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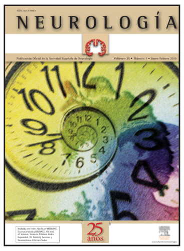

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ORIGINAL ARTICLE

# Proposals to improve adherence to immunomodulatory therapies in patients with multiple sclerosis

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**KEYWORDS**
Adherence;
Multiple sclerosis;
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**Abstract**

*Introduction:* The objective of this work was to assess the factors identified in the Global Adherence Project (GAP) in disease-modifying therapy (DMT) in patients with multiple sclerosis (MS) and to propose measures directed at improving adherence. It was proposed to prepare questionnaires to detect patients at risk of non-adherence before and during the follow-up.

*Methods:* Two meetings were held by Spanish researchers involved in the GAP project. Factors associated with non-adherence were grouped in therapy-, patient-, disease- and health care professional-related factors. Four working groups were created. Each group studied one individual, factor, taking into account the stages of diagnosis, management and administering treatment, follow-up and discontinuation or change of treatment. A draft of proposals and tools (questionnaires) was agreed.

*Results:* Patients should be provided with summaries of treatments, in a positive and simple way, and have time to discuss any doubts. Questionnaires should be given to patients at the start of treatment and during follow-up, so that individual characteristics can be assessed in order to monitor their adherence and act accordingly. Patients should be instructed in the management of the most common adverse reactions.

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*Conclusion:* Therapeutic education to improve adherence to treatments and identification of non-adherent patients is recommended. We propose 2 questionnaires, initial and follow up, to stratify patients depending on their adherence

**PALABRAS CLAVE**
Adherencia;
Esclerosis múltiple;
Inmunomoduladores

## Herramientas para mejorar la adherencia al tratamiento con inmunomoduladores en pacientes con esclerosis múltiple

### Resumen

*Introducción:* El objetivo de este trabajo fue evaluar los factores, identificados en el estudio global de adherencia (GAP), asociados con la adherencia a los fármacos inmunomoduladores (IMA) en pacientes con esclerosis múltiple (EM) para proponer medidas directas que mejoren la adherencia. Se propuso elaborar cuestionarios que permitiesen detectar, previamente y durante el seguimiento, a pacientes en riesgo de falta de adherencia.
*Métodos:* Se celebraron dos reuniones con investigadores participantes en el estudio GAP en España. Se agruparon factores relacionados con la no adherencia asociados al tratamiento, paciente, enfermedad y profesionales de la salud. Se formaron 4 grupos de trabajo. Cada grupo trabajó de forma individual sobre un factor teniendo en cuenta el diagnóstico de la EM, manejo y aplicación de la medicación, seguimiento y retirada o cambio de tratamiento. Se acordó un borrador de propuestas y herramientas (cuestionarios).
*Resultados:* Se debe proporcionar a los pacientes un resumen de las características de los tratamientos, de modo positivo y simple, así como tiempo para plantear dudas. La entrega de cuestionarios a los pacientes al inicio del tratamiento y durante el seguimiento para evaluar características individuales puede ayudar a conocer su grado de adherencia y actuar en consecuencia. Los pacientes deben ser educados en la identificación y el manejo de las reacciones adversas.
*Conclusiones:* Se recomienda la educación terapéutica para favorecer la adherencia a los tratamientos e identificar a los pacientes no adherentes. Proponemos 2 cuestionarios, de inicio y de seguimiento, para poder estratificar a los pacientes en función de su adherencia.

## Introduction

Poor adherence to treatment in chronic diseases is an increasing problem worldwide that affects not only individuals but also society as a whole.[1] Multiple sclerosis (MS) is a chronic disease requiring long-term treatment. The World Health Organization defines adherence to treatment as "the extent to which a person's behaviour -taking medication, following a diet, and/or executing lifestyle changes- corresponds with agreed recommendations from a healthcare provider. It involves the patient's active, voluntary, and collaborative participation".[1]

Poor adherence to treatment results in poor healthcare outcomes: medical and psychosocial complications and misuse of medical resources that leads to increased personal and healthcare costs. Consequently, from a sociological perspective, intervening in adherence to treatment may influence patient health positively without the need for a specific improvement in the medical treatment that the patient is currently undergoing.

