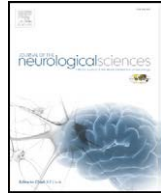




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## Decisions on multiple sclerosis immunotherapy: New treatment complexities urge patient engagement

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### ABSTRACT

For patients with multiple sclerosis (MS) involvement in treatment decisions becomes ever more imperative. Recently new therapeutic options have become available for the treatment of MS and more will be licensed in the near future. Although more efficacious and easier to administer, the new drugs pose increased risks of severe side effects. Also, new diagnostic criteria lead to more and earlier MS diagnoses. Facing increasingly complex decisions, patients need up-to-date evidence-based information and decision support systems in order to make informed decision together with physicians based on their autonomy preferences. This article summarizes recently terminated and ongoing trials on MS patient education and decision aids conducted by the authors' study groups. Programs on relapse management, immunotherapy, and for patients with suspected and early MS have been developed and evaluated in randomized controlled clinical trials. It could be shown that the programs successfully increase knowledge and allow patients to make informed decisions based on their preferences. For the near future, we aim to develop a modular program for all relevant decisions in MS to increase patients' self-management and empower patients to develop their individual approach with the disease. Faced by a disease with many uncertainties, this should enhance patients' sense of control. Still, it remains a challenge to adequately assess decision quality. Therefore, a study in six European and one Australian centers will start soon aiming to establish adequate tools to assess decision-making quality.

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### 1. Introduction

In 2009 it became clear that the incidence of progressive multifocal leucoencephalopathy (PML), a severe complication of natalizumab treatment, is 1:1000 in multiple sclerosis (MS) patients treated for 2 or more years [1]. Since natalizumab is highly effective in patients with active relapsing MS, decisions about its use are among the most difficult in neurology. Such decisions are paradigmatic for a shared decision-making (SDM) approach [2]. While every effort is made to monitor the risk of natalizumab treatment and to improve PML outcomes, it is ultimately the patient who takes the risk. The situation is further complicated by its fluidity. As data on patients treated for longer periods (i.e. over 3 years) become available, it is possible that the risk increases further and the drug is withdrawn from the market. Moreover the ultimate decision will depend not only on the

effectiveness of natalizumab and PML incidence but also on PML outcomes. Guidelines on natalizumab treatment emphasize the need for continuing availability of information and periodic renewal of consent [3].

In the near future, complexity of treatment decisions will further increase as new drugs become available. Fingolimod and cladribine [4,5] are two oral drugs in the licensing process. Both drugs are promising in terms of efficacy and ease of administration, but potentially more risky than interferons and glatiramer acetate.

Shared decision making (SDM) is an ethical requirement: Within such a partnership, both physicians and patients have responsibilities as recently reasserted by the UK General Medical Council [6]. Above this, effectiveness of SDM interventions has repeatedly been shown. A recent systematic review [7] showed that decision support techniques for people facing health treatments or screening decisions, consistently produced increased knowledge and satisfaction, and optimized health care utilization, but data on health status were inconsistent. However, based on the concept that health is more the ability of an individual to adapt than a defined state [8], we do believe that providing information increases options for adaptation and therefore also for health.

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On one hand information on MS is abundantly available while only few sources can be considered reliable or accurate. On the other hand patients keep claiming information needs and their desire for greater understanding is expressed not only by patients who want a leading role in medical decisions, but also by those who prefer a doctor-led approach [9]. Providing patient information is a complex health care intervention, with information structured and presented in variable formats; nevertheless such interventions can be assessed for content validity and replicability, and for effectiveness. In 2000 the UK Medical Research Council produced a guidance which was revised in 2008 providing clear indication on how to develop and evaluate complex interventions which can be applied to the development and testing of evidence-based patient information (EBPI) aids [10]. In parallel the CONSORT statement has recently been extended to randomized controlled trials (RCTs) of nonpharmacological interventions, giving advice on how to report results of such trials [11]. Complex intervention trials are challenging for several reasons, but in particular because of the limited number of suitable outcome measures. This is the case for questionnaires assessing MS knowledge and risk knowledge, where the two recently published instruments are notable exceptions [12,13]. Previous work showed that risk knowledge in German MS patients was poor and that EBPI increased risk literacy [13,14]. Another study found that early information about such a sensible issue as possible cognitive dysfunction was appreciated by MS patients [15].

