Interventions to support risk and benefit understanding of disease-modifying drugs in Multiple Sclerosis patients: A systematic review

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Abstract

Objective: The present review evaluates interventions that have been designed to improve understanding of the complex risk-benefit profiles of disease-modifying drugs (DMDs) in patients with Multiple Sclerosis (MS).

Methods: A systematic search conducted using PubMed, Embase, Google Scholar and PsycINFO identified 15 studies. Interventions which provided treatment information were present across a range of study designs. A narrative synthesis was conducted due to heterogeneity of research findings.

Results: Interventions providing treatment information ranged from comprehensive education programmes to booklets of a few pages. MS patients favoured the interventions they received. Understanding of overall treatment information and treatment risks specifically, generally improved following interventions. Yet overestimation of treatment benefits persisted. There was no conclusive effect on DMD decisions. No superior intervention was identified.

Conclusion: Interventions designed to improve understanding of DMD risk and benefit information are moderately successful.

Practice implications: Additional support provided to MS patients beyond routine healthcare can generally improve understanding of the complex risk-benefit profiles of DMDs. Future interventions need to ensure that patients with symptoms that may confound understanding can also benefit from this additional information.

Keywords

Multiple Sclerosis; disease-modifying drugs; evidence-based patient information; risks; benefits; understanding; intervention; systematic review

1. Introduction

Multiple Sclerosis (MS) is a chronic inflammatory disorder of the central nervous system, which progresses at different rates between individuals [1]. MS patients experience a range of symptoms, including depression [2–4], anxiety [2,5], fatigue [3,6] and cognitive impairments [5,7,8], which likely confounds patients' general understanding and ability to recall important information. This could be problematic for MS patients when deciding a course of treatment.

The treatments currently available to MS patients are disease-modifying drugs (DMDs). Although DMDs do not target symptoms of MS, they can potentially reduce the number of relapses and delay progression of disease [9]. Yet the rate at which these benefits occur vary between DMDs and can even vary within individuals treated with the same medication. In general, MS patients are initially offered treatments with long-term safety profiles and limited adverse risks, but these are only moderately successful [10]. These treatments are also known as first-line DMDs. More aggressive treatments may be considered when initial therapies are not effective. DMDs at this stage offer higher benefits but potentially adverse effects, including Leukaemia, Cardiotoxicity, and Progressive Multifocal Leukoencephalopathy (PML) [9–13]. MS patients are therefore faced with complex risk-benefit profiles of DMDs when deciding on the best course of treatment.

An understanding of the risks and benefits of treatments is one of the many components required for an effective shared treatment decision. Shared decision-making is a highly recommended concept in patient-centered healthcare and refers to the mutual exchange of information between patients and health professionals during decision-making, such as decisions made about the most suitable treatment course [14,15]. This approach is particularly suited to chronic conditions such as MS, where the risk-benefit profiles of treatments are complex and need to be effectively communicated in order to inform and engage patients in treatment decisions [16,17]. Thus, it is reasonable to expect that improving MS patients' understanding of complex risk-benefit profiles of DMDs can have an impact on treatment decision-making.

To facilitate understanding, patients should ideally be presented with treatment options and treatment risk-benefit profiles in a clear and coherent manner [14,18]. Yet DMD information provided to MS patients during routine healthcare is not always clear or coherent [19–21]. This may explain why many MS patients actively seek DMD information elsewhere [22,23]. This external information may not be accurate or up-to-date, which could lead to further misunderstanding of treatment information. Interventions have been designed to provide information about the risks and benefits of DMDs that patients may seek beyond routine healthcare. Although such interventions aim to provide accurate information about DMD risks and benefits, it is also important to consider the way this information is presented. This is because understanding of treatment risks and benefits can be influenced by particular graphical [24–26] or numerical formats [27–29], the framing of information [30–32] and how comparisons of risks and benefits are communicated [33–35]. Thus, an ideal intervention will give patients unbiased and accurate treatment information using effective presentation methods in order to optimise the understanding of DMD risks and benefits, and consequently result in informed treatment decisions.

Köpke, Solari, Khan, Heesen and Giordono [36] recently reviewed 10 interventions designed to aid patient understanding of MS related information, which includes two interventions that specifically provided information about the risks and benefits of DMDs. Although all interventions reviewed were different in many respects, understanding of the disease generally improved post-intervention. Despite this improvement there was no conclusive effect on decision-making. This review, however, was limited to randomised controlled trials only, which does not allow for a comprehensive evaluation of all interventions that provide MS information beyond routine healthcare, particularly information on the risks and benefits of DMDs [36].

To the best of our knowledge, the present systematic review is the first comprehensive evaluation of interventions primarily designed to improve understanding of risks and benefits of DMDs for MS patients. This review will also explore the effects of these interventions on patients' treatment decisions.

2. Methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations were used as guidelines for the presentation of this review [37]. A protocol for the present review was not previously published or registered.

2.1. Systematic literature search

The systematic literature search was conducted in November 2016 using PubMed, Embase, Google Scholar and PsycINFO. Uniform search terms were developed and used with all databases (see table 1).

2.2 Eligibility criteria

The inclusion criteria for the studies in the present review were peer-reviewed studies in English, with human adults and with patients of any clinical subtype of MS. No date restriction was applied. Studies were not limited to any particular study design. No restrictions were placed on the type of control group. Studies were required to have interventions about either real DMD information or information about fictitious treatments which would eventually support understanding of DMD information. Interventions were defined as any additional strategy or decision-aid which provided treatment information beyond that given during routine healthcare. Studies with some evaluation of these interventions were retained.

Studies were excluded if they evaluated educational interventions for complementary medicines or medications for the management of MS symptoms. Studies assessing patients' understanding for disease diagnosis or prognosis were not eligible for inclusion. Studies without any form of educational intervention, with interventions based on other aspects of MS such as cognition or self-management, interventions aimed primarily at health professionals, an intervention protocol for an upcoming study with no existing data, or interventions not exclusive to patients with MS, were also excluded from the review.

All titles and abstracts were screened. Studies that were considered relevant from additional reference checking were also included. At this stage, 96 studies were considered for eligibility and full texts were subsequently accessed (see figure 1).

2.3. Data extraction

Data extraction forms were created to extract relevant information from the full texts, and assess their eligibility into the final review. Extraction was initially carried out by one reviewer (GR) and was verified by another (DL). Any discrepancies were resolved by discussion. Following data extraction, 81 studies were excluded from the final review in line with the exclusion criteria (see figure 1).

Baseline characteristics of participants were extracted from the 15 shortlisted studies, comprising (where reported) age, type of MS, disease duration, time since diagnosis and current DMD. Study design and methodology was recorded. Information about the interventions was further extracted, including the content, length, presentation methods and any additional details of how the interventions were conducted.

