for reviewing the studies. However, it is important to acknowledge that such a qualitative review is subject to greater analysis bias than a quantitative systematic review. There were also differences in study design, methodology and patient characteristics between studies in the review, which limits conclusions from such findings. This reflects the lack of uniformity across studies that address MS patients' understanding of medications. The present review also does not constitute an exhaustive search of studies or research findings; for example, the primary authors of studies were not contacted to resolve or expand on study findings owing to time and resource constraints. However, it seems unlikely that supplementary results or additional outcome measures could produce less heterogeneous results.

4.2. Conclusion

The present review was the first to our knowledge to systematically gather evidence about patients' understanding of the risks and benefits of DMD during their standard healthcare system, and their preferences for these risks and benefits; factors which can likely impact shared decision-making. Despite the heterogeneous findings, it seems that current ways of providing DMD risk and benefit information are not generally uniform or effective. MS patients tend to underestimate treatment risks and overestimate treatment benefits, with some patients finding comprehension especially difficult. MS patients prefer treatments offering extremely low levels of adverse risks, but are willing to accept higher risks in exchange for substantial long-term improvements.

Practical implications of this review are providing extra support to ensure all patients are effectively informed about the complex risk-benefit profiles of MS DMDs, and ensuring patients' preferences for treatment risks and benefits are taken into account during the shared decision-making process.

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Conflict of Interest

GR has no disclosures.

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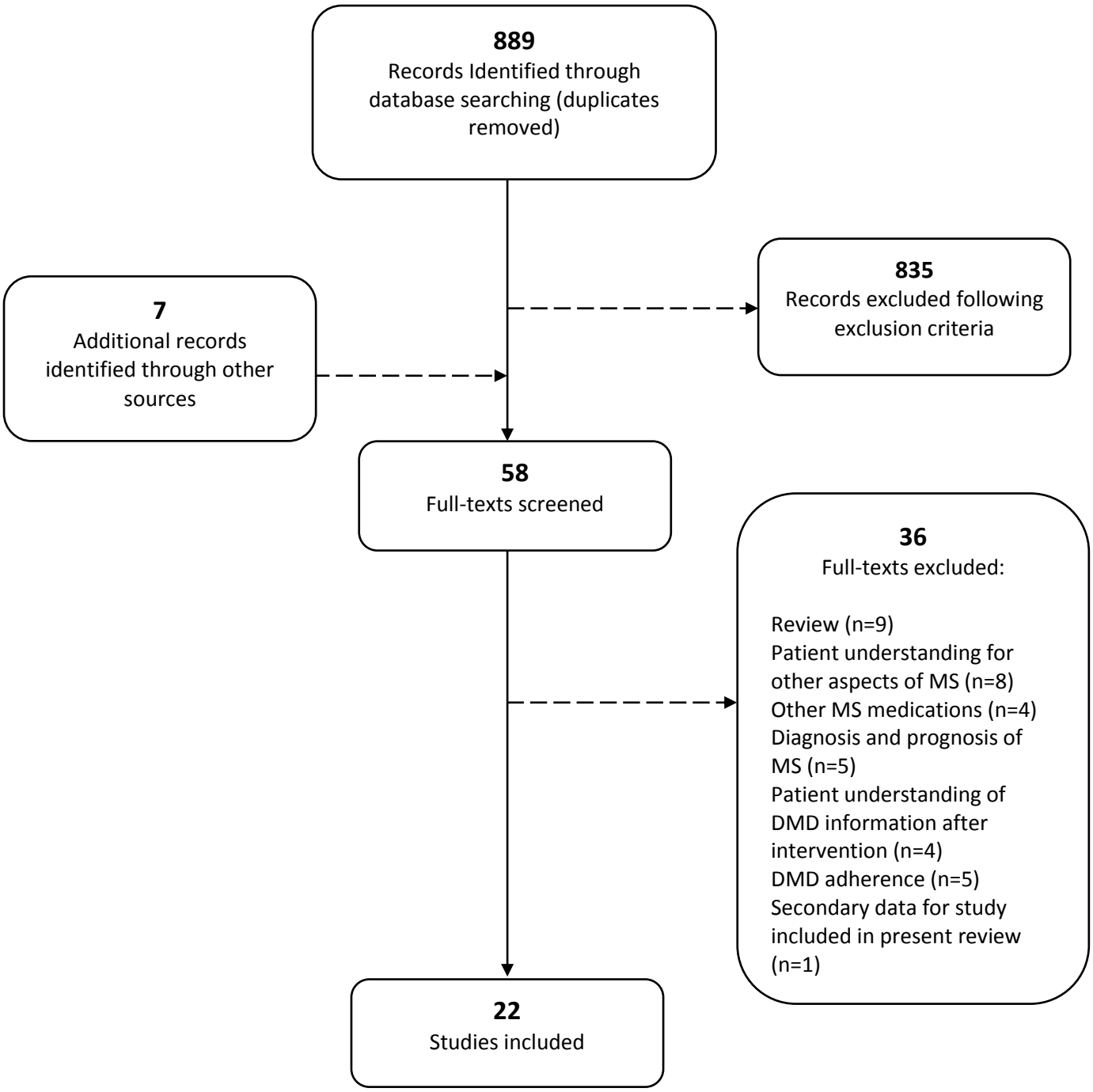

