Data analysis plan

Mediators of treatment efficacy in "Exposure-based Cognitive Behavior Therapy vs Traditional Cognitive Behavior Therapy for Fibromyalgia" (NCT05058911)

This plan was completed on 11 May 2023 and describes a secondary study of mediators of treatment efficacy in a randomized controlled trial of Internet-delivered exposure-based cognitive behavior therapy (Exp-CBT) versus Internet-delivered traditional cognitive behavior therapy (T-CBT) for fibromyalgia.

Variables of interest

Variables of interest were administered before treatment, each week during treatment, and after treatment, resulting in 11 measurement points over the main phase of the trial.

Outcome
Fibromyalgia severity (Fibromyalgia Impact Questionnaire; FIQ)

Potential mediators
Avoidance behavior (Psychological Inflexibility in Pain Scale – Avoidance subscale; PIPS-A)
Catastrophizing (Pain Catastrophizing Scale; PCS)
Hypervigilance (Pain Vigilance and Awareness Questionnaire; PVAQ)
Overdoing (Patterns of Activity Measure – Pain – Overdoing subscale; POAM-O)
Pacing (Patterns of Activity Measure – Pain – Pacing subscale; POAM-P)
Physical activity (Godin-Shephard Leisure-Time Exercise Questionnaire; GLEQ)

Theoretical framework: hypothesized relationships

Hypotheses with regard to mediation are listed in Table 1. All potential mediators will also be evaluated with regard to temporal precedence, i.e., whether change in the potential mediator systematically precedes change in the outcome. In all cases where the main test of mediation is not exploratory, we expect change in the potential mediator to systematically forego change in the outcome. Notably, however, because measurements were conducted on a weekly basis, the test of temporal precedence will pertain to week-by-week time-lagged effects only. This