The impact of the interventions on either understanding of treatment information overall or understanding of treatment risks and benefits specifically was also extracted in the present review and incorporates data from self-report and objective measures. Patient's feedback on the interventions was also retained. Relevant data for the present review was obtained from numerical information in texts, tables and graphs, and statistical analysis.

2.4. Quality assessment

Quality of publications was independently examined by two reviewers (GR and DL) using the Effective Public Health Practice Project (EPHPP) quality assessment tool for quantitative studies [38]. This particular tool was chosen because it can evaluate all types of quantitative studies in the health care setting [39], has high inter-rater reliability [39] and is often considered ideal for systematic reviews [40]. As per the tool, the final quality rating was derived from the rating of six measures: selection bias, study design, confounders, blinding, data collection methods, and withdrawals or drop-outs (see table 2).

Quality was further assessed for educational interventions within the studies, based on their reporting of criteria for evidence-based patient information. Eight different criteria were chosen and adapted from Bunge and colleagues [18], depending on the extent of evidence and relevance to both simple and complex educational interventions (see table 3).

3. Results

3.1 Study design and participant demographics (table 4)

Fifteen studies were shortlisted in the review, and comprised interventions which were primarily designed to improve understanding of DMD risk and benefit information in MS patients. Four studies in this review evaluated interventions using a randomised controlled procedure [41–44]. A type of control group was present in seven studies [41,42,44–48] and baseline scores prior to the intervention were recorded by ten studies [42,43,47–53].

Five of the 15 studies were considered to be of a high quality [41–43,48,49], with three studies deemed weaker in quality [44,50,54] (see table 2). Four of the 15 studies had interventions that fulfilled or reported at least 4 of the 8 criteria for evidence-based patient information. The most commonly reported criteria in the interventions were the use of comprehension enhancing tools, involvement of patients in the development process and inclusion of numerical data (see table 3).

A total of 2552 MS patients were included across 15 studies and had a range of MS disease subtypes, comprising: 79(3.1%) CIS patients, 1064 (41.7%) RRMS patients, 214 (8.4%) PPMS patients and 391 (15.3%) SPMS patients. The remaining MS patients had unclear or unreported MS disease subtype (31.5%). The mean age of patients was 43.1 years (range: 37– 50). One study did not allow for calculation of mean age [49] and two studies only presented median or mode values for age [46,52]. Two studies also included 105 non-MS patients, with a mean age of 43.5 years [45,54].

Nine studies reported patients' disease duration from initial MS symptoms [42–44,46,47,50,53–55], with an average of 9.2 years. Five studies reported time since MS diagnosis [41,42,48,51,52], with an average of 5.8 years.

Only one included study reported patients' objective cognitive status [45]. Patients were assessed on the California Verbal Learning Test-II (CVLT-II), Wisconsin Card Sorting Test-64 (WCST) and the Digit Span subtest from Wechsler Adult Intelligence Scale. MS patients were considered to be cognitively impaired if they scored below the 5th percentile of at least one cognitive measure [45].

A total of 1384 (54.2%) MS patients had taken disease-modifying drugs during the course of their disease and 188 (7.4%) MS patients had not taken a DMD. The remaining studies did not specify DMD status (980 MS patients, (38.4%)). Of studies reporting MS patients' current DMD, 273 patients were on the first-line treatment interferon-beta [42,49,51], and the remaining patients were taking second-line treatments, with 53 patients on Mitoxantrone [50], 173 patients on Natalizumab [46,55] and 98 patients on Fingolimod [52]. In majority of these studies, DMD status was known by treating physicians or researchers involved with the study [46,47,49–52,55] .

3.2 Intervention characteristics (table 5)

Intervention type. The majority of interventions contained a booklet or leaflet for MS patients [41–44,46,48,50,51,53,55]. These leaflets ranged from providing comprehensive information (120 pages, [41,48]; 57 pages [42]) to short summaries [46,50,53]. The booklet length was unclear in four studies [41,44,51,55]. Four interventions which included booklets also contained an additional intervention component [41,42,48,51]. A short vignette of information was read aloud in one intervention but was not handed to patients in the form of a booklet or leaflet [45].

Multicomponent educational programmes were utilised as an intervention in five studies. Four of these programmes were conducted by health professionals [48,49,51,52] and one education programme was conducted by a non-medical person [42].

Intervention content. All, bar two interventions [49,53], provided some form of treatment risk information to patients with MS. Interventions also included information about: treatment benefits [36,41,43,45,47–49,53,54], alternative DMDs available to patients [42,45,47,48], efficacy studies for DMDs [42,48,52–54], DMD decision-making [41,42,48,54], administration of DMDs [51,52,54] and tailored information about DMDs for patients' disease subtype [41,55].

Intervention presentation methods. Many different methods to present information were employed in the interventions. Methods which provided numerical information was manipulated by some studies, for instance by presenting or giving explanations for absolute risk numbers [41,43,50,53], relative risk numbers [43] and confidence intervals [44]. Four studies used graphical formats in the form of either pictograms [41,43,53] or bar graphs to convey

treatment information [54]. One study focused on whether the information was framed in a positive or negative manner [41].

Some interventions also provided treatment information using interactive methods, defined as involving patient in the intervention process, which includes: questions and answers [42,47,48,51], discussions in person [42,47,48,51], role-playing [48], recognition cues [45], information presented in short successions [45] and interactive exercises presented at the end of interventions [41,42,47,52]. Media and technology was used to present treatment information in two studies [36,48,49,54].

Together, these strategies were designed to optimise understanding of the risks and benefits of DMDs.

2.3 Intervention outcomes (table 6)

Understanding of overall treatment information. Four studies looked at understanding of overall treatment information with no particular focus on the risks or benefits of treatments. All employed an objective comprehension questionnaire to assess understanding, but maximum scores ranged from 6 to 18.

Despite no significant difference in the understanding of treatment information between a non-clinical control group and MS patients without cognitive impairment, both groups were significantly better than cognitively impaired MS patients [45]. The control and MS cognitively unimpaired group showed greater understanding following information provided in short successions or when recognition cues were provided to aid recall of information, compared to when treatment information was provided in an uninterrupted block [45]. A similar trend was observed in the cognitively impaired MS group. However, this group also showed a significant improvement in understanding when recognition cues were given alongside treatment information provided in short successive steps, in comparison to information provided in successive steps alone [45]. In two other studies, a significant increase in understanding of overall treatment information was also evident following intervention when compared to both baseline understanding [52] and a control group receiving standard information [44]. However, there was no significant improvement on patients' understanding post-intervention when the control group received identical content as the intervention in a non-interactive form [47].

To note, studies differed in the content of the intervention, as only two of the four studies provided information about real DMDs [47,52]. Further, only some items in the questionnaires used to assess patients' understanding focused specifically on treatment-related information.

In summary, although there is a trend towards an improvement in understanding of overall treatment information following intervention, this cannot be established with studies employing different interventions and comparison groups.

