How many injections did you miss last month?

A simple question to predict Interferon β-1a adherence in multiple sclerosis

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Introduction Adherence to therapy is crucial for Multiple Sclerosis (MS) patients to obtain the full benefits of their treatment. In particular, subcutaneous Interferon β-1a (Rebif®) can be administered by RebiSmart®, an electronic auto-injector recording dose history which may be useful for adherence monitoring. However, poor adherence to DMTs has been related to different reasons and patients characteristics, with difficulties in predicting the likelihood of long-term adherence with subsequent effects on MS outcomes.

Objectives The present study aims to investigate: 1) adherence to Interferon β-1a in a clinical setting; 2) predictors of poor adherence during clinical observation; and 3) subsequent clinical correlates.

Methods *Inclusion criteria:* Diagnosis of relapsing-remitting MS; treatment with Interferon β-1a for at least 6 months before the first recorded injection; use of the RebiSmart® for at least 6 months (patients were contacted by phone a week before the time of their first scheduled visit in 2014, and asked to carry to the Centre their device).

Interferon β-1a adherence: Adherence was calculated as the percent ratio between the number of self-administered injections, and the number of injections that should have been administered during the observation period; in addition, subjects were divided in fully adherent (no missed dose during the observation period), or not fully adherent, subsequently categorized if the first missed dose was during the first month of observation or later (early missing or late missing).

Sample size estimation: In linear regression analyses, considering the presence of 8 variables in fully adjusted models and an estimated R2 equal to 0.455, a total sample size of 108 subjects was able to detect a Power of 0.75 (alfa=0.05).

	MS subjects (n=114)
Age, *years*	35.8 ± 10.4 (19.1-58.7)
Sex, *male/female*	33/81 (28.9/71.1%)
Education, *primary/secondary/university*	13/71/30 (11.4/62.3/26.3%)
Disease duration, *years*	8.108 ± 9.082 (0.500-19.6)
Treatment duration, *years*	2.939 ± 3.319 (0.500-12.3)
Interferon β-1a dosage, *low/high*	29/85 (28.4/74.6%)
Observation period, *years*	1.536 ± 0.961 (0.500-4.068)
Adherence, *%*	95.0 ± 9.0 (39.3-100.0)
Time to first missing dose, *early/late/none*	17/54/43 (14.9/47.4/37.7%)
Baseline EDSS	2.8 ± 0.8 (1.5-5.5)
Occurrence of clinical relapse, *number*	39 (34.2%)
Time to first relapse, *years*	0.935 ± 0.793 (0.09-3.086)
Annualized Relapse Rate	0.313 ± 0.566 (0.000 – 3.263)

Results Adherence was not associated with the occurrence of clinical relapse (p=0.206), the ARR (p=0.110), and the time to first relapse (p=0.212). However, adherence was associated with treatment duration (coeff.=-0.007; p=0.020).

Adherence resulted significantly lower in early missing, as compared to late missing (Figure 1). Early missing was more likely to be associated with the occurrence of a clinical relapse, but not late missing, as compared to fully adherent (Figure 2). The ARR resulted higher in early missing, as compared to late missing, and to fully adherent (Figure 1). The time to the first relapse was shorter in early missing, as compared to fully adherent, but not to late missing (Figure 1).