Figure 1. Flow diagram for included studies: Primary aim and secondary aim

Table 1. Search terms for Systematic review: Primary aim and secondary aim

Search terms for Systematic Review
(Multiple AND Sclerosis) AND (patients OR people OR persons OR patient) AND (risk OR benefit OR side effect) AND (treatment OR medication OR therapy OR medicine OR medical OR therapies OR therapeutics OR Pharmaceutical preparations) AND (perception OR understanding OR comprehension OR awareness OR knowledge OR information OR communication OR preference OR decision-making)

Table 2. Quality assessment of studies investigating MS patients' understanding of DMD risks and benefits: Primary aim

First author (year)	Selection bias	Study design	Confounders	Blinding	Data collection method	Withdrawals and dropout	Overall quality rating
Mohr (1996)	Moderate	Moderate	-	Moderate	Strong	Strong	***Strong***
Heesen (2003)	Weak	Weak	-	Moderate	Weak	Weak	***Weak***
Heesen (2004)	Moderate	Weak	-	Moderate	Strong	Moderate	***Moderate***
Vlahiotis (2010)	Weak	Weak	-	Moderate	Moderate	Weak	***Weak***
Visser (2011)	Weak	Moderate	-	Moderate	Weak	Moderate	***Weak***
de Seze (2012)	Weak	Weak	-	Moderate	Strong	Weak	***Weak***
Hofmann (2012)	Weak	Moderate	-	Moderate	Weak	Weak	***Weak***
Kopke (2014)	Strong	Strong	Strong	Strong	Strong	Strong	***Strong***
Syed (2014)	Weak	Moderate	-	Moderate	Moderate	Weak	***Weak***
Abolfazli (2014)	Weak	Weak	-	Moderate	Weak	Strong	***Weak***
Zimmer (2015)	Moderate	Moderate	-	Moderate	Moderate	Strong	***Moderate***

Overall quality rating: Strong=no weak ratings; Moderate=one weak rating; Weak=two or more weak ratings.

Table 3. Quality assessment of qualitative studies investigating MS patients' understanding of DMD risks and benefits: Primary aim

First author (year)	Clear aims	Appropriate methodology	Appropriate design	Appropriate recruitment strategy	Data collection method	Researcher and participant relationship considered	Ethical issues considered	Rigorous data analysis	Statement of findings	Is the research valuable?
Miller (2001)	Yes	Yes	Yes	Yes	Yes	No	Unclear	Yes	Yes	Yes
Miller (2006)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Miller (2012)	Yes	Yes	Yes	Yes	Unclear	Yes	Unclear	Yes	Yes	Yes

Quality assessed using the Critical Appraisal Skills Programme tool (CASP); all categories marked as either Yes, No or Can't tell/unclear.

Table 4. Quality assessment of studies investigating MS patients' preferences for treatment risks and benefits: Secondary aim.