This paper summarizes recently terminated and ongoing RCTs on MS patient information and education aids and gives an overview on an upcoming study.

## 2. EBSIMS – evidence-based self-management program in MS relapses (ISRCTN73885145)

Based on a number of pre-studies [13,14,16] an EBPI program on relapses and relapse therapy in MS was developed. The program consisted of two parts: a preparatory 30-page brochure and a 4-hour educational program with information provision, working with decision trees, and group discussions, allowing participants to reflect on their preferences, and also to hear and discuss other participants' experiences with relapse management. Additionally, participants were offered an oral corticosteroids prescription to be used in case of relapse as a treatment option to enhance self-management. The program was compared to a two-page standard information leaflet. Participants were 150 relapsing MS patients with high disease activity from three German centers [17]. Based on existing guidelines recommending i.v. corticosteroid therapy for relapses in spite of lack of solid evidence [16], it was hypothesized that the intervention would lead to altered treatment decisions as indicator for increased patient autonomy and SDM. Therefore, the primary outcome measure was the proportion of relapses with oral or no corticosteroid therapy. Other outcomes included risk knowledge, perceived decision autonomy, quality of life, and disability status. During two years of follow-up, in the intervention group 78% of relapses were treated with oral or no corticosteroids compared to 56% in the control group ( $p < 0.0001$ ). Patients' risk knowledge as well as perceived autonomy of treatment decision making was significantly higher in the intervention group ( $p < 0.0001$ ). Patients reported less visits ( $p = 0.03$ ) and less phone calls to physicians ( $p = 0.04$ ). Quality of life, disability status, and adverse events of corticosteroid therapies were comparable between groups. Interestingly, intervention group patients had less relapses during the two study years, while in the two years before the study, relapse rates were comparable between groups. In the intervention group, patients only had a mean relapse rate of 1.9 on study, while in the control group it was 2.7 showing a significant difference ( $p = 0.017$ ) (Fig. 1). It is unlikely that this finding is attributable to reporting bias since, besides patients' judgment about possible relapses, symptoms were ascertained by phone interviews with the

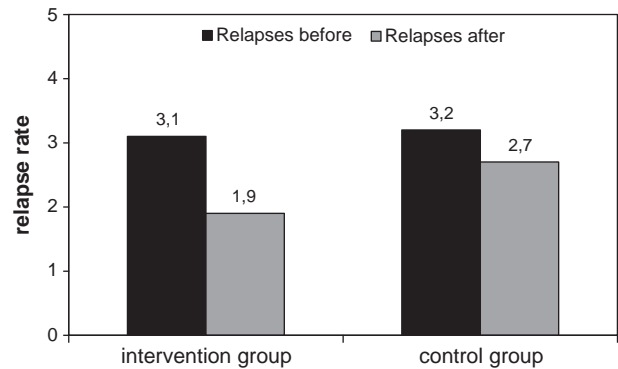


Fig. 1. Relapse-rate reduction through 2 years of follow-up in EBSIMS. Results show 0.8 less relapses in educated patients through 2 years of monitoring (t-test,  $p = .017$ ).

patients which were scheduled every three months. Furthermore, phone interview reports were assessed independently by two blinded neurologists to judge if reports indicated a definite, possible or no relapse. Although questioned for a long time, increasing evidence now shows that stressful life events may trigger MS relapses [18,19]. This finding of a reduced relapse rate in the intervention group suggests that the increased sense of control conferred by the intervention might have had a counterregulatory effect on stress levels. However further research is required to support this finding, including the investigation of possible immune and endocrine mechanisms.

