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REVIEW OF PATIENT-REPORTED OUTCOME MEASURES FOR DAYTIME FUNCTIONING

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OBJECTIVES: 'Daytime functioning' is a widely used outcome to describe quality of patients' functional performance during daytime and gaining popularity as an efficacy outcome in pharmaceutical interventions. The purpose of this study was to conduct a review of the literature and identify studies and patient-reported outcome instruments that purport to measure daytime functioning. **METHODS**: A search was conducted of the English-language studies published between January 1950 and June 2008 using Medline. Key terms used were 'daytime function and questionnaires', 'daytime functioning and quality of life', 'daytime functioning and questionnaires', and 'daytime functioning and quality of life'. Studies that observed functional performance from adult population were exclusively selected and of those articles, patient-reported questionnaires were identified. Validity of instruments was assessed based on reported psychometric properties. **RESULTS**: Total of 55 articles were identified. Studied patient population had sleep disorders (including apnea) (n = 47), cancer (n = 2), restless leg syndrome (n = 2), allergic rhinitis (n = 1), Alzheimer's disease (n = 1), coronary artery disease (n = 1), overactive bladder (n = 1), and Parkinson's disease (n = 1). Of these, 45% (n = 25) articles included a patient-reported outcome questionnaire that claimed to measure daytime functioning. The remaining articles (55% n = 30) included objective measurement to describe daytime function performance or used questionnaires without the supporting evidence of reliability, validity and interpretability. After excluding duplicated PRO-questionnaires, 13 tools were identified and changes in patients' functioning were observed from different areas; generic disease state (i.e. health, social support and activities survey) (n = 4), sleep disorders (n = 4), psychiatry (n = 3) and fatigue (n = 1). **CONCLUSIONS**: Not all studies that purport to measure daytime functioning used validated PRO tools to measure changes in daytime functioning. The criteria of defining daytime functioning were differed among different disease states. Future studies that will investigate the domain of daytime functioning, it is recommended to select appropriate validated PRO instruments that can support the intended claim.

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FACTORS DRIVING PATIENT SELECTION OF PRIMARY MEDICATION FOR MULTIPLE SCLEROSIS

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OBJECTIVES: To evaluate the factors driving selection of the primary medication for multiple sclerosis (MS) by patients. **METHODS**: Baseline data from ROBUST, which is a 12-month, US prospective, observational, open-label, single-arm, multi-center outcomes study of Interferon β-1b given every other day for relapsing forms of MSwere analyzed. At baseline, patients were asked to rate the importance of factors that are typically considered before making a decision to select the primary medication to treat MS (on a scale of 1 = not at all important through 5 = very important). Twelve factors were evaluated: how well medication works, how much medication is given per dose, convenience of taking medication, convenience of storing medication, frequency of administration, information in product decision kit, injection needle of the medication, personal research, doctor recommendation, family opinion, opinion of other MS patients and recommendation of MS advocacy groups. Mean scores on each factor were compared across patient sociodemographic characteristics, primary medication types and disease severity. **RESULTS**: At baseline, a total of 99 reported taking medication to treat their MS and thus provided responses on the items of interest. In this sample, 80.8% were females, 61.6% married, 70.4% below 50 years old and 82.8% White. Among all patients, the highest importance scores were received for how well the medications controls MS progression (Mean [95% Confidence Interval] = 4.72 [4.57–4.86]) followed by their doctor's recommendation (4.57 [4.41–4.72]), the convenience of taking the medications (3.88 [3.63–4.13]), personal research (3.81 [3.56–4.05]) and the convenience of storing the medication (3.71 [3.44–3.98]). These factors and their order of importance remained consistent across patient sociodemographic characteristics, primary medication types and disease severity. **CONCLUSIONS**: Contributing to the limited published research about factors considered by patients when selecting primary medication for their MS, this analysis found that medication effectiveness to control MS progression and doctor recommendation are the most important drivers of medication selection.