Treatment risk understanding. The understanding of treatment risks in MS patients following intervention was assessed by five studies, using real DMD information in four studies [42,48,50,54] and a hypothetical treatment information in another [43].

Following a short leaflet about risks of taking Mitoxantrone, MS patients showed a significant increase in accurate risk understanding of Leukaemia, an adverse risk associated with the medication [50]. This risk was initially underestimated by 58% of MS patients [50]. Underestimation of risk persisted in 18% of MS patients following intervention. Improved risk understanding was not dependent on demographic factors, disease duration or the available scientific evidence at treatment initiation. However, patients with large errors on the Medical Data Interpretation Test (MDIT), which assessed the ability to handle probability data, showed an underestimation of Leukaemia risk after reading the leaflet [50]. Following an intervention with a 4-hour education programme combined with a 57-page leaflet, understanding of the first-line DMD risks significantly improved for patients in the intervention group compared to MS patients in the control group [42]. The authors further combined the scores of risk understanding with patient's attitude towards their current DMD, which they termed as the score of being informed. According to this measure, patients in the intervention group were significantly better informed than the control group [42]. Similar results were seen with another multi-component intervention, consisting of a 2-hour and 4-hour education programme, in addition to a 120-page information brochure [48]. In comparison to the control group receiving standard information brochure and a rehabilitation programme, the intervention group showed a significant increase in DMD risk understanding at 2 weeks and 6 months post-intervention [48].

One study measured risk understanding using self-report questions after trialling a DMD informational website for interferons [54]. Over 80% of MS patients stated that they found the presented risk information really or extremely clear and easy to understand [54].

Using hypothetical treatment information, Kasper and colleagues [43] showed that the ability to recall treatment risks from pictograms to frequencies was generally low. However the authors noted that risks were recalled more accurately than benefits [43]. Mean errors in recalling risks from pictograms which displayed figures consecutively were significantly lower as opposed to pictographs with random arrangement of figures [43]. Patients that attributed high personal risk of becoming wheelchair dependent within two years showed a small correlation with overestimation of risk following intervention [43].

Overall, understanding of treatment risks showed an improvement of reasonable accuracy post-intervention despite the variety of interventions employed across the reviewed studies, and studies using a mixture of self-report and objective measures.

Treatment benefit understanding. Understanding of treatment benefits was assessed objectively by four studies post-intervention [43,46,49,53] and with self-report measures by one study [54].

Following a 3-page information booklet, MS patients showed significant improvements in understanding of interferon benefits post-intervention when compared to baseline [53]. The authors did note that around 99 of 169 patients were still not able to understand the information after intervention [53]. Following another educational intervention, there was a significant reduction in patients that were overly optimistic about the general benefits of their DMD, even though overestimation persisted in about 33% of individuals [49]. At baseline, approximately 34% of MS patients were unrealistically optimistic about the benefits of their medication on disease progression specifically. Yet post-intervention, the number of MS patients overestimating these specific benefits about their DMD increased to about 40% [49]. Likewise, in another study, MS patients believed that their medication will provide a greater reduction of risk for a maximum walking distance of 100m following the short leaflet-based intervention on Natalizumab, in comparison to

physicians [46]. Even with hypothetical treatment information, MS patients overestimated the benefits of a fictitious treatment by more than 100% following intervention [43].

Using self-report measures, over 75% reported that the interferon benefits presented in a DMD informational website were really or extremely clear and that graphical presentations of treatment benefits were easy to understand [54].

In summary, initial overestimation of treatment benefits seemingly persists despite interventions that provide treatment benefit information beyond routine healthcare, although many patients report their own understanding of treatment benefits following intervention as high.

Personal risk perception. Beyond understanding of treatment risk, two studies also assessed personal perception for treatment risks following interventions that provided information about real DMDs [46,50]

Following a short leaflet about Natalizumab, 84% of MS patients were willing to accept a 1 in 100 or higher risk of PML, an adverse side-effect of the medication, compared to only 51% of physicians; showing a significant difference [46]. The authors noted that PML risk acceptance was not correlated with understanding of DMD information [46]. Patient's personal risk attribution of PML as an adverse risk of Natalizumab was deemed significantly lower than the PML risk they attributed to Natalizumab generally post-intervention [46]. However, since baseline measures were not recorded in the study, it is difficult to determine whether personal risk attribution changed as a result of the intervention or was previously low at baseline. In another study which did record baseline measures, MS patients showed a significant increase from baseline for both general and personal risk attribution of the adverse risks associated with Mitoxantrone after reading the informational booklet [50]. Yet similar to the previous study, personal risk attribution of the adverse risks of the DMD was significantly lower than general attributed risk of adverse risks by the MS patients [50].

In summary, two studies show that patients attribute lower personal risks of taking their current DMD than general risks they attribute to the DMD, despite improved understanding of their DMD risks post-intervention.

Treatment decisions. Five studies recorded MS patients' decision or their attitude for decisions for their current DMD following intervention [41,42,46,54,55].

Using self-report likert-scales, MS patients in the intervention group were found to be significantly more critical about their current DMD compared to baseline and control group, even after four weeks following intervention [41]. Likewise, patients were critical towards current DMD after intervention in another study although this attitude did not persist beyond two weeks [42]. In another study, patients reported feeling confident in their decision to choose interferons after receiving information about interferons beyond routine healthcare [54]**.**

MS patients in the intervention group did not show significant differences to the control group in progress of DMD decisions during follow-up in two studies [41,42]. When compared with physicians' decisions however, a considerably higher number of patients opted to continue the Natalizumab DMD post-intervention [46]. Although for the same medication following another intervention, 60% of MS patients discontinued treatment if they had the highest risk of PML, compared to 24% patients with the second-highest PML risk [55]. No patient discontinued the treatment post-intervention in the lower risk groups [55].

In summary, the studies in the present review show a trend towards a critical attitude towards their DMD post-intervention with some discontinuation due to these attitudes, although the impact on patients' decisions was generally inconclusive in the long-term.

Intervention feedback. MS patients in **six** studies provided feedback on the interventions using self-report measures. Relative to the control group, MS patients in the intervention group felt better informed and felt that important questions had been adequately answered even after six months following intervention [41]. Similarly, MS patients deemed the intervention they received as important and felt that this did not increase worries [50]. In fact, 84% of MS patients stated that they would recommend the intervention to other patients [50]. Majority of patients reported the intervention as useful, and were particularly satisfied with specific training they received during the intervention [51]. Likewise, there was a significant increase in patients perception of being informed, in addition to the feeling of certainty and confidence of being able to handle all treatments following a DMD information intervention [52]. Over 80% of MS patients trialling an informational website reported that the website was easy to navigate, easy to understand and was

useful [54]. Following informational materials explaining confidence intervals, patients in the intervention group consistently rated the information as being understandable, relevant and beneficial [44].