## 3. IMPECT – implementation of an education program for corticosteroid therapy in MS in care

This study aimed to implement the EBSIMS program reported above into routine care. Here, 31 health care professionals from self-help groups and rehabilitation clinics took part in a one-day train-the-trainer program and subsequently 261 patients took part in the relapse management program. Results showed that the trainers understood the main goals and took advantage of the program. Patients showed higher risk knowledge and increased decision autonomy preferences. Patient preference on treatment decisions was autonomous or based on an informed choice in 49%, shared with the physician in 45%, and physician-led in 6% only. Effects were less marked compared to the EBSIMS trial, as expected for an implementation study, although the study confirmed the program's transferability into clinical practice: patients appreciated evidence-based information about relapse management and viewed EBPI and presentation of scientific uncertainty as a chance for decision autonomy.

## 4. ISDIMS – informed shared decision-making in MS immunotherapy (ISRCTN25267500)

This German multi-center RCT [20] investigated the effectiveness of a decision aid on MS immunotherapy in 305 MS patients. The decision aid was an exhaustively developed 120 page booklet, which was compared to a number of self-help organization leaflets. The primary endpoint was the fitting of patients' preferred roles (as assessed before the patient–physician decisional encounter) with the realized role reported after the encounter, and measured by the Control Preference Scale (CPS) [21]. We did not find the hypothesized increase in realized roles in the intervention group: It is noteworthy that the proportion of patients preferring an active role in treatment choices was very high at baseline as compared to previous surveys on autonomy preferences (Fig. 2). This might have been due to the recruitment method which, by employing advertisements in local newspapers and self-help organization publications, selected patients with more active information-seeking style. Two more factors may have contributed to the trial's findings: the intervention did not have

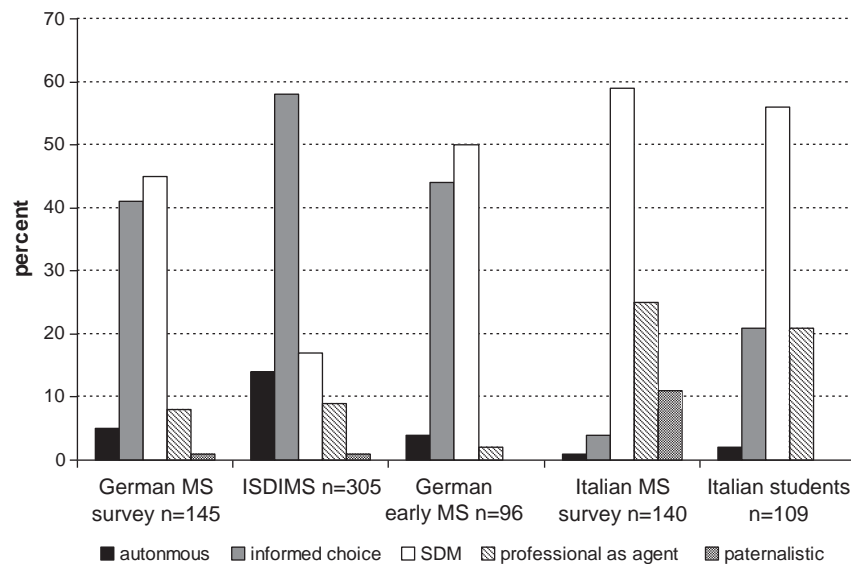


Fig. 2. Comparison of preferred role on the Control Preference Scale between samples.

an interactive component and physicians' attitudes to the decision-making process were not assessed. However we could show that patients in the intervention group did process the information more deeply.

A subsample of 77 encounters were videotaped and physicians' performance was rated with the Observing-Patient-Involvement (OPTION) instrument [22], while the degree of SDM from the patient perspective was rated with the SDM-Questionnaire [23] and with the above mentioned CPS in the post consultation version [21]. As expected, patients gave higher ratings of involvement compared to raters' observations. Interestingly, although referring to very similar items, low or even no correlations were shown between observed and perceived SDM. These results are in line with other studies showing discordance between ratings of communication assessed from different viewpoints [24] and indicate the need for a critical appraisal of existing measurement approaches of SDM. Thereby we do believe that a triangulated approach measuring the degree of SDM as judged by patients', physicians', and independent observers' perspective is needed.