Between 19% and 39% of MS patients abandon treatment during the first 3 years. Of these, between 10% and 20% do so during the first 6 months.[2,3] Discontinuation rates in clinical trials are between 8% and 15%.[4] This difference in adherence levels between clinical trials and general clinical practice[4,5] is due to the fact that patients are monitored more closely in clinical trials.

Treatments for MS are administered long term and require the regular intake of medication. Patients tend to be reluctant to start treatment for a number of reasons, including: fear of side effects, doubts about drug effectiveness, difficulties in understanding the information provided, the prospect of considering indefinite treatment, the perception that drug administration is difficult or painful (fear of needles), and socio-cultural factors[2,4] (interference with patient lifestyle). In the GAP study,[6] the most common reason for non-adherence was forgetfulness (50.2%), followed by injection-related factors (32.0%) that included the following aspects: being tired of injections, skin reactions, needle phobia, pain at the site of injection, unwillingness to inject oneself, and lack of help with injection. Other factors associated with non-adherence included longer duration of disease and treatment, poorer quality of life, and a greater number of neuropsychological problems.[6]

In order to improve adherence, the factors that affect it must be acted upon.[7]

This work addresses issues related to adherence to disease-modifying therapy (DMT) in patients with MS, in particular at the beginning, through an improved doctor-patient relationship. The work also proposes measures that can be applied easily in daily living, to assess and improve our patients' adherence to treatment.

The ideal method for measuring adhesion should be sensitive, specific, offering a quantitative and continuous measurement, reliable, reproducible, applicable in different situations, fast, and economical. The assessment of adherence may be conducted directly: electronic dosage sensors,[8] measuring drug concentrations in plasma, or quantifying any alterations due to its application. Adherence can also be assessed indirectly: records of dispensed medication, count of returned medications, and questionnaires. This methodology has been applied in other diseases such as diabetes, hypertension, rheumatic diseases, mental illness, etc. To date, only the antiretroviral treatment adherence questionnaire has been validated.[9,10]

The present study focuses on the preparation of questionnaires that would help to detect, before initiating treatment and during follow up, those patients at risk of non-adherence to DMT treatment.

## Method

In September 2005, the GAP study on adherence of patients with relapsing remitting MS (RRMS)[6] treated with DMT was launched in 22 countries (172 centres), including Spain. The study protocol was approved by the relevant Ethics Committees for Clinical Research and the corresponding local and national authorities were notified, following all current legal guidelines.

After analysing the results of the GAP study,[6] two meetings of researchers participating in the study on a local level were held in Spain in October 2006 and February 2007. Factors were grouped by association with non-adherence to treatment, patient, disease, and healthcare professional. A total of 4 working groups were formed, with each group studying 1 individual factor, taking into account MS diagnosis, treatment management and administration, follow-up, and treatment discontinuation or change. A draft of proposals and tools (questionnaires) was agreed upon.

## Results

### MS Diagnosis (first outbreak and high risk) and treatment decision making

#### Start of treatment

In patients with active MS, starting treatment with DMT as soon as possible after the definitive diagnosis of MS is recommended, as well as after the first outbreak suggestive of a demyelinating disease in patients at risk of developing MS.[11] The accumulated experience points to the need for early treatment. Patients should understand why it is advisable to start treatment.

#### Approach to patient treatment

- —Once the neurologist has informed the patient of the diagnosis and, insofar as possible, of the prognosis, the patient should be presented with treatment options.[12-15] This should be handled in a positive and simple fashion, providing all the available data on efficacy, safety and tolerability.
- —It is advisable to stress that the purpose of the medication is to modify the natural course of the disease. The medication is not symptomatic; consequently, changes in short-term functional status should not be expected.
- —It is advisable to provide the patient with oral or written information about the characteristics of each treatment[12-15] (indication, administration guidelines, adverse reactions, storage conditions).
- —Patients must be informed that the use of DMT is compatible with corticosteroid treatment for outbreaks and the various drugs being used to treat symptoms such as spasticity, tremor, or depression, as well as the majority of drugs used to treat concomitant diseases (antibiotics, anti-inflammatory drugs, etc.).