Despite the diversity of the DMD interventions employed in these six studies, self-report measures indicate that patients generally perceive any type of interventions as favourable in facilitating understanding of DMD information.

4. Discussion and Conclusion

4.1. Discussion

The present systematic review evaluated 15 interventions designed to improve MS patients' ability to understand complex risk-benefit profiles of DMDs. Studies in the review included MS patients with different clinical subtypes and those taking a variety of DMDs. Studies employed a range of outcome measures and not all studies included baseline data or control group. Some studies had methodologies that precluded firm conclusions.

Interventions within the present review provided treatment information using booklets, websites, vignettes and education programmes. Half of the interventions included some form of interactive component [41,42,45,47,48,51,52]. Yet, there was no apparent advantage of interactive versus passive interventions on understanding. There was also no apparent benefit of longer and multicomponent interventions in comparison to shorter and basic interventions such as leaflets in the current review. From this, it can be presumed that interventions which are easier to administer and require fewer resources may be just as beneficial to employ as longer interventions. Moreover, less than half of the interventions manipulated or explained the formats used to present treatment information, such as framing, numerical formats or graphical formats [41,43,44,50,53,54]. This is surprising considering that presentation formats are a key criteria for an effective evidence-based educational intervention [18] and can significantly impact understanding of treatment information [25,26,28,34,35]. Therefore, the use of presentation formats should be carefully considered when designing an educational intervention.

In general, it was difficult to make comparisons between these interventions since they were very diverse in their content and administration. In particular, it was not possible to draw conclusions about the most effective intervention

which could improve understanding of DMD information in MS patients. However studies that recorded patient's feedback of the interventions all received favourable reviews [41,44,50–52,54], which indicates that any form of intervention providing DMD information beyond routine health-care are generally well-accepted by MS patients.

In terms of the impact of interventions, four interventions improved understanding of overall information provided during intervention, despite using very different interventions and study designs [44,45,47,52]. For treatment risk knowledge specifically, MS patients initially showed an underestimation of treatment risks during routine healthcare, but showed greater understanding of both real and hypothetical treatment risks post-intervention. This improvement in risk understanding seemed related to multicomponent interventions [42,48], information which was easier to understand [43,50,54] and when personal risk attribution was perceived as low [43]. However, it was not possible to determine the extent to which these interventions were able to improve understanding of both adverse risks and side-effects that are less severe but commonly associated with DMDs. Nevertheless, interventions designed to improve understanding of treatment risks could be very beneficial for patients making treatment decisions, since even very small changes in the risks of DMDs can have a huge impact on treatment choice [56,57]. In fact, some studies in the present review showed a trend towards patients becoming critical or discontinuing treatment when risks were better understood [41,43,46,55]. This suggests that patients are likely to review decisions for their current DMD following new and enhanced understanding of treatment risks. Considering this, it is important that patients perceive information accurately about DMD risks when making initial treatment decisions, so that the true risks associated with their chosen treatment are in line with patients' preferences. Although, some studies in the review showed that despite greater understanding of treatments risks, MS patients seemed to underestimate their personal chance of developing these risks [46,50]. Interventions in the future could therefore attempt to converge personal risk attribution with accurate understanding of treatment risks, to ensure patients are able to apply the knowledge they gain from the intervention and make informed treatment decisions based on personal preferences.

Improvements in understanding the benefits of treatments were less pronounced. Objectively, many patients did not understand or tended to overestimate the benefits of taking their treatment, even after receiving additional information

[43,46,49,53]. This can be problematic for selecting a course of treatment, as patients are more likely to prematurely discontinue treatment if DMD benefits are perceived as higher than actual benefits [49,58]. Such poor adherence to DMDs can have both direct and indirect costs for MS patients [59]. However, patients did not significantly change their treatment decisions following intervention, similar to the review by Kőpke and colleagues [36], it is difficult to determine the effects of accurate understanding of treatment information on treatment adherence and shared treatment decision-making. This affirms that understanding of treatment information is simply a precursor to effective shared decision-making and other key factors such as patient autonomy, patient preferences or decision regret, would also need to be addressed in interventions to directly improve shared treatment decision-making [15,60–62]. Such interventions or decision aids were present in only three of the 15 included studies in the current review [41,42,48]**.**

Additional factors which can likely influence patient's understanding of DMD information were not fully explored by interventions in the present review. Patients' numeracy and literacy skills have the ability to modify understanding of the risks and benefits of treatments, with lower skills often leading to larger number of errors [63–65]. This was only explored in one study within the present review, where patients unable to interpret numerical data demonstrated the least accuracy in understanding the treatment risk information even after intervention [50]. Aspects of cognitive functions affected by MS itself are also likely to influence patient understanding, including: verbal and visual-spatial memory [8,66], information-processing speed [5] and decision-making [67,68] . Yet only one interventional study monitored cognitive impairments of MS patients in the current review [45]. This study showed that fictitious treatment understanding in MS patients with cognitive impairments was considerably lower compared to MS patients who do not present these symptoms. However, following additional cueing during intervention, the same level of understanding and recall was shown in cognitively impaired MS patients compared with cognitively intact MS patients [45]. Hence, future interventions providing treatment information to MS patients may benefit from ensuring that patients of all abilities, and those presenting cognitive impairments due to MS, are able to benefit from the additional information given beyond routine healthcare.

A limitation of the present systematic review was the difficulty in drawing robust conclusions or conducting a meta-analysis for the efficacy of interventions as a result of the different outcome measures employed. A narrative synthesis was considered to be the most appropriate format for reviewing the studies. It is important to acknowledge that such a qualitative review is subject to greater analysis bias than a quantitative systematic review.

4.2. Conclusion

The present review was an inclusive attempt to compare different types of interventions which provide treatment information beyond routine healthcare, while evaluating their efficacy on understanding of treatment risks and benefits. Despite the heterogeneous findings, it is conceivable to conclude that interventions providing treatment information beyond routine healthcare are preferred by MS patients and have the potential to improve understanding of overall treatment information, particularly treatment risks. Understanding of treatment benefits do not seem to be reliably improved by the reviewed interventions. There was no conclusive effect of interventions on MS patients' decisions for DMDs. No particular intervention type emerged as reliably efficacious. Interventions that were longer and comprehensive performed similar to shorter interventions requiring fewer resources. There is a need for a standardised information-based tool which can draw on the strengths of currently available interventions and which can improve understanding of both the risks and benefits of treatments.

4.3. Practice implications

The implication from this review is that MS patients appreciate interventions which provide information about the risks and benefits of DMDs beyond routine healthcare. Future interventions need to ensure that effective presentation methods are employed to optimise understanding of DMD information during decision-making, and that MS patients of all abilities and those presenting cognitive impairments can also benefit from the additional support.

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Conflict of Interest

GR has no disclosures.