### 5. SIMS trial – structured information interview in people with newly-diagnosed MS (ISRCTN81072971)

This Italian multi-center RCT assessed the effectiveness of an information aid on 120 newly-diagnosed MS patients [26]. The information aid, developed from a literature review and with direct participation of MS patients and health professionals [9], consisted of a 1-hour personal interview with a physician using a navigable CD, and a take-home booklet. Patients were randomly assigned to MS diagnosis disclosure (current practice at the center;  $n=60$ ) or current practice plus the information aid ( $n=60$ ). The primary composite endpoint were scores in the highest tertile of MS knowledge [12] and satisfaction with care [25] questionnaires, one and six months after diagnosis disclosure. Other endpoints were: safety, between-group differences in questionnaire scores, treatment adherence, extra contacts/consultations, switching of care center, changes in Hospital Anxiety and Depression Scale (HADS), and CPS scores. At one month, 30 (50%) intervention and 8 (13%) control patients achieved the primary endpoint (odds ratio [OR] 6.5; 95% confidence interval [CI] 2.6–16.0;  $p \leq 0.001$ ); figures at six months were 26 (43%) intervention and 11 (18%) control patients (OR 3.4, 95% CI 1.5–7.8;  $p = 0.04$ ). There were no serious adverse events and no anxiety increase related to intervention exposure [26].

An ongoing qualitative study has been designed to seize the value of the information aid and its components, considering the experiences of SIMS-trial participants. The qualitative study consists of a focus group meeting of the physicians who participated in the personal interview with the navigable CD, a focus group meeting of the patient caring neurologists, and in-depth individual interviews with patients who received the information aid (purposeful sampling).

### 6. Suspected MS – what to do?

With the new McDonald diagnostic criteria a MS diagnosis can be made earlier [27]. The usefulness of earlier MS diagnosis for the patient remains to be determined. An uncertain diagnosis can elicit patients' anxiety and complaints, increase the search for second opinions and extra consultations, and defer disease coping [28]. On the other hand establishing MS does not mean giving a clear estimate about prognosis and the general perception of the disease by the public is bad. Moreover, an earlier diagnosis implies the treatment of benign cases, that represent about 20–40% depending on the criteria used and on the study population [29–32]. Results of early treatment studies in the so called clinically isolated syndrome are not strongly convincing: A recent Cochrane review indicates that only 14 out of 100 patients profit from early immunotherapy as they will not have a second relapse within 2 years of study [33]. Any effect of early immunotherapy on disease course is still to be proven. In earlier studies we could show that German patients with established MS retrospectively appreciated to be early informed about a possible MS diagnosis [34]. In a recent pilot study a leaflet on MS diagnostic testing distributed to patients with MS suggestive symptoms and to recently diagnosed MS patients was highly appreciated and recommended for other patients [35].

### 7. PEPADIP – patient education program about diagnosis, prognosis and early MS treatment (ISRCTN12440282)

After diagnosis of possible or certain MS a period follows in which patients develop their own disease concepts and disease-coping strategies. In this period patients are particularly vulnerable and often develop anxiety and depression [36]. Sometimes this is related to difficulties in interpreting symptoms and diagnostic tests such as MRI. Therefore, especially in this period, patients need unbiased and understandable information. These include information about the accuracy of diagnostic tests and indicators of patients' individual

prognoses. Considering the now available early therapies, patients are also in need of information about expected results of immunotherapy. In the ongoing PEPADIP trial (Table 1) a 4-hour education program and 50 page information brochure is compared to a stress and coping group education session of similar length in patients with possible or certain MS within 2 years from diagnosis. The education program covers MS pathogenesis, diagnostic criteria (including a critical reflection on sensitivity and specificity, and predictive values of tests), and information about early treatment trials and their inherent uncertainties, leading to a model of action (Fig. 3). The primary endpoint is informed choice using an adapted version of the Multidimensional Measure of Informed Choice [37] based on the concept of planned behavior [38]. Within this measure risk knowledge, attitude towards a behavior (i.e. treatment) and uptake of the behavior are assessed and rated. Secondary endpoints are the Control Beliefs in Illness and Health Scale [39], autonomy preferences measured by the CPS [21], anxiety and depression measured by the HADS [40], and decisional conflict and satisfaction as assessed by the Decisional Conflict Scale [41].