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HEALTH-RELATED QUALITY OF LIFE, EDSS AND TIMED 25-FOOT WALK IN A MULTIPLE SCLEROSIS POPULATION OF A REAL-WORLD OBSERVATIONAL OUTCOMES STUDY: BASELINE DATA FROM ROBUST

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OBJECTIVES: To explore the association of baseline health-related quality of life (HRQoL) and clinical measures of disability and motor functioning in a real-world observational study of multiple sclerosis (MS) patients. **METHODS**: The Real-World Betaseron® Outcomes Study (ROBUST) is a US, prospective, 12-month, observational, single-arm, open-label, multi-center outcomes study of interferon beta-1b given every other day for MS. A total of 226 patients were registered at 52 neurologists' sites. Clinical measures and patient outcomes were reported by physicians and patients via a web-based data capture tool. The Kurtzke Expanded Disability Status Scale (EDSS) and Timed 25-foot Walk (T25FW; in seconds) were measured by the neurologist at baseline to evaluate patient disability and motor functioning. HRQoL was measured at baseline for 191 patients via the SF-12 Health Survey. For this analysis, EDSS and T25FW were categorized into five (0, 1–2, 2.5–4, 4.5–5.5, 6) and two (< = 7, >7 sec) groups, respectively. SF-12 results were summarized by Physical Component Score (PCS-12) and Mental Component Score (MCS-12). Analysis of variance methods were used to explore the association of baseline HRQoL and clinically measured EDSS and T25FW. **RESULTS**: At higher EDSS scores (i.e., worsening disability), both physical and mental HRQoL were lower; however, this association was only statistically significant for PCS-12 (p = < .001 for PCS-12, p = 0.707 for MCS-12). For PCS-12, among adjacent EDSS groups, pairwise differences were statistically significant between EDSS = 1–2 vs. EDSS = 2.5–4 (44.0 vs. 37.2; p = .0004), suggesting a marked worsening of physical HRQoL at or above the disability threshold of EDSS = 2.5. Both PCS-12 and MCS-12 were higher for the group with better ambulation: T25FW < = 7 sec vs. T25FW >7 sec (43.5 vs. 37.0, p < 0.001 for PCS-12; 43.9 vs. 41.0, p = 0.079 for MCS-12). **CONCLUSIONS**: Physical HRQoL is associated with functional impairment assessed via the EDSS and T25FW. This suggests that the PCS-12 component of the generic HRQoL tool reflects clinical functional impairment in MS patients.

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RESPONSIVENESS AND CLINICAL IMPORTANT DIFFERENCES OF THE FUNCTIONAL ASSESSMENT OF MULTIPLE SCLEROSIS: RESULTS OF A LARGE MULTINATIONAL OBSERVATION STUDY

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OBJECTIVES: Health related quality of life (HrQoL) is an important outcome in multiple sclerosis (MS). As part of the measurement system "Functional Assesment of Chronic Illness Therapy (FACIT)" targeted to the management of chronic illnesses, the Functional Assessment of MS (FAMS) is a self-reported questionnaire assessing patient-reported treatment effects in MS studies. Although the FAMS is validated in MS, the link between meaningful clinical efficacy and FAMS score changes remains unclear. Objective was to determine anchor-based "clinical important differences" (CID) in FAMS total score (FAMS TS) and FAMS trial outcome index (FAMS TOI) using disability as measured by the Expanded Disability Status Scale (EDSS). **METHODS**: 6 months data from a prospective, observation study (BetaPlus) in patients with relapsing MS were used. All patients had been switched from another drug to interferon beta-1b 1–3 months before inclusion. The EDSS, the FAMS-TS, the FAMS-TOI were assessed at baseline and 6 months, with 1078 respondents at baseline and 950 at follow-up. Regression analysis was used to estimate CID of FAMS change scores by three anchor categories of EDSS change ("deteriorated", "unchanged", "improved"). Distribution based measures (standardized effect size (SRM)) were used to quantify the strength of CID. **RESULTS**: CID at 6 months was 5.65 [95% confidence interval: 0.75;10.56] (FAMS TS) and 4.22 [0.02;8.42] (FAMS TOI). All coefficients for "EDSS improved" were significantly larger than for "EDSS unchanged" with SRM of 0.24 and 0.23, respectively. **CONCLUSIONS**: CID estimates are provided for improvement in HRQOL in patients with MS over a six-month period. The results are inline with published CID of FACIT instruments ranging from 4 to 8 units in patients with cancer. The estimated CID can assist clinicians and health policy makers in evaluating significance of short-term treatment effects of medical as well as non-medical interventions (e.g. patient support programmes).