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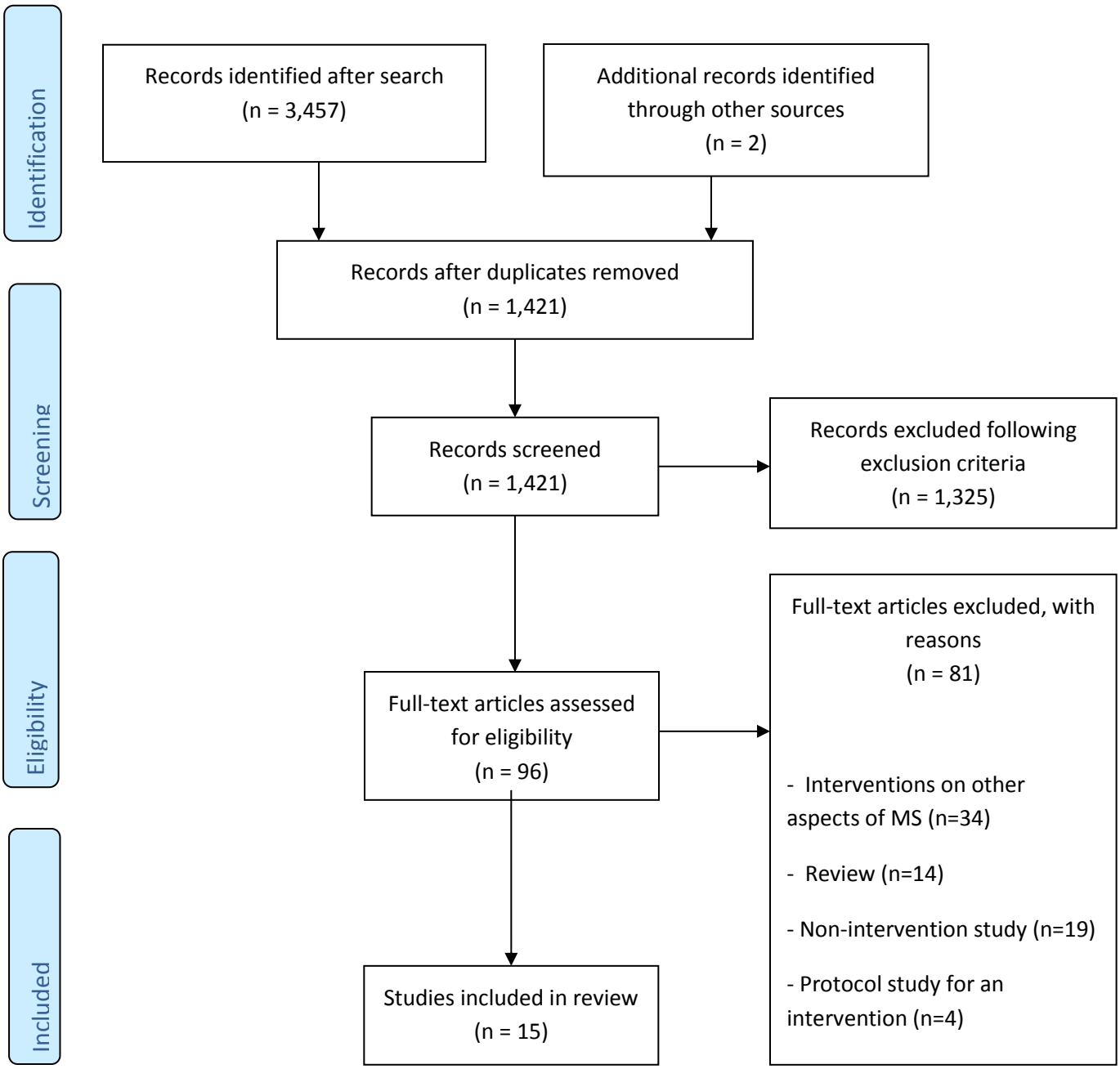

Figure 1. PRISMA flow chart for selection process of studies in systematic review

Table 1. Search terms for systematic review.

Search terms
(Multiple AND Sclerosis) AND (patients OR people OR persons OR patient) AND (risk OR benefit OR side effect OR treatment OR medication OR therapy OR medicine OR medical OR therapies OR therapeutics OR pharmaceutical preparations) AND (format OR framing OR educating OR design OR informing OR health literacy OR strategy OR program OR intervention OR communicating OR information OR education OR learning) AND (perception OR understanding OR comprehension OR awareness OR knowledge OR decision-making)

Table 2. Quality assessment of studies evaluating interventions to improve patient understanding of DMD information in MS

Study (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***
Kasper 2006	Moderate	Moderate	Strong	Moderate	Strong	Weak	***Moderate***
Kasper 2008	Strong	Strong	Strong	Strong	Moderate	Strong	***Strong***
Basso 2010	Weak	Strong	Strong	Moderate	Strong	Moderate	***Moderate***
Heesen 2010	Moderate	Moderate	Moderate	Weak	Moderate	-	***Moderate***
Kasper 2011	Strong	Strong	Strong	Moderate	Moderate	Strong	***Strong***
Hofmann 2012	Weak	Moderate	-	Moderate	Weak	Weak	***Weak***
Tur 2012	Moderate	Weak	Strong	Moderate	Strong	Moderate	***Moderate***
Feicke 2014	Moderate	Strong	Strong	Weak	Strong	Strong	***Moderate***
Köpke 2014	Strong	Strong	Strong	Strong	Strong	Strong	***Strong***
Friedel 2015	Moderate	Moderate	-	Moderate	Moderate	Weak	***Moderate***
Zimmer 2015	Moderate	Moderate	-	Moderate	Moderate	Strong	***Moderate***
Colombo 2016	Weak	Weak	-	Weak	Moderate	-	***Weak***
Kopke 2016	Moderate	Strong	Strong	Moderate	Strong	Strong	***Strong***
Rahn 2016	Weak	Strong	Strong	Moderate	Strong	Weak	***Weak***

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

Table 3. Quality assessment of content and administration of evidence-based patient information: Criteria adapted from Bunge and colleagues (2010)

Study (first author, year)	**Numerical data (*e.g. frequencies*)**	**Graphs (e.g. *bar chart, pictograph)***	**Balanced framing**	**Pictures and drawings**	**Clear layout (*e.g. size of font*)**	**Plain language and readability**	**Comprehension enhancing tools (*e.g. mind maps)***	**Development process (*e.g. feedback from patients*)**
Mohr 1996	x	-	-	-	-	-	-	-
Kasper 2006	x	x	-	-	-	x	-	x
Kasper 2008	x	x	x	-	x	x	-	x
Basso 2010	-	-	-	-	-	x	x	-
Heesen 2010	-	-	-	-	-	-	-	-
Kasper 2011	-	x	-	x	-	-	-	-
Hofmann 2012	x	-	-	-	x	-	-	-
Tur 2012	-	-	-	-	-	-	-	x
Feicke 2014	-	-	-	-	-	-	x	x
Köpke 2014	-	-	-	-	-	-	x	x
Friedel 2015	-	-	-	-	-	-	x	-
Zimmer 2015	-	-	-	x	-	x	x	-
Colombo 2016	x	x	-	-	x	x	x	x
Kopke 2016	-	-	-	-	-	-	x	x
Rahn 2016	x	-	-	x	-	-	x	x