First author (year)	Selection bias	Study design	Confounders	Blinding	Data collection method	Withdrawals and dropout	Overall quality rating
Prosser (2002)	Moderate	Weak	-	Moderate	Strong	Strong	***Moderate***
Kasper (2008)	Strong	Strong	Strong	Strong	Moderate	Strong	***Strong***
Johnson (2009)	Weak	Weak	-	Moderate	Strong	Strong	***Weak***
Tur (2013)	Moderate	Moderate	Moderate	Weak	Moderate	Strong	***Moderate***
Abolfazli (2014)	Weak	Weak	-	Moderate	Weak	Strong	***Weak***
Wilson (2014)	Moderate	Weak	-	Moderate	Moderate	Moderate	***Moderate***
Bruce (2015)	Moderate	Weak	-	Moderate	Moderate	Weak	***Weak***
Fox (2015)	Weak	Weak	-	Moderate	Moderate	Weak	***Weak***
Wilson (2015)	Moderate	Weak	-	Moderate	Weak	Strong	***Weak***

Overall quality rating: Strong=no weak ratings; Moderate=one weak rating; Weak=two or more weak ratings

Table 5. Patient and study characteristics, and results of quantitative studies investigating MS patients' understanding of DMD risks and benefits: Primary aim

First author (year)	Quality rating	Study design and methodology	Recruitment location	Sample size	Age (mean)	Type of MS (n)	DMD	Real/faux information	Self-report or objective measure	Outcome measure(s)	Results
Mohr et al., (1996)	Moderate	Questionnaire: Baseline data from a pre-post intervention study	Outpatient clinics	99	-	Not specified	Interferon beta-1b	Real	Objective	DMD benefit understanding: Survey items from BSQ	Relapse rate: Expected <10% reduction ('overly pessimistic group') = 4% patients Expected 10-30% reduction ('accurate group') = 39% patients Expected >50% reduction ('overly optimistic group') = 57% patients Disease progression: Expected no change = 40% patients Expected slower progression = 26% patients Expected some restoration of function = 29% patients Expected return to normal function = 4% patients
Heesen et al., (2003)	Weak	Postal questionnaire: observational study	MS patient organisation	434	Women=44; Men=43	Not specified	DMD not specified	Real	Self-report	Understanding of overall DMD information: 3 questions from 13-item questionnaire	52% of patients not informed at time of diagnosis; 28% of patients informed after several months of diagnosis; 71% of patients received sufficient information
Heesen et al., (2004)	Weak	Postal questionnaire: observational study	MS outpatient clinic	169	44	RRMS (*75*); PPMS (*75*); Unclear (*19*)	DMD not specified	Real	Objective	DMD risk understanding: 10 questions about DMD risks out maximum 19	34% answers correct
									Self-report	DMD risk understanding: VAS rating:	63% of perceived knowledge

										Perceived MS risk knowledge	
Vlahiotis et al., (2010)	Weak	Postal survey: observational study	American health insurance database	2022	-	PPMS (*78*); RRMS (*1493);* SPMS (*213*) Other (*29*); Unknown (*209*)	Interferon-beta 1a IM; Interferon beta 1a SC; Interferon-beta 1b; Glatiramer acetate; Mitoxantrone	Real	Self-report	DMD benefit understanding: Survey questions	DMD helps MS: Females=79%; Males=72%
									Self-report	Understanding of overall DMD information: Survey questions	Awareness of other treatment options: Females= 85% ; Males = 80%
Visser et al., (2011)	Weak	Postal survey: Observational study	Hospitals; MS Patient organisation	1371	Benign MS & RRMS = 47[1]; SPMS= 51[1]; PPMS= 52[1]	Benign MS (*251)*; RRMS (*525*); PPMS (*120*); SPMS (*399*); Unknown (*76*)	DMD not specified	Real	Self-report	Understanding of overall DMD information: 1 item from 72-item questionnaire; Enough treatment information received?	'Taking first DMD' group: 81% patients agree; 9% patients neutral; 10% patients disagree;
											'Changed DMD' group: 84% patients agree; 7% patients neutral; 9% patients disagree
											'Stopped DMD' group: 74% patients agree; 15% patients neutral; 11% patients disagree
de Seze et al., (2012)	Weak	Postal questionnaire: Observational study	Hospitals and community practise	202	41	RRMS (*202)*	Interferon-beta 1a; Interferon-beta 1b; Glatiramer acetate	Real	Self-report	Understanding of overall DMD information: 'Well informed about treatment?'	Totally agree=35%; Partly agree=40%; Partly disagree=14%; Totally disagree=5%; No opinion=2%
									Self-report	DMD benefit understanding	Reduced relapse frequency with current DMD: Totally agree=50%; Partly agree=40%; Partly disagree=6%; Totally disagree=2%; No opinion=3%