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COSTS AND HEALTH-RELATED QUALITY OF LIFE IN PATIENTS WITH GILLES DE LA TOURETTE'S SYNDROME

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OBJECTIVES: To assess the costs and the health-related quality of life (HrQoL) of patients with Gilles de la Tourette's syndrome (GTS) in Germany **METHODS**: Direct and indirect costs as well as HrQoL were evaluated in 200 patients with GTS in three outpatient departments in Germany. Economic data was provided in a patient diary over a three-months-period. Costs were analyzed from the perspective of the statutory health insurance. Indirect costs were calculated by the human capital approach. HrQoL was measured using the EuroQol instrument. Depression was assessed using the Beck Depression Inventory (BDI) and clinical symptoms with the Yale Tourette Syndrome Symptom list (YTSSL) and the Shapiro-Tourette-Syndrome-Severity-Scale (STSSS). **RESULTS**: Direct costs amounted to €635 during the evaluation period. Indirect costs totalled to €2500. Major cost components were: drug costs (€350) and in-stays (€300). Patients with GTS proved to have a worse HrQoL than a representative sample of the general German population. In GTS patients the most affected EQ-5D domains were anxiety/depression (57.1%), pain/discomfort (47.5%), and daily activities (38.4%). The mean EQ VAS score was 65.4 ± 21.9. The patients had a mean BDI score of 12.3 ± 9.9, which was considerably worse compared to a representative German sample with a mean BDI score of 6.45 ± 5.2. The mean STSSS value was 3.24 ± 1.1. There was no significant difference between genders with respect to tic severity. A significant correlation for BDI, age, YTSSL, STSSS, subjective efficacy of

drug treatment, occupational advancement, current work status, and direct cost was detected in univariate analyses. **CONCLUSIONS**: To our best knowledge this is the first observational study on the burden of GTS in Germany. With annual total costs of about €12,500, GTS places a notable financial burden on society. HrQoL is considerably reduced in patients with GTS. While tic treatment is important, co-morbidities such as depression should be regarded more seriously.

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IMPROVEMENT IN HEALTH-RELATED QUALITY OF LIFE IN MULTIPLE SCLEROSIS PATIENTS ON NATALIZUMAB IN THE UNITED STATES

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OBJECTIVES: To assess change in health-related quality of life (HRQoL) over time in MS patients treated with natalizumab in a "usual care setting" in the United States (US). **METHODS**: MS patients starting natalizumab were invited to participate in a 1-year longitudinal health outcomes study assessing their experiences with natalizumab. MS patients complete self-reported assessments prior to natalizumab initiation and after the 3rd, 6th and 12th natalizumab infusions. The current analysis reports the change in general HRQoL assessments using the SF-12v2 from baseline through the 6th natalizumab infusion. Physical and Mental Component Summary (PCS and MCS, respectively) scores were computed at each assessment. PCS and MCS scores range from 0 to 100, with higher scores indicating better HRQoL. The a-priori study hypothesis was that patient-reported HRQoL improves over time with longer duration of natalizumab treatment. Statistical regression models were used to evaluate changes in HRQoL over time after controlling for the number of natalizumab infusions, age, years since MS diagnosis, baseline disease disability and functional status, comorbidity burden, and number of drugs used prior to natalizumab. **RESULTS**: Data for 296 patients were analyzed. The mean age was 47 +/– 11 years and the majority of patients were female (78%). The mean number of years since MS diagnosis was 11 +/– 9 years. After controlling for covariates, a statistically significant increase (improvement) in PCS scores (BL 34 +/– 11, 3rd 36 +/– 12 and 6th 36 +/– 11; $p < 0.0001$) and MCS scores (BL 43 +/– 12, 3rd 47 +/– 11 and 6th 48 +/– 11; $p < 0.0001$) was observed from baseline through the 6th infusion. **CONCLUSIONS**: Patients reported significant improvements in both physical and mental aspects of HRQoL over 6 months of treatment, suggesting an improved effect of natalizumab over time. These results document the improvement in HRQoL of MS patients receiving natalizumab in the usual care setting and are consistent with clinical study findings.