X = criteria reported; - = criteria unreported or not present

Table 4. Study design and participant demographics

Study (first author, year)	Quality ratings	Methodological design	Recruitment method	Sample size	Mean age in years	Type of MS (n)	Disease duration and time since diagnosis (years)	Current DMD status	Real/faux risk-benefit information
Mohr 1996	Moderate	Pre-post intervention study	Outpatient clinics	99	-	Not specified	-	Interferon beta-1b	Real
Kasper 2006		Pre-post intervention study	Outpatient clinics	169	44	RRMS (75); PPMS (75); Unclear (19)	Disease duration (7.7)	DMD (*103*); No DMD (*66*)	Real
Kasper 2008	Strong	Double-blind RCT	Newspapers; web-sites; National self-help journal	297	43	CIS *(45)*; RRMS *(153*); PPMS (*31);* SPMS (*59);* Unclear (9)	Time since diagnosis: IG (8.9) CG (8.3)	Not specified	Real
Basso 2010	Moderate	Questionnaire	Newspapers; Newsletter of MS society; MS support groups	36	MS patients without cog impairments (48); MS patients with cog impairment (45); CG (38)	RRMS (14); Unclear (22);	-	Not specified	Real - Unrelated to DMD
Heesen 2010	Moderate	Questionnaire	MS outpatient clinics	69	40[3]	Not specified	Disease duration (11)	Natalizumab	Real
Kasper 2011	Strong	RCT	MS outpatient clinic; Centre of Neurology; MS society	111	43	Not specified	Disease duration (7.5)	Not specified	Faux

Hofmann 2012	Weak	Retrospective cohort study	Patients allocated Mitoxantrone in last 9 years (*database of hospitals and private clinics*)	575	50	RRMS (*49*); PPMS (*76*); SPMS (*258*); Other (*4*); Unclear (*188*)	Disease duration (28.9)	Mitoxantrone (53); Terminated Mitoxantrone (522)	Real
Tur 2012	Moderate	Survey	MS clinics	104	JCV seropositive (38); JCV seronegative (37)	RRMS	Disease duration: JCV positive (13.72) JCV negative (11.73)	Natalizumab	Real
Feicke 2014		Quasi-experimental study design	MS clinics; private practise	64	IG (42); CG (37)	RRMS (*35*); PPMS (*2*); SPMS (*2*); Unclear (*25*)	Disease duration: IG (0.97) CG (1.64)	DMD (*45*); No DMD (19)	Real
Kopke 2014	Strong	Double-blind RCT	MS outpatient clinics	192	37	CIS (*27*); RRMS (133*)*; Unclear *(32*)	Disease duration: IG (4.3) CG = 4.0 Time since diagnosis: IG (1.4) CG (1.2)	Not specified	Real
Freidal 2015	Moderate	Prospective longitudinal study	MS clinics	174	40	RRMS (125); Unclear (49)	Time since diagnosis (4.84)	Interferon-beta 1b Previous DMD (82); No previous DMD (75)	Real
Zimmer 2015	Moderate	Pre-post intervention study	MS Centre	98	41[4]	Unclear	Time since diagnosis (4.6[4])	Fingolimod Previous DMD (67);	Real

							No previous DMD (31)	
Colombo 2016	Survey	Press release; Website adverts; Newsletters; E-mail invitations; Meeting presentations	344 MS patients (*276*) Family reporting about MS patients (*68*)	MS patients (*43*); Family reporting about MS patients (*45*)	MS patients: RRMS (*203*); PPMS (*12*); SPMS (*32*); Unclear (*29*) Family reporting about MS patients: RRMS (*26*); PPMS (*3*); SPMS (*13*); Unclear (*26*)	Disease duration: MS patients (9); Family reporting about MS patients (9)	DMD not specified	Real
Kopke 2016	Prospective controlled trial	Rehabilitation centres	156	IG (42); CG (43)	CIS (5) RRMS (*105*); PPMS (*13*); SPMS (*14*); Unclear (*19*)	Time since diagnosis: IG (7) CG (9)	DMD (88); No DMD (68)	Real
Rahn 2016	Pilot RCT	MS day hospital; MS self-help society; Other self-help initiatives	64	IG (47); CG (44)	CIS (2) RRMS (*42*); PPMS (*2*); SPMS (*13*); Unclear (*5*)	Disease duration: IG (9); CG (10)	DMD (29); No DMD (35)	Faux

Absolute numbers reported, unless specified. Abbreviations: CG, Control group; CIS, clinically isolated syndrome; Cog, Cognitive; DMD, Disease-modifying drug; IG, Intervention group; MS, Multiple Sclerosis; PPMS, primary progressive multiple sclerosis; RCT, Randomised controlled trial; RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis. [3]=Mode value; [4]=Median value

Table 5. Outcomes of DMD informational interventions

Study (first author, year)	Intervention type	Control group	Intervention content	Intervention presentation format	Baseline recorded	Self-report or objective measure	Outcome measure	Results
Mohr 1996	Education session (*conducted by a MS Nurse)*	None	Information about treatment benefits	Videotape	Yes	Objective	DMD benefit understanding: Survey items from BSQ (*follow up: immediate)*	Relapse rate: Expected <10% reduction ('overly pessimistic group'): Baseline = 4% patients; Post-intervention = 1% patients Expected 10-30% reduction ('accurate group'): Baseline = 39% patients; Post-intervention = 66% patients Expected >50% reduction ('overly optimistic group'): Baseline = 57% patients; Post-intervention=33% patients
								Disease progression: Expected no change: Baseline = 40% patients; post-intervention = 20% Expected slower progression: Baseline = 26% patients; post-intervention = 41% Expected some restoration of function: Baseline = 29% patients; post-intervention = 37%

								Expected return to normal function: Baseline = 4% patients; post-intervention = 2%
Kasper 2006	3-page information booklet	None	Interferon DMD benefits; Clinical trial information about interferons	Control event rate; Experimental event rate; Absolute risk reduction; Pictograms	Yes	Objective	DMD benefit understanding: Three items (*follow up: immediate)*	Control event rate: Pre-intervention = 10% Post-intervention = 43% Significant difference (p<.001) Experimental event rate: Pre-intervention = 33% Post-intervention = 43% Significant difference (p=.043) Absolute risk reduction: Pre-intervention = 21% Post-intervention = 41% Significant difference (p<.001)
Kasper 2008	120-page new Information booklet; Worksheet	80-page booklet of routinely available information	Basics of how risks are presented; Tailored approach to disease subtype; Risk-benefits of	Probabilities; Absolute numbers; Pictograms of risks and benefits;	Yes	Self-report	Evaluation of intervention: VAS (*follow up: >6 months)*	IG = rated value of information higher than CG (p<.001) IG = better informed than CG (p<.001) IG = felt more important questions were answered adequately than CG (p<.001)