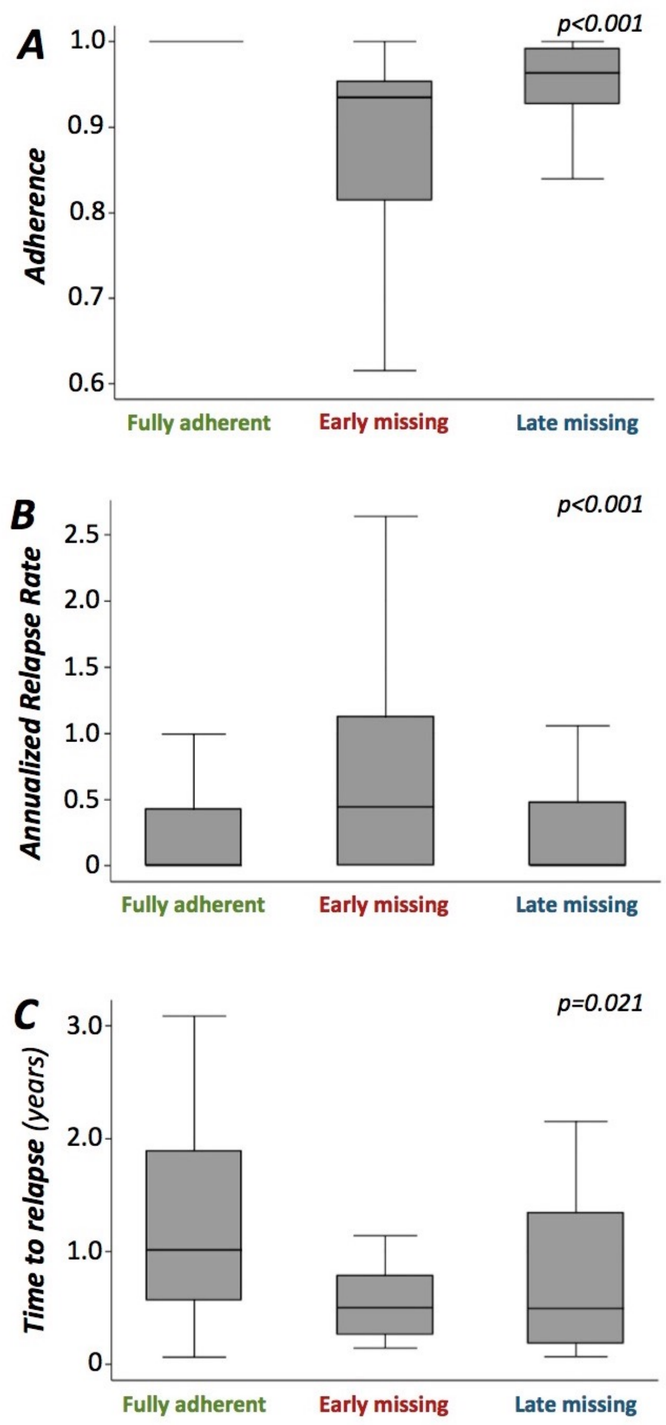

Figure 1. *Box-and-Whisker plots show relationships between categories of time to first missed dose (fully adherent, missing a dose during the first month of observation -early-, or missing a dose after the first month of observation -late-) and adherence, annualized relapse rate, and time to the first relapse. P-values are shown from analysis of variance. In particular, early first missed dose presented lower adherence rates (85.1±16.7%), as compared to late first missed dose (94.7±6.3%) (p<0.001) (A); early missed dose presented higher annualized relapse rate (0.781±0.968), as compared to late missed dose (0.253±0.486) (p=0.002), and to fully adherent (0.215±0.361) (p=0.001), after post hoc Bonferroni correction (B); early missed dose presented reduced time to the first relapse (0.602±0.471 years), as compared to fully adherent (1.206±0.891 years) (p=0.032), but not to late missed dose (0.787±0.756 years) (p=0.508), after post hoc Bonferroni correction (C).*

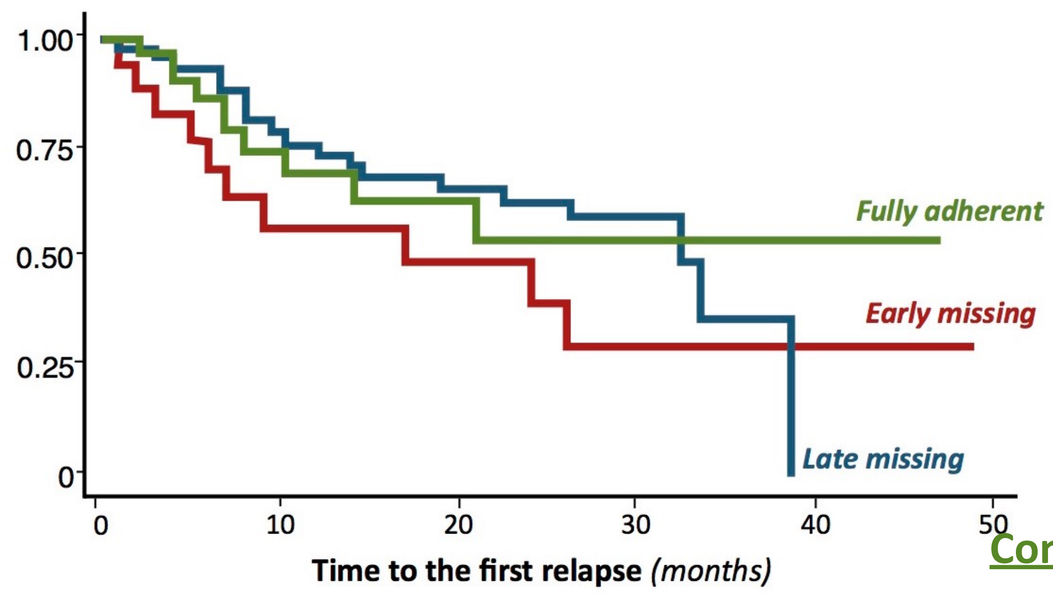

Figure 2. *Kaplan-Meier plot estimates the likelihood of clinical relapses for subjects missing for the first time a dose during the first month of observation (17 subjects with a mean follow-up of 1.637±1.052 years, early missing, light dotted grey), missing for the first time a dose after the first month of observation (54 subjects with a mean follow-up of 1.810±0.849 years, late missing, dark dotted grey), or fully adherent to the treatment (43 subjects with a mean follow-up of 1.151±0.950 years, black). In particular, early missing dose (p=0.018, OR=4.155, 95%CI=1.271-13.580), and at least in part late missing dose (p=0.408, OR=1.454, 95%CI=0.681-2.713), were more likely associated with the occurrence of a clinical relapse, as compared to fully adherent.*

Conclusions The current study showed that the time to the first missed dose is the earliest and most significant correlate of treatment adherence and of clinical outcomes, suggesting an easy way to assess and categorize adherence of MS patients in a clinical setting. In fact, through a simple question it might be possible to estimate a potential poor adherence over time, allowing the clinician to implement specific adherence programs for this sub-population [8], in order to avoid clinical worsening which would predictably lead to treatment escalation to more expansive and risky second line treatment options.

Selected references **1)** Devonshire V, et al. The Global Adherence Project (GAP): A multicenter observational study on adherence to disease-modifying therapies in patients with relapsing-remitting multiple sclerosis. Eur J Neurol 2011;18:69–77. **2)** Lugaresi A, et al. Fostering adherence to injectable disease-modifying therapies in multiple sclerosis. Expert Rev Neurother 2014;14:1029–42. **3)** Lugaresi A. RebiSmartTM (version 1.5) device for multiple sclerosis treatment delivery and adherence. Expert Opin Drug Deliv 2013;10:273–83. **4)** Steinberg SC, et al. Impact of Adherence to Interferons in the Treatment of Multiple Sclerosis. Clin Drug Investig 2010;30:89–100. **5)** Uitdehaag B, et al. Impact of exposure to interferon beta-1a on outcomes in patients with relapsing-remitting multiple sclerosis: exploratory analyses from the PRISMS long-term follow-up study. Ther Adv Neurol Disord 2011;4:3–14.