**8. PEPIMS – patient education program about immunotherapy in MS (ISRCTN83438362)**

Based on findings of the ISDIMS trial, an extended program has been developed. The first part is a 2-hour group education program covering basic aspects of evidence-based medicine as e.g. criteria to assess the quality of clinical trials and basic information enabling patients to work with the information booklet that patients receive at the end of the first session. The second part, administered one week later, is a 4-hour interactive session in which information given in the first part is deepened and discussed. Here, patients intensely discuss reasons and preferences concerning decisions for or against immunotherapy. Also, in role-plays they work on strategies on how to best communicate with physicians in order to enable SDM. The program is now being tested in a controlled trial (Table 1). To avoid selection bias of already highly autonomous patients as seen in earlier studies, the trial is performed with consecutive patients from German rehabilitation clinics specialized in MS. To avoid contamination, a non-randomized control group design is used: First, consecutive patients are screened for inclusion in the control group. After the estimated number of control group patients has been achieved, subsequent

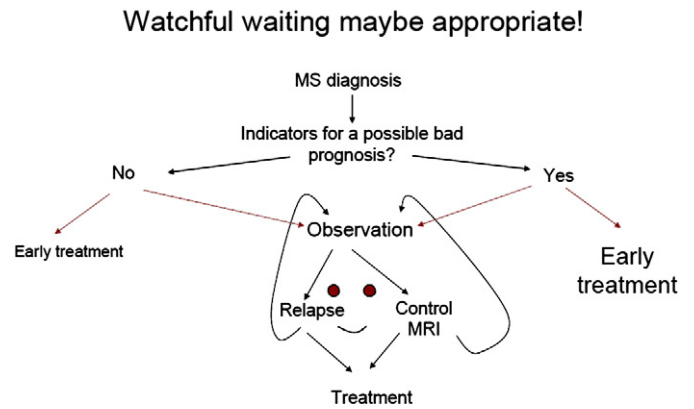


Fig. 3. Summary slide of the PEPADIP education program.

patients are screened for inclusion in the intervention group. Primary and secondary outcome measures are the same as in PEPADIP.

**9. AutoMS – autonomy preferences, risk knowledge and decision making in MS**

Given that earlier work indicated differences between German and Italian MS patients [42], a European initiative to establish common tools to assess decision-making quality in six European and one Australian centers has recently been funded (Gemeinnützige Hertie Stiftung). The AutoMS study ([www.automsproject.org](http://www.automsproject.org)) will revise and migrate the CPS [21], one of the best-established tools for measuring role preferences in decisions about treatment [43], into a self-administered electronic version. AutoMS will also develop a risk knowledge questionnaire for RRMS patients based on consensus. Starting from previous tools [12,13], a basic set of items will be discussed in focus groups with MS patients and health professionals. In another AutoMS subproject a recently developed questionnaire based on the theory of planned behavior [38] will be further developed to assess the factors impacting on patient attitudes to immunotherapy. Finally, AutoMS will refine an observer-based rating tool assessing the patient–physician interaction during the consultation [22] as a potential outcome measure in studies aiming at

**Table 1**  
Overview of controlled clinical trials.

	EBSIMS	ISDIMS	SIMS trial	PEPADIP	PEPIMS
Participants	Relapsing MS	Definite or probable MS	Newly-diagnosed MS	Early or suspected MS	Definite or probable MS
Topic	Educational program (relapse management)	Decision aid (immunotherapy)	Information aid (etiology, pathogenesis, diagnosis, prognosis, emotions, parenthood, treatments)	Decision aid (diagnosis, prognosis, early treatment)	Decision aid (immunotherapy)
Design	RCT	RCT	RCT	RCT	CT
Centers	3 German	Multi-center German	5 Italian	7 German	3 German
Intervention	Brochure + 4 h education group session	Brochure	Add-on personal interview with a physician using a navigable CD + take-home booklet	Brochure + 4 h education group session	Brochure + 2 h + 4 h education group sessions
Comparator	Two-page information leaflet	Self-help organization leaflets	Current practice	4 h stress and coping group session	Self-help organization information on immunotherapy
Primary endpoint	No relapse treatment or oral corticoid treatment	Preferred and realized roles [21]	MS knowledge [12] and satisfaction with care [26]	Informed choice [37]	Informed choice [37]
Follow-up	2 years	1 year	6 months	1 year	6 months
Patient no.	150	305	120	190	150
Status	Published	Published	Published	Recruitment completed	Recruiting