			DMD; Decision-making	Positive and negative framing; Interactive exercise			DMD decisions: VAS (*follow up: baseline, >4 week, >6 month)*	Positive attitude of current DMD: Baseline: CG=62%; IG=65% Post-intervention: IG more critical towards DMD than CG (>4 week; p<0.008) Progress in decision: No sig difference between IG and CG
Basso 2010	Treatment disclosure vignette (5 paragraphs of 2-5 sentences each) – read aloud to people with MS	Treatment - disclosure vignette (5 paragraphs of 2-5 sentences each) – read aloud to healthy people	Information about treatment; Treatment benefits and its likelihood; Treatment risks and likelihood; Alternative treatments and their risks-benefits	1. Information read aloud uninterrupted; 2. Information read aloud in 'chunks' without recognition cues 3. Information read aloud in 'chunks' with recognition cues	No	Objective	General understanding of information: comprehension questions (max. 10 points) (*follow up: immediate)*	Uninterrupted (mean score): CG (n=12): 8.63 MS-unimpaired (n=24): 7.79 MS-cog impaired (n=12): 5.58 Information read aloud in 'chunks' (mean score): CG: 9.94 MS-unimpaired: 8.96 MS-cog impaired: 8.25 Information read aloud in 'chunks' with recognition cues (mean score): CG: 9.88 MS-unimpaired: 9.38 MS-cog impaired: 9.33 CG: Chunking and recognition cueing better than uninterrupted (p<.001)

								MS-unimpaired: Chunking and recognition cueing better than uninterrupted (p<.001) MS-cog-impaired: Recognition cueing better than chunking and uninterrupted; chunking better than uninterrupted (p<.001)
Heesen 2010	3-page leaflet	3-page leaflet given to physician's	Information about natalizumab-associated PML	Unclear	No	Self-report	DMD benefit understanding: average *(follow-up: immediate)*	Risk of maximum walking distance of 100m after Natalizumab: Patients = 40% to 10% Physicians = 10% to <10% 10-year risk of being wheelchair-bound after Natalizumab: Patients = 40% to 10% Physicians = 30% to 10% Progression free after 2 years of Natalizumab: Patients = 50% Physicians = 50%
						Self-report	DMD risk understanding: VAS *(follow-up: immediate)*	Patient's general PML risk attribution = 4.5 No significant difference with physician
						Self-report	DMD risk perception: 4 risk options and VAS *(follow-up: immediate)*	Stop Natalizumab at following risk levels of PML: 2:10,000: Patients = 17%; Physicians = 49% 1:100: Patients = 29%; Physicians = 48% >1:100: Patients = 29%; Physicians = 3%

								Patient's personal PML risk attribution = 2.7
						Self-report	DMD decisions: VAS (0-10) *(follow-up: immediate)*	Willingness to continue treatment (mean VAS score): Patients = 9.0 Physicians = 6.1
Kasper 2011	Booklet	None	Risk-benefit profiles of a faux DMD: 'Relevant scenario' (*related to medication)* Risk-benefit of non-medical problem: 'Neutral scenario' (*not related to medication)*	Pictograms showing risks-benefits without numerical or verbal explanation; Graphical explanation of absolute and relative risk reduction;	No	Objective	DMD risk understanding of 'relevant scenario' (related to medication) *(follow-up: immediate)*	Mean errors of frequencies of side-effects: 'Unsorted pictogram' group = 15.7% (s.d. 12.4) 'Sorted pictogram' group = 10.8% (s.d. 9.6) Total = 11.4%; Mean error = +15.0

				Graphical explanation of benefit vs. no-benefit of DMD			DMD benefit understanding of 'relevant scenario' (related to medication) *(follow-up: immediate)*	Mean errors of frequencies of benefits: 'Unsorted pictogram' group = 20.2% (s.d. 20.4) 'Sorted pictogram' group = 16.8% (s.d. 16.1) Total = 16.5%; Mean error = +17.7
							DMD decisions: *(follow up: immediate)*	No correlation between DMD choice and understanding of treatment information
						Self-report	Evaluation of intervention: Preference for pictograms *(follow up: immediate)*	Preference for 'unsorted pictograms' = 2%
Tur 2012	Booklet	None	Risk factors of PML; Risk of discontinuing Natalizumab; Tailored to individual PML risk	Unclear	No	Self-report	DMD decisions: discontinuation of Natalizumab treatment (*follow up: immediate)*	Patients with highest PML risk = 60% discontinued treatment Patients with second-highest PML risk = 24% discontinued treatment Patients JCV seronegative = 0% discontinued treatment Patients JCV seropositive for less than 2 years = 0% discontinued treatment

Hofmann 2012	5-min leaflet	None	Summary of LK and CT risks; General risk knowledge of Mitox	Absolute risk numbers; Probability data	Yes	Objective	DMS risk understanding: Risk choice from 4 options *(follow-up: immediate)*	Risk of Leukemia: Baseline estimation of risk: Accurate risk at 8:1000 = 40% Underestimation of risk at 8:10,000 = 58% Overestimation of risk = 1% Post-intervention estimate of risk: Accurate risk at 8:1000 = 79% Underestimation of risk at 8:10,000 = 18% Overestimation of risk = 4%
						Self-report	DMD risk perception: General risk perception and individual risk perception using VAS *(follow-up: immediate*	Post-intervention: Significant increase of risk perception for Leukemia and cardiotoxicity (p<.05) Baseline and post-intervention: General risk perception higher than individual risk perception (p<.001).
						Self-report	Evaluation of intervention: VAS rating (0-10) *(follow-up: immediate)*	Intervention considered important by most patients = 1.1 median VAS rating Intervention did not increase worries = 4.7 median VAS rating Recommend intervention to others = 85%

Feicke 2014	420min training program (*conducted by trained neurologist, psychologists or MS Nurse)*	Brochure with same content as training	Seven modules including: Risks and benefits of DMDs; DMD options; General info about DMDs	Discussions; Mind maps; rating scales; interactive exercises; Q&A	Yes	Objective	General understanding of information: 14 comprehension questions (*follow up: baseline, immediate, > 6 month)*	Mean score at baseline: CG = 10.70 IG =10.77 No significant difference Mean score post-intervention (immediate): CG = 11.61 IG =12.52 No significant difference Mean score post-intervention (>6 months): CG = 11.88 IG =11.77 No significant difference
Kopke 2014	57-page new educational booklet ; 4-hr education programme (*conducted by a non-medical person*)	5 page information leaflet; 4-hr education programme for stress management in MS	Recent evidence of early MS DMD; DMD efficacy studies; DMD options in early MS; Risks-benefits of DMDs in early MS; Decision-making exercise and discussion	PowerPoint presentation; Q&A; Group discussion; Guided discussion; Interactive exercises	Yes	Objective	DMD risk understanding: 19-item questionnaire *(follow-up: baseline; >2 weeks*)	Mean risk knowledge at baseline; IG = 10.6 CG = 9.4 Mean risk knowledge (>2weeks): IG = 12.3 CG = 10.2 Significant difference (p<.001)
						Self-report	DMD decision-making: PBMS *(follow-up: 2 weeks, 6 and 12 months)*	IG more critical of DMDs than CG; IG felt less social pressure towards DMD uptake DMD status (>6 months) IG (n=41): Newly initiated DMD = 16 Discontinued = 5 CG (n=51)