											Delay in treatment progression with current DMD: Totally agree=36%; Partly agree=50%; Partly disagree=9%; Totally disagree=2%; No opinion=5% Optimistic about MS due to DMD: Totally agree=28%; Partly agree=45%; Partly disagree=17%; Totally disagree=7%; No opinion=3%
Hofmann et al., (2012)	Moderate	Postal questionnaire: Retrospective cohort study	Database of hospitals and private clinics	575	50	RRMS (*49*); PPMS (*76*); SPMS(*258*); Other (*4*); Unknown (*188*)	Mitoxantrone	Real	Objective	DMD risk understanding: Risk choice from 4 options about Mitoxantrone side-effects	Leukaemia: Accurate risk choice = 40% patients Underestimated risk = 58% patients Cardiotoxicity: Accurate risk choice = 16% patients Underestimated risk = 82% patients
Köpke et al., (2014)	Strong	Telephone and postal questionnaire: Baseline data from Double-blind RCT	MS outpatient clinics	192	37	CIS (*27*); RRMS (*133*); Unclear (*32*)	Interferon-beta; Glatiramer acetate	Real	Objective	DMD risk understanding: 'Good risk knowledge' defined as minimum 12 answers from possible 19	IG at baseline (n-93) 35% patients with 'good risk knowledge' CG at baseline (n=99): 23% patients with 'good risk knowledge'
Syed et al., (2014)	Weak	Structured questionnaire: Baseline data from longitudinal study	Home support service	2390	42	Not specified	Interferon-beta 1a	Real	Self-report	Understanding of overall DMD information: 3 items from survey	44% of patients felt extremely well informed (n=1265)

Abolfazli et al., (2014)	Weak	Postal questionnaire: Observational study	MS patient organisation	425	34.3	Not specified	Interferons	Real	Objective	Understanding of overall DMD information	Greater understanding associated with: High level of education (p=0.0010) Delay between onset of symptoms and definite MS (p=0.0190) Increased mobility (p=0.220) Younger age (p=0.030) Females (p=0.001) Ability to self-inject (p=0.003)
Zimmer et al., (2015)	Moderate	Questionnaire : Baseline data from pre-post intervention study	MS Centre in hospital	98	41[1]	Not specified	Fingolimod	Real	Objective	Understanding of overall DMD information: 18-item questionnaire	Median score=6 out of 18 (IQR-=4-8) Greater understanding associated with: Females (p=0.02) Patients in a relationship compared to singles (p=0.03)
									Self-report	Understanding of overall DMD information: VAS (0-10); Perception of being informed	Number of patients with following scores (n-97): Score < 7 = 78 Score =>7 = 19

Absolute numbers reported, unless specified. Abbreviations: BSQ, Betaseron questionnaire; CG, control group; CIS, clinically isolated syndrome; DMD, disease-modifying drug; IG, intervention group; MS, Multiple Sclerosis; PML, progressive multifocal leukoencephalopathy; PPMS, primary progressive multiple sclerosis; RCT, randomized controlled trial; RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis; VAS=visual analogue scale.
1=Median, 2=Range

Table 6. Patient and study characteristics, and themes from qualitative studies investigating MS patients' understanding of DMD risks and benefits: Primary aim

First author (year)	Quality rating	Study design and methodology	Recruitment location	Sample size	Age (mean)	Type of MS (n)	DMD	Real/faux information	Self-report or objective measure	Outcome measure(s)	Results
Miller et al., (2001)	-	Qualitative interviews	MS centre	15	28-55[2]	RRMS (*15*)	Interferon beta-1a	Real	Self-report	DMD benefit understanding: Themes from qualitative analysis	Overestimating benefit of DMD: *"I look at Avonex as my saviour. I probably expected a lot more from it than I was going to get, realistically"* (pg. 242)
Miller et al., (2012)	-	Qualitative interviews	MS centre; Natalizumab infusion centre	20	43	RRMS (*20*)	Natalizumab	Real	Self-report	DMD risk understanding: Themes from qualitative analysis	Low risk perception for DMD: *"I didn't feel that it was going to a big risk for me because I trust my doctors, and I don't think they really pushed it if they didn't feel confident"* (pg. 41) High risk perception for DMD: *"I'm sure anybody who goes on Tysabri from the moment they make that decision…worry about PML".* (pg. 42) *"I was so afraid to try Tsyabri, you know, the warnings and the labels are just, they're so scary."* (pg. 42)