Patients should be given all the information and then allowed time to ask questions. Sometimes patients need time to think about which drug to choose. That is why it is useful to provide written information on the practical aspects of treatment and to arrange a second appointment so patients can attend with questions or with a decision about which treatment to start.

#### Other available sources

Educational programs and support groups through patient societies and pharmaceutical companies are very helpful for patient education and support.

#### Sharing information about treatment with family

The average age of onset of MS is between 20 and 40 years, the period in life in which a person is making plans regarding personal projects, careers, and so forth and putting them into action. When a person is diagnosed with a chronic disease like MS, it is not only the patient who suffers. The family will also witness and share events, worries, and doubts that arise during the process. Family support is very important and necessary because families are sometimes the only carers.

- —Patients must decide with whom and when they want to share the information. However they should be encouraged to attend consultation accompanied by a close family member who can help make decisions and/or receive instructions on drug administration, the use of auto-injectors, etc.
- —If the patient is a minor or has a disability that means he or she cannot self-inject, it is essential for a guardian who will take responsibility to be present.

—Spending some time providing support to caregivers is important and often neglected. Living with a chronically ill patient alters behaviours and involves a burden that requires attention.[16]

**What kind of emotional response can be expected when treatment is proposed?**

—The most common reactions shown by patients include the following: fear when informed of the need for injection treatment (they are unsure whether they will be able to inject themselves, local adverse effects, fear of needles, and apprehension); optimism about available treatment and current research in this field; and doubts about the effectiveness of the treatment and the impact of DMT on their quality of life.

—The feelings patients have towards DMT vary throughout the course of the disease. For there to be suitable communication between the patient and the medical team, it is very important to know which stage of treatment acceptance the patient is in.

It may be useful to provide patients with a questionnaire at the start of treatment to assess their individual characteristics. As a result of the work meetings, the proposed questionnaire shown in Annex 1 was prepared.

## Managing and administering medication

### How should patients be taught to manage medication?

—Providing the characteristics of the chosen drug.[12-15]

—The healthcare team should teach patients:

—How to avoid local reactions at the site of injection.[17-21]

—Injection techniques and how to manage the auto-injector.

—How to treat influenza-like syndrome.[17-21]

## Monitoring

### Efficacy and safety

—It is important to establish regular follow-up appointments with the patient to assess efficacy (clinical evaluation of outbreaks and disability and paraclinical evaluation through magnetic resonance) and safety (clinical and laboratory evaluations[22]) of the drug.

—Once the patient begins treatment, monitoring should be scheduled every month, or earlier if necessary. When patients are tolerating the treatment well, the frequency of regular visits can be reduced to every 3-6 months.

—It is important to suggest ways for the patients to incorporate the medication into their daily lives, and reinforce the idea that the aim of the treatment is to control their disease, not to become an additional burden. (For example, auto-injection helps to increase patient independence).

—Providing additional information if needed.

### Level of adherence

—It should not be assumed that adherence to treatment is correct; patients should be asked during follow-up visits about possible missed doses.

—Patients should be encouraged to express their doubts.

—Families should be involved if the patient agrees: patients and family/partners should be encouraged to follow the treatment correctly.

—Care should be taken to detect patients who are disheartened by the treatment, to offer them greater support.

—Patients should not be blamed for their level of adherence. It is important to find out the reasons behind poor adherence.

—In follow-up visits, it may be useful to provide patients with a questionnaire to assess their mood, management of adverse reactions, whether they have understood the explanations given, etc. The working group proposed the questionnaire presented in Annex 2.

—The importance of follow-up should be highlighted. Diaries or calendars can be used to help the doctor to check patient treatment compliance during consultation. It is also useful to use telephone alarms and/or for the healthcare team to make regular calls to remind the patient, especially during the first few months of treatment and after two years. Likewise, it is very important for the patient to have telephone access to the healthcare team in case any questions or doubts should arise.

—Consultations are necessary every 3-6 months to examine the injection sites, evaluate systemic side effects, and carry out laboratory tests.

—If low or no adherence is detected, the patient should be included in specific educational programs.

### Treatment discontinuation or change. Analysis of treatment failure

It is important to take into account the following aspects:

—Respect the right of patients to refuse treatment.