								Newly initiated DMD = 18 Discontinued = 12
Freidal 2015	Practical education; telephone consultations; home visits; (*conducted by MS Nurses*); written guide; DVD	None	Injection techniques; management of side-effects; storage and transportation; possible side-effects; importance of adherence	Q&A; private telephone and home consultations	Yes	Self-report	Evaluation of intervention: 6-point likert scale (1=very good to 6=insufficient) (*follow-up: >3 months*)	Mean patient ranking: Satisfaction with medication application (n=114) = 1.11 Satisfaction with injection training (n=111) = 1.23 Satisfaction with telephonic care (n=58) = 1.43 Intervention useful? Yes = 64 Little = 16 No = 3
Zimmer 2015	60-minute talk for treatment-experienced patients; 90-minute talk for newly diagnosed patients; text and picture cards; take-home manufacturers leaflet (*conducted by MS Nurse)*	None	Efficacy and mode of action; administration, pauses and non-adherence; storage; pharmacy, costs and insurance; side-effects and how to understand information leaflet; risks and prevention; monitoring over time	Interactive talk; text cards with pictures to accompany talk; 'memory cards' at end with key points	Yes	Objective	General understanding of information: questionnaire (*follow-up: immediate*)	Median score (maximum 18): Pre-test = 6 Post-test = 14

						Self-report	Evaluation of intervention: VAS (0 = not at all informed, to 10 = totally informed) (*follow-up: immediate*)	Perception of being informed: Pre-intervention: Score < 7 = 78; Score > 7 = 19 Post-intervention: Score < 7 = 0; Score > 7 = 97 Certainty of being able to handle all treatment: Pre-intervention: Score < 7 = 64; Score > 7 = 33 Post-intervention: Score < 7 = 1; Score > 7 = 96 Confidence in being able to handle all treatment aspects: Pre-intervention: Score < 7 = 19; Score > 7 = 78 Post-intervention: Score < 7 = 1; Score > 7 = 96
Colombo 2016	Website	None	Interferon DMD benefits; Interferon DMD risks; Strength of evidence; Areas of uncertainty; Long-term adverse effects; Glossary; Patient stories; Description of	Short and detailed info; Bar graphs; frequencies; verbal info in tables	No	Self-report	DMD benefit understanding (*follow-up: immediate*)	Interferon benefits clear? (n=304) No = 6% Somewhat = 19% Really/extremely = 75% Graphic presentation of interferon benefits easy to understand? (n=304) No = 3% Somewhat = 18% Really/extremely = 79%

			participant characteristics from clinical trials; Questions to ask neurologists; Practical information about interferons			Self-report	DMD risk understanding (*follow-up: immediate*)	Interferon risks clear? (n=304) No = 4% Somewhat = 12% Really/extremely = 84% Tables of interferon risks easy to understand? (n=304) No = 3% Somewhat = 12% Really/extremely = 85%
						Self-report	DMD decision-making (*follow-up: immediate*)	Confident about interferon decision? (n=286) No = 9% Somewhat = 29% Really/extremely = 62%
						Self-report	Evaluation of intervention: (includes non-clinical intervention (n=89)) (*follow-up: immediate*)	Website easy to navigate? (n=418) No = 2% Somewhat = 5% Really/extremely = 93% Information easy to understand? (n=433) No = 1% Somewhat = 12% Really/extremely = 87% Information useful? (n=433) No = 2% Somewhat = 14% Really/extremely = 84%
Kopke 2016	120-page information brochure; 2-	Printed information material;	Information about evidence of DMDs;	Powerpoint presentations;	Yes	Objective	DMD risk understanding (*follow up:*	Adequate risk knowledge: (> 8 correct answers):

	hour education programme; 4-hour education programme (*programme conducted by 2 trained MS nurses or psychologists*)	standard rehabilitation programme	Decision-making with consultants; Risks and benefits of new oral therapies	Discussions; Q&A; role-play		*baseline, >2 weeks, >6 months*)	Baseline: CG = 22.5% IG = 20.6% 2-weeks post intervention: CG = 31% IG = 54.1% Significant difference from baseline (p<.007) 6-months post intervention: CG = 31.2% IG = 48.2% Significant difference from 2 weeks (p=0.058) Mean risk knowledge (0-19): Baseline: CG = 6.51 IG = 6.06 Non-significant difference (p>.05) 2-weeks post intervention: CG = 7.31 IG = 8.85 Significant difference (p<.004) 6-months post intervention: CG = 7.12 IG = 8.05 Non-significant difference (p>.05) Improvement in risk knowledge (>2 weeks to >6 months): CG= 0.59 IG = 2.52 Significant difference (p<0.001) Improvement in risk knowledge (baseline to >6 months):

								CG= 0.46 IG = 2.12 Significant difference (p=0002)
Rahn 2016	Patient information materials	Standard information	Explanation of confidence intervals, used to explain DMD risks and benefits	An example story to explain confidence intervals (unrelated to MS)	No	Objective	General understanding of information: 6 questions (*follow up: immediate*)	Mean correct answers: CG = 3.8 IG = 4.8 Significant difference (p=0.002)
						Self-report	Evaluation of intervention: Likert scale (1 = not at all, to 10 = very) (*follow up: immediate*)	Understandable? CG = 4.5 IG = 6.5
								Relevant? CG = 6.6 IG = 7.6
								Improvement in subjective knowledge? CG = 4.8 IG = 6.6
								Beneficial intervention? CG = 6.0 IG = 7.8

Absolute numbers reported, unless specified. Abbreviations: CG, Control group; CIS, clinically isolated syndrome; Cog, Cognitive; CK; Cardiotoxicity; DMD, Disease-modifying drug; IG, Intervention group; LK, Leukemia; MDMIC, Multi-Dimensional Measure of Informed Choice; MS, Multiple Sclerosis; PBMS, Planned Behaviour in MS questionnaire; PML, progressive multifocal leukoencephalopathy; PPMS, primary progressive multiple sclerosis; Q&A, Questions and answers; RCT, Randomised controlled trial; RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis; VAS, visual analogue scale; UTD, Understanding Treatment Disclosure Scale.