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PATIENT REPORTED OUTCOMES IN THE EARLY STAGES OF MULTIPLE SCLEROSIS: THE BEGIN STUDY

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OBJECTIVES: Reports from clinical trials suggest that physical activity (PA) can be beneficial for multiple sclerosis (MS) patients. However, participation in PA was found to be low in MS patients with substantial physical disability. We assessed levels of PA and their interaction with depression and health related quality of life (HRQoL) in early-stage MS patients. **METHODS**: The BEGIN study (Betaferon® treatment and Exercise data Gathering IN early MS) is an international prospective observational study of early-stage MS patients, including clinically isolated syndrome suggestive of MS, treated with Betaferon®. PA levels were assessed by the International Physical Activity Questionnaire (IPAQ) and a pedometer, and depression using the Center for Epidemiological Studies Depression Scale (CES-D), and HRQoL with the EuroQoL 5 dimension (EQ-5D) utility scale and Visual Analogue Scale (VAS) score. **RESULTS**: PA data were collected from 609 patients (68.0% women) in 16 countries in Europe, Asia, Australia and Latin America. Mean age was 36.3 years (SD = 9.9). The median MET-minutes/week derived from IPAQ at baseline was 3349 (SD = 3616), with 25.2%, 32.5% and 42.6% of patients categorized as low, moderate and high PA level, respectively. The median steps per day were 6,728 (IQR = 4,942). A negative Spearman's rank correlation was found between the steps per day and depressive symptoms ($p < 0.01$).Mean depression scores decreased monotonically in higher IPAQ categories. EQ-5D utility and VAS scores were on average 0.7 (SD = 0.2) and 71.7 (SD = 19.5), respectively. The steps per day showed to be positively correlated with both VAS ($p = 0.01$) and utility ($p < 0.01$) outcomes. **CONCLUSIONS**: PA in early-stage MS patients was found to be positively associated with HRQoL. Adding the results of the longitudinal data after two years of follow-up may lead to further insights regarding the role of PA in early-stage MS patients and its relation to HRQoL.

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IMPROVEMENT IN PATIENT SATISFACTION WITH INCREASING NATALIZUMAB TREATMENT DURATION IN MULTIPLE SCLEROSIS PATIENTS IN THE UNITED STATES

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OBJECTIVES: To assess patient-reported treatment satisfaction with natalizumab in MS patients in the United States (US). **METHODS**: MS patients initiating natalizumab were invited to participate in a longitudinal study. Patients complete self-reported assessments prior to natalizumab initiation and then after the 3rd, 6th and 12th natalizumab infusions. As part of the baseline (BL) assessment, patients reported their satisfaction with MS drugs used prior to natalizumab initiation. For the follow-up assessments, patients reported their satisfaction with natalizumab treatment. Patient self-reported measures included satisfaction with treatment effectiveness, convenience of use, and global treatment satisfaction scales from the Treatment Satisfaction Questionnaire. Each scale consists of 3 items, with responses measured on a 7-point Likert Scale ranging from 1 (low) to 7 (high). Individual item responses are added and scores are transformed to a 0 to 100 scale with higher scores indicating higher satisfaction. This analysis evaluates the change in satisfaction from baseline through the 6th natalizumab infusion after controlling for number of natalizumab infusions, age, years since MS diagnosis, baseline disease disability and functional status, comorbidity burden, and number of MS drugs used prior to natalizumab. **RESULTS**: Data from 296 patients indicated that 78% are female, the mean age is 47 ± 11 years and the mean time since MS diagnosis is 11 ± 9 years. Almost all (97%) patients used at least one other MS drug before natalizumab. After controlling for covariates, significant increases in effectiveness (BL 44.22 ± 8.62, 3rd 61.91 ± 6.87 and 6th 69.48 ± 4.96, $p < 0.0001$), convenience (BL 60.80 ± 6.27, 3rd 79.18 ± 3.25 and 6th 79.69 ± 0.42, $p < 0.0001$), and global satisfaction (BL 62.46 ± 3.92, 3rd 75.36 ± 3.92 and 6th 76.51 ± 3.92, $p < 0.0001$) were observed. **CONCLUSIONS**: Patients' satisfaction with natalizumab increased with increasing treatment duration. Patients reported higher levels of satisfaction with treatment effectiveness, convenience of use, and global satisfaction while receiving natalizumab compared to their satisfaction levels with MS drugs received before initiating natalizumab.