—Inform patients about the possibility of not responding to the first treatment prescribed and having to discontinue it, leaving the door open to other alternatives.

—Make it clear that changing treatment is an option (as a result of adverse events, laboratory abnormalities, lack of efficacy, etc.).

### Questionnaires to assess predisposing factors to treatment non-adherence: initial questionnaire (annex 1) and follow-up questionnaire (annex 2)

The initial questionnaire contains 10 sections that evaluate demographic, social, and emotional factors, as well as knowledge about the disease and proposed treatment, needle phobia, and knowledge about adverse reactions. It includes an additional section for women related to the pregnancy intentions.

The patient follow-up questionnaire consists of 10 sections that evaluate the method of treatment administration; whether the patient is adhering to treatment; the support of the healthcare team, family or friends; methods used by patients to remember to take their medication; emotional and cognitive aspects; and knowledge about the disease, treatment, and adverse reactions.

## Discussion

Adherence to chronic therapy is a dynamic process that must be controlled and is influenced by different factors acting simultaneously.[7] The consequences of non-adherence affect everyone: poorer adhesion means reduced treatment efficacy.[1] This in turn leads to faster deterioration and decreased recovery prospects, increased consumption of health resources with more frequent and longer hospitalizations, and greater suffering for patients and their close friends and family.

Medication is only a part of the complex web comprised by the treatment of all the problems resulting from a disease like MS. For many patients, not taking their medication every day helps them to feel less different and to forget to some extent about that negative aspect of their life, thus concentrating more on their everyday problems. Not taking their medication is consequently an unconscious desire to forget about the disease, whereas taking the medication is an unpleasant reminder.[23]

Patients with MS may be affected by cognitive impairment (43%-65%).[24] This alteration results in a characteristic and rather homogeneous neuropsychological profile. The most salient features of that profile are reduced speed of information processing and impaired attentional, memory, and executive functions. Visuospatial deficits[25] may sometimes be observed as well.

Nurses, psychologists, and rehabilitation specialists play a key role.[6] They encourage patients to keep going, to take up again things that they have left half-done or to begin projects that they had not previously managed to start. They also teach patients to deal with or avoid situations that can trigger new disease outbreaks.

Analysis of factors involved in treatment adherence is the starting point from which to develop a simple questionnaire that can be completed by patients in 10 minutes and that makes quick identification of patients requiring special attention possible.

The sequence followed by other working groups in adherence include systematic review of factors influencing adherence[6] such as those related to drugs (adverse effects, mode of presentation, and complexity of administration), individual factors (living with the disease), and social elements (type of work and schedules). It is also important to know which aspects healthcare workers consider necessary for maintaining an adequate degree of adhesion. Consequently, expert meetings (such as ours) should be arranged or questionnaires on the subject given to professionals.[26]

We propose the questionnaires presented in the annexes. These are useful for 2 reasons: first, to assess which patients may be at a greater risk of non-adherence at the start of treatment (Annex 1) and, second, to facilitate monitoring of adherence during follow-up (Annex 2). Consequently, appropriate measures can be taken to ensure a closer monitoring of patients who show an *a priori* increased risk of non-adherence. This would also facilitate monitoring of a therapeutic aspect often forgotten when the response to treatment is good, as is the case with adherence. We thought it appropriate to present this project due to the therapeutic repercussions of adhesion. We also wished to bring this to the attention of health professionals to facilitate monitoring.

## Conclusion

Therapeutic education is recommended in the management of all patients with MS to help them with adherence to treatment and to identify non-adherent patients. We propose 2 questionnaires, an initial one and a follow-up one, to stratify patients according to their level of adherence.

## Conflict of interest

The GAP study was financed by Biogen Idec Iberia.

