An Online Self-Management Intervention for Patients with Fibromyalgia – an RCT
Analysis Plan

25-7-2022

Baseline Characteristics and Differences

Descriptive statistics (means and standard deviations in case of normally distributed variables or medians and interquartile ranges in case of non-normally distributed variables, and numbers and percentages in case of categorical variables) will be reported for the following baseline characteristics:

- Sociodemographic variables: age, sex, marital and relationship status, education
- Disease- and treatment related variables: medication, duration of fibromyalgia, physical and psychological comorbidities, (previously) received treatments for fibromyalgia
- Other: frequency of internet use, internet use proficiency, extraversion and neuroticism

Differences in baseline characteristics between the intervention group and control group will be examined, and between patients who completed the intervention and those who did not. For continuous outcomes, T-tests or independent samples median tests (when non-normally distributed) will be conducted. For categorical outcomes, χ2 -tests will be conducted.

Analyses

All main analyses will be carried out following the intention-to-treat (ITT) principles. As linear mixed models are well-suited to handle missing values, missing data from drop-outs will not be imputed. Person-mean imputation will be applied when necessary to calculate scale scores. The analyses will be conducted (1) with the inclusion of covariates (primary analysis), (2) without the inclusion of covariates (sensitivity analysis) and (3) per protocol (i.e., comparing only the patients who completed the intervention with patients in the control group as a sensitivity analysis) with and without the inclusion of covariates.

Main Analyses

To compare changes in primary and secondary outcome variables during the study period between patients in the intervention and control groups, linear mixed models will be fitted using full maximum likelihood estimation. The models will include fixed effects of time as three dummy variables: 'short-term' for baseline vs. post-intervention, 'mid-term' for baseline vs. 6-week follow-up, and 'long-term' for baseline vs. 3-month follow-up. To indicate the effect of the intervention across time, the fixed effects of interactions between group (i.e., intervention or control group) and timepoint will be included as again three dummy variables: short-term*group, mid-term*group, and long-term*group. Finally, the fixed effects of the covariates age (centered) and sex will be included. The models will include random effects of intercept and the addition of random effects of slopes will be tested with Likelihood Ratio Tests (i.e., the difference in -2LL between the alternative model and the null model using a χ^2 distribution). For each model, the variance-covariance matrix leading to the optimal model fit (i.e., the lowest Akaike's Information Criterion) will be selected using restricted maximum likelihood estimation. Values of $p < .05$ (two-tailed) will be considered as significant.

Assumptions

For each final model, the assumptions of normality, homoscedasticity and linearity will be checked by examining Q-Q plots, scatterplots of residuals versus predicted values, and scatterplots of predicted values versus observed values, respectively. In case assumptions are not met, transformations will be applied. Histograms of the residuals will be inspected for outliers. An outlier will be corrected manually if the outlier is a clear result of an error. Otherwise, the influence of an outlier will be examined by comparing results with and without the outlier. If the outlier is influential, a transformation will be applied. If not, the outlier will be retained.

Effect Sizes

Between-group effect sizes will be calculated for each outcome at post-intervention (T2), 6-week follow-up (T3), and 3-month follow-up (T4). Cohen's *d* effect sizes will be obtained by

performing independent T-tests in SPSS with change scores (compared to baseline) as dependent variables and group as predictor. Effect sizes of 0.2, 0.5, and 0.8 will be considered as small, medium, and large, respectively (Cohen, 1988).

Minimal Clinically Important Improvement

The number and percentage of participants in the intervention and control group that showed minimal clinically important improvement will be calculated for the primary outcome pain coping, defined as an increase of at least 10% on the VAS pain coping scale at T2. This number is in line with previous recommendations on minimal clinically important improvement in VAS pain (Dworkin et al., 2008). Differences in minimal clinically important improvement in pain coping between the intervention and control group will be compared with the $\chi 2$-test.

Other Study Parameters

Cost-effectiveness

The main research question of the cost-effectiveness analyses is to investigate the cost-effectiveness of the intervention versus standard care from a societal perspective. In order to study the potential efficiency from a societal perspective, both the medical consumption (direct costs) and productivity losses (indirect costs) will be calculated. Quality-adjusted life years (QALYs) will be computed in order to perform a cost-utility analysis. Utilities (EQ-5D) will be based on the mean values for the patients at three occasions (baseline, post-treatment and three months follow-up).

Interim Analysis

Not applicable.

References

Cohen J. *Statistical power analysis for the behavioral sciences.* Hillsdale, N.J.: L. Erlbaum Associates, 1988.

Dworkin RH, Turk DC, Wyrwich KW, et al. Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials: IMMPACT recommendations. J Pain. 2008;9(2):105-121. doi:10.1016/j.jpain.2007.09.005