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INTERPRETING SCORES ON THE MULTIPLE SCLEROSIS-SPECIFIC PRIMUS AND U-FIS OUTCOME MEASURES

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OBJECTIVES: Estimating the minimal important difference (MID) of patient reported outcome (PRO) measures is important to guide interpretations of scores and for assessing treatment efficacy in clinical trials and studies. The current study was designed to estimate the MID of newly developed PROs for Multiple Sclerosis (MS); The Patient Reported Indices for Multiple Sclerosis (PRIMUS; which includes Activity and Quality of Life (QoL) scales) and Unidimensional Fatigue Impact Scale (U-FIS). The measures have been shown previously to be unidimensional, valid and reliable. **METHODS**: Data were taken from the TRANSFORMS study, a multi-country phase III study evaluating the safety and efficacy of oral fingolimod compared to IFNβ-1a i.m. in relapsing-remitting MS patients. PRO assessments were completed at baseline, 6 and 12 months. Measures included the PRIMUS-Activities (scored 0–30), PRIMUS-QoL (scored 0–22), U-FIS (scored 0–66) and EQ-5D. For PRIMUS and U-FIS scales, a high score indicates more severe impact. Both anchor (published EQ-5D MID values) and distribution (0.2 and 0.5 effect sizes, standard error of measurement) based approaches were employed. Anchor-based MID values were assessed both for individuals who improved or deteriorated according to EQ-5D MID values. Triangulation of results provided the final PRIMUS and U-FIS MID estimates. **RESULTS**: Trial sample: n = 1292, 67.3% female, mean age =36.2 (SD = 8.5), mean MS duration =7.4 years (SD = 6.2). Anchor and distribution based MID's ranged from 0.9–2.9 (PRIMUS QoL), 0.7–2.3 (PRIMUS Activities) and 2.4–7.3 (U-FIS). Triangulation resulted in the following MID values; PRIMUS Activities 1.5 for individuals improving or deteriorating; PRIMUS QoL 1.5 for individuals improving or deteriorating and U-FIS 4.5 for those improving and 5.0 for those deteriorating. **CONCLUSIONS**: The analyses provide preliminary information on the interpretation of scores on the scales. The MID values will aid the assessment of treatment efficacy in clinical trials and studies.

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ASSOCIATION OF HEALTH-RELATED QUALITY OF LIFE AND RELAPSE IN THE PREVIOUS YEAR AMONG MULTIPLE SCLEROSIS PATIENTS: BASELINE DATA FROM ROBUST

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OBJECTIVES: To measure the association of health-related quality of life (HRQoL) and pre-baseline relapse among multiple sclerosis (MS) patients in a real-world observational study. **METHODS**: The Real-World Betaseron Outcomes Study (ROBUST) is a 12-month, US prospective, observational, open-label, single-arm, multi-center outcomes study of interferon beta-1b given every other day for MS. Patient outcomes, including relapse history, were reported independently by both patients and physicians via a web-based data capture tool. A total of 226 patients were registered across 52 sites, and 193 completed the baseline survey. Analysis of variance methods were used to measure the association of SF-12 Health Survey (SF-12) scores and pre-baseline relapse descriptors (relapse status, frequency, severity of typical and worst relapse). SF-12 results were summarized by Physical Component Score (PCS-12) and Mental Component Score (MCS-12). **RESULTS**: Both physical and mental scores were lower among patients reporting to be in relapse at baseline (N = 78) than among those reporting to be relapse-free at baseline (N = 115); however, the difference was statistically significant only on the MCS-12 (43.9 vs. 40.5; $p = 0.045$). Reduction of both PCS-12 and MCS-12 were strongly associated with increasing frequency of patient