Miller et al., (2006)	-	Qualitative interviews	MS clinic	20	39-64[2]	RRMS (*20*)	Glatiramer acetate	Real	Self-report	DMD benefit Understanding: Themes from qualitative analysis	Benefits of glatiramer acetate: *"…the importance of getting on to these ABC drugs – Avonex, beta interferon and Copaxone – is to start as soon as you have symptoms"* (pg. 39) *"This way (injecting glatiramer acetate) I feel like I am doing something progressive to help it."* (pg. 39) "*And I have researched the ingredients, and it is so natural"* (pg. 40)

Absolute numbers reported, unless specified. Abbreviations: DMD, Disease-modifying drug; MS, Multiple Sclerosis; PML, progressive multifocal leukoencephalopathy; RRMS, relapsing-remitting multiple sclerosis. 2=Range

Table 7. Patient and study characteristics, and results of quantitative studies investigating MS patients' preferences for treatment risks and benefits: Secondary aim

First author (year)	Quality rating	Study design and methodology	Recruitment location	Sample size	Age (mean)	Type of MS (n)	DMD	Real/faux information	Self-report or objective measure	Outcome measure(s)	Results
Prosser et al., (2002)	Weak	Survey: Observational study	MS clinics	56	38	RRMS (*56*)	Interferon-beta 1a; Interferon-beta 1b; Glatiramer acetate	Faux	Objective	Preferences for treatment benefits: Gamble question (*drug with relapse-free days compared with dug offering 50% chance of immediate reduction but 50% chance of not working)*	Mean=14.6 relapse-free days
Kasper et al., (2008)	Strong	Questionnaire: Baseline data from RCT	Newspapers; websites; national self-help journal	297	43	CIS (*45*); RRMS (*153*); PPMS (*31*); SPMS (*59*); Unclear (*9*)	DMD not specified	Real	Self-report	Preferences for treatment benefits: Likert scale	Moderately optimistic towards current DMD: IG group at baseline =65% patients; CG group at baseline =62% patients
Johnson et al., (2009)	Moderate	Survey: Observational study	MS patient organisation; Natalizumab clinical trial patients	651	47	Not specified	Natalizumab	Real	Objective	Preferences for treatment risk-benefit profiles: Mean annual risk acceptable to patients	Mean annual risk for 'slow progression benefit' (No. of relapses in next 5 years reduced from 4 to 1; disability progression delay from 5 to 8 years) 0.31% of PML death or disability; 0.30% of death by liver failure; 0.35% of death by leukaemia

											Mean annual risk for 'clinically relevant benefit' (No. of relapses in next 5 years reduced from 4 to 1; disability progression delay from 3 to 5 years) 0.38% of PML death or disability; 0.39% of death by liver failure; 0.48% of death by leukaemia Mean annual risk for 'largest tested benefit' (No. of relapses in next 5 years reduced from 4 to 0; disability progression delay from 1 to 8 years) 0.74% of PML death or disability; 1.02% of death by liver failure; 1.08% of death by leukaemia
Tur et al., (2013)	Moderate	Survey: Observational study	MS centre; Hospital	136	Natalizumab group = 38; Other DMD group = 39	Not specified	Natalizumab; First-line DMDs	Faux	Objective	Preference for treatment risks: five risk levels for five presented therapeutic scenarios	Mean scores for level of risks accepted: Patients taking Natalizumab (n=114): Very low risk=8.85; Low risk=8.49; Medium risk=7.47; High risk=4.29; Very high risk=3.01 Patients taking any other DMD (n=22): Very low risk=7.50; Low risk=6.32; Medium risk=4.76; High risk=2.43; Very high risk=1.58

Abolfazli et al., 2014	Weak	Questionnaire: Observational study	MS patient organisation	425	34.3	Not specified	Interferons	Real	Self-report	Preference for treatment benefits: 5-point Likert scale across 13 questions	Optimistic about current DMD = 20% to 90% patients Optimistic about DMD associated with: Lack of functional problem (p=0.004) No MS family history (p=0.029) Knowledge of interferons (p=0.001)
Wilson et al., (2014)	Moderate	Questionnaire: Conjoint analysis	MS clinic	289	42	RRMS (*289)*	Interferons; Natalizumab; Glatiramer acetate; Fingolimod; Rituximab	Faux	Objective	Preference for treatment risk-benefit profiles: Estimated acceptable risk for various DMD benefits	For 1% risk of DMD severe side-effects, patient preference for treatment decreased by 5 times
									Objective	Preference for treatment risks: Odds ratio	Minor side effect: Headache flu=0.98 Mood change=0.91 (p<0.001) Severe side effect: 0.05% = 0.70 (p<0.001) 0.10% = 0.60 (p<0.001) 1%=0.22 (p<0.001)
									Objective	Preference for treatment benefits: Odds ratio	Progression prevention: 2 years=1 4 years=1.36 (p<0.001) 10 years=2.46 (p<0.001) Delay in relapse: 1 year=1 2 years=1.20 (p<0.001) 5 years=1.53 (p<0.001) Symptom improvement: None=1 Mild=1.75 (p<0.001) Substantial=3.68 (p<0.001)