EBSIMS = Evidence-based self-management in MS relapses; ISDIMS = Informed shared decision-making in MS; PEPIMS = Patient education program about immunotherapy in MS; PEPADIP = Patient education about diagnosis, prognosis and early MS treatment; SIMS = Structured information interview in people with newly-diagnosed MS.

evaluating and enhancing SDM. All instruments produced will be harmonized between the participating countries. Questionnaires and other patient-reported tools will be linguistically validated in the target languages.

## 10. Conclusions

Patients are increasingly considered as partners in medical decision making and MS is a paradigmatic disease for a SDM approach. Different studies since 2002 have shown that MS patients appreciate communication of medical data, including the uncertainties necessarily attached to these data. An increase of satisfaction with health care through enhanced risk knowledge has consistently been shown in our studies and other clinical settings [7]. Presently, there is no gold standard for measuring patient involvement and clear data on the change of roles in medical encounters through SDM interventions are lacking. Data on altered health status or activity and participation according to the WHO definition are also far from clear. However, the above summarized EBSIMS trial very clearly showed changes in health behavior, i.e. a changed pattern of steroid treatment for relapses and fewer medical encounters.

As noted in the “2009 European Charcot Foundation Symposium”, we are approaching a new era of treatment in MS. After more than a decade of modestly effective but fairly safe drugs, we now have more effective but also more risky drugs. As the number of treatment options multiplies, patients’ involvement in treatment decisions becomes even more imperative. Well informed patients are also important for rapidly recognizing and communicating side effects, which must be picked up by equally sensitive physicians, and reported in international databases.

Although in the developed countries we now work in a setting of expert patients and doctors as service providers, there is still the image of physicians as shamanistic healers in at least a part of the population. Physicians need to take into account differing preferred roles of patients partly determined by their medical condition as well as by cultural and personal factors [42]. Therefore it has been argued that communicating “the truth” needs to be quite different in patients with very similar biomedical conditions [44]. In this perspective truth is more a bidirectional construct than an individual matching of probabilities. In the SDM approach a shared understanding of what is scientifically known is the starting point of this construct. While trust in a physician seems to be redundant in purely autonomous patients and might be blind in patients preferring paternalistic counseling, it is also a prerequisite in the SDM model [45]. These findings underline that the quality of a physician–patient relationship is a major factor enabling SDM.

The UK National Institute’s for Health and Clinical Excellence (NICE) grade A recommendation for an information pack specific for newly-diagnosed MS patients did not refer to evidence derived from the MS research area. It was mainly based on extrapolating evidence from stroke and cancer patients [28]. Hopefully, the next update will report evidence obtained from trials with MS patients.

We aim at developing a modular program for MS patients’ education to enhance self-management, to empower patients to share decisions with their health care providers and to develop their individual approach with the disease. Faced by a disease with many uncertainties, sense of control should be enhanced through this approach.

More specifically, we hypothesize the following: First, active patients are more effective in communicating their values to physicians and therefore are better supported and receive improved health care. Second, patients’ critical weighting of treatment effects and monitoring during treatment courses reduce the risk of ineffective or harmful therapies. Third, consultations are more goal-oriented and efficient as patients are better informed. Fourth, patients with a better understanding of clinical research methods are more willing to participate in high quality clinical trials.

## Conflict of interest

CH has received grants from Merck-Serono and Teva-Aventis as well as speaker honoraries from Biogen Idec. AS has received board membership fee from Novartis and speaker honoraria from Sanofi-Aventis. SK is supported by a rehab-fellowship grant from the National MS Society, USA. AG was supported by a FISIM (Fondazione Italiana Sclerosi Multipla) research fellowship. JK has no conflict of interest.

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