## Annex 1. Initial questionnaire for the patient: questionnaire to identify non-adherence risk factors

| | INITIAL QUESTIONNAIRE | YES | NO | Comments |
|---|---|---|---|---|
| 1. | Educational / cultural level | No education | | ☐ |
| | | Primary education | | ☐ |
| | | Secondary Education | | ☐ |
| | | Vocational training | | ☐ |
| | | University studies | | ☐ |
| 2. | Are you employed / self-employed? | ☐ | ☐ | |
| | 1. Profession | | | |
| | 2. Do you have to travel frequently for work reasons? | ☐ | ☐ | |
| 3. | Do you live alone? | ☐ | ☐ | |
| | If you live with someone, indicate with whom: | | | |
| | 1. Family | ☐ | | |
| | 2. Partner | ☐ | | |
| | 3. Friend | ☐ | | |
| 4. | Do you have the support of your family / partner / friends? | ☐ | ☐ | |
| 5. | Have you understood the explanations given to you about? | | | |
| | 1. The disease | ☐ | ☐ | |
| | 2. The fact that fever and heat can aggravate your symptoms? | ☐ | ☐ | |
| | 3. Treatment: when you can start treating the disease, efficacy, administration method | ☐ | ☐ | |
| | 4. Adverse reactions and how to treat them | ☐ | ☐ | |
| | 5. The fact that some of your symptoms may worsen at the start of the treatment | ☐ | ☐ | |
| | 6. The importance of adhering to your treatment | ☐ | ☐ | |
| 6. | Who administers your medication? | You | | ☐ |
| | | Relative | | ☐ |
| | | Partner | | ☐ |
| | | Friend | | ☐ |
| | | Nurse | | ☐ |
| 7. | Are you afraid of needles? | ☐ | ☐ | |
| | Is your partner / helper afraid of needles? | ☐ | ☐ | |
| 8. | Have you suffered any memory loss? | ☐ | ☐ | |
| 9. | Do you feel depressed? | ☐ | ☐ | |
| 10. | Do you feel motivated to start treatment? | ☐ | ☐ | |

| | | | | |
|---|---|---|---|---|
| For women: | | | | |
| Do you intend to become pregnant? | | ☐ | ☐ | |
| | If so, are you aware of the need to suspend the treatment before becoming pregnant? | ☐ | ☐ | |

## Annex 2. Patient monitoring questionnaire: follow-up adherence evaluation questionnaire

| FOLLOW-UP QUESTIONNAIRE | | YES | NO | Comments |
|---|---|---|---|---|
| 1. | Do you understand the characteristics of your treatment? | ☐ | ☐ | |
| | 1. Route of administration | ☐ | ☐ | |
| | 2. Importance of following the treatment | ☐ | ☐ | |
| | 3. Frequency of administration | ☐ | ☐ | |
| | 4. Adverse reactions: what they are, how long they last, how to control them | ☐ | ☐ | |
| | 5. The need or not to store the drug in a cold place | ☐ | ☐ | |
| 2. | Do you believe in the benefits of the treatment? | ☐ | ☐ | |
| 3. | Do you use any method to remember to take the treatment? | ☐ | ☐ | |
| | If you do, indicate which: | | | |
| 4. | Have you ever missed a dose or altered the dose? | ☐ | ☐ | |
| | If so, indicate:<br>When,<br>How many times,<br>Why | | | |
| 5. | Do you tolerate the treatment well? | ☐ | ☐ | |
| 6. | Have you had any problems with the injection technique? | ☐ | ☐ | |
| | If so, indicate which kind | | | |
| 7. | Do you feel supported by the healthcare team? | ☐ | ☐ | |
| 8. | Do you feel supported by your family, partner, and friends? | ☐ | ☐ | |
| 9. | Have you noticed any memory loss? | ☐ | ☐ | |
| 10. | Are you able to fit your treatment into your daily activities well? | ☐ | ☐ | |