Bruce et al., 2015	Weak	Questionnaire: Probability discounting	MS Clinics	77	Adherent =43.26; Non-adherent =45.03	RRMS	Not specified	Faux	Objective	Preferences for treatment risk-benefit profiles: Medical Decision Making Questionnaire	Chosen treatment benefit related to side-effect probability (p<.001) interaction between side effect and group (adherent and non-adherent) for treatment benefits chosen (p<.001) Improbable side-effects predict treatment adherence = 83.1%
Fox et al., 2015	Weak	Survey: Observational study	North American Research Committee on Multiple Sclerosis (NARCOMS) Registry	5446	52.7	Not specified	Not specified	Faux (*cure for MS*) and Real (*Natalizumab)*	Objective	Preference for treatment risk: Standard gamble paradigm	Median risk tolerance for both scenarios=1:10,000 Faux DMD scenario: No risk tolerance=23% Tolerate any risk=3.6% Faux DMD risk tolerance associated with: No disability=1:100,000 versus wheelchair-bound=1:1000 (p<.0001); Male=1:2000 versus females=1:50,000 (p<.0001); Patients caring for dependents=1:100,000 versus not caring for dependents=1:10,000 (p<.0001); Patients taking DMD=1:50,000 versus not taking DMD=1:50,000 (p=0.002); Patients taking Natalizumab=1:1,000 versus not taking Natalizumab=1:50,000 (p<0.0001); Patients who routinely use seatbelt=1:50,000 verus those

											who do not routinely use seatbelt=1:5000 (p=0.0007) Natalizumab scenario: No risk tolerance=15% Tolerate any risk=3.3% Natalizumab scenario risk tolerance associated with: No disability=1:100,000 versus wheelchair-bound=1:1000 (p<0.0001); Male=1:2000 versus females=1:10,000 (p<.0001); Patients caring for dependents=1:50,000 versus not caring for dependents=1:10,000 (p=0.004); Patients taking Natalizumab=1:750 versus not taking Natalizumab=1:10,000 (p<0.0001); Patients who routinely use seatbelt=1:10,000 versus those who do not routinely use seatbelt=1:1000 (p<0.0001)
Wilson et al., 2015	Weak	Survey: Conjoint analysis	MS Clinic	50	42.7	RRMS	Glatiramer acetate; Interferon beta; Natalizumab; Rituximab; Fingolimod; No-treatment	Faux	Objective	Preference for treatment risk	Common adverse effects (significance to reference): Increased risk of infection=reference Injection-site reactions=-0.16 Headaches, aches, flu=0.02 Changes in mood=-0.82 (p<0.001) Severe adverse effects: 0%=reference 1%= -1.15 (p<0.001) 10%= =3.06 (p<0.001)

			30%= -3.82 (p<0.001)
	Objective	Preference for treatment benefit: Conjoint analysis	Clinical outcomes – β coefficient values compared with baseline treatment profile: Prevents symptom progression for 1 year=0.12 (p<0.001); Prevents one relapse per year=0.05; Prevents MRI progression for 1 year=0.17 (p=0.002)
			Patient symptoms - β coefficient values compared with baseline treatment profile: Improved mildly=0.81 (p<0.001) Improved moderately=0.83 (p<0.001) Improved rarely but substantially=1.03 (p<0.001)
	Objective	Preference for treatment risk-benefit profiles: Conjoint analysis	Patients willing to accept 30% adverse risk for 32 years prevention of disease progression Patients willing to accept 10% adverse risk for 25 years prevention of disease progression

Absolute numbers reported, unless specified. Abbreviations: CIS, Clinically Isolated Syndrome, DMD, Disease-modifying drug; MS, Multiple Sclerosis; PML, progressive multifocal leukoencephalopathy; PPMS, primary progressive multiple sclerosis; RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis; VAS, visual analogue scale. 1=Median, 2=Range