## References

1. Informe de la Organización Mundial de la Salud. Adherence to Long-Term Therapies-Evidence for Action. Ginebra: Organización Mundial de la Salud; 2003.
2. Taus C, Taffi R, Morelli M, Fié A, Angeleri VA, Sgolastra M, et al. Adherence to IFNB therapy in MS: An Italian Clinical Setting. Mult Scler. 2001;7 Suppl.1:S65.
3. Tremlett HL, Ogel J. Interrupted therapy: Stopping and switching of the ß-interferons prescribed for MS. Neurology. 2003;61:551-4.
4. Río J, Porcel J, Téllez N, Sánchez-Betancourt A, Tintoré M, Arévalo MJ, et al. Factors related with treatment adherence to interferon ß and glatiramer acetate therapy in multiple sclerosis. Mult Scler. 2005;11:306-9.
5. Stuart WH, Cohan S, Richert RR, Achiron A, Ramo T, Patti M, et al. Selecting a disease-modifying agent as platform therapy in long-term management of multiple sclerosis. Neurology. 2004;63:S19-27.
6. Devonshire V, Lapierre Y, MacDonell R, Ramo C, Patti F, Fontoura P, et al. The Global Adherence Project: A multicentre observational study on adherence to disease-modifying therapies in patients suffering from relapsing-remitting multiple sclerosis. Mult Scler. 2006;12 Suppl.1:S82.
7. Brandes DW, Callender T, Lathi E, O'Leary S. A review of disease-modifying therapies for MS: maximizing adherence and minimizing adverse events. Curr Med Res Opin. 2009;25:77-92.
8. Lugaresi A. Addressing the need for increased adherence to multiple sclerosis therapy: can delivery technology enhance patient motivation? Expert Opinion. Drug Deliv. 2009;6:995-1002.
9. Tafur-Valderrama E, Ortiz C, Alfaro CO, García-Jiménez E, Faus MJ. Adaptación del ''cuestionario de evaluación de la adhesión al tratamiento antirretroviral'' (CEATC-VIH) para su uso en Perú. Ars Pharm. 2008;49:183-98.
10. Remor E. Valoración de la adhesión al tratamiento antirretroviral en pacientes VIH+. Psicothema. 2002;14:262-7.
11. Polman CH, Reingold SC, Edan G, Filippi M, Hartung HP, Kappos L, et al. Diagnostic criteria for multiple sclerosis: 2005 revisions to the ''McDonald Criteria''. Ann Neurol. 2001;58:840-6.
12. Ficha Técnica autorizada de Avonex® 30mcg/0,5 ml.
13. Ficha Técnica autorizada de Betaferón®.
14. Ficha Técnica autorizada de Rebif®.
15. Ficha Técnica autorizada de Copaxone®.
16. Cassidy CA. Using the transtheorical model to facilitate behaviour change in patients with chronic illness. J Am Nur Practitioners. 1999;11:281-7.

17. Frohman E, Phillips T, Kokel K, Pelt JV, O'Leary S, Gross S, et al. Disease modifying therapies in multiple sclerosis: strategies for optimizing management. Neurologist. 2002;8:227-36.
18. Leuschen MP, Filipi M, Healey K. A randomized open label study of pain medications (naproxen, acetaminophen and ibuprofen) for controlling side effects during initiation of IFN beta-1a therapy and during its ongoing use for relapsing-remitting multiple sclerosis. Mult Scler. 2004;10:1-8.
19. Río J, Nos C, Bonaventura I, Arroyo R, Genis D, Sureda B, et al. Corticosteroids, ibuprofen, and acetaminophen for IFNß-1a flu symptoms in MS. Neurology. 2004;63:525-8.
20. Langer-Gould A, Moses HH, Murray TJ. Strategies for managing the side effects of treatments for multiple sclerosis. Neurology. 2004;63:S35-41.
21. Galetta SL, Markowitz C. US FDA-Approved Disease-Modifying Treatments for Multiple Sclerosis. CNS Drugs. 2005;19:239-52.
22. Dirección General de Farmacia y Productos Sanitarios. Escala de toxicidad clínica. Protocolo de petición de tratamiento de la esclerosis múltiple con interferón beta-1b. Madrid: Ministerio de Sanidad de Consumo; 2007.
23. Bacon J, Riber L, Tamar Fromm, Safier M, Herbert J. Motivational style as a predictor of attitude and adherence to injection therapy for MS. In: European Committee for treatment and research in MS. 2006 September 27-30.
24. Rao SM, Leo GJ, Bernardin L, Unverzagt F. Cognitive dysfunction in multiple sclerosis. I. Frequency, patterns, and prediction. Neurology. 1991;41:685-91.
25. Arnett P, Forn C. Evaluación neuropsicológica en la esclerosis múltiple. Rev Neurol. 2007;44:166-72.
26. Roca M, Cañas F, Olivares JM, Rodríguez A, Giner J. Adherencia al tratamiento en la esquizofrenia: congreso clínico Español. Actas Esp Psiquiatr. 2007;35 Suppl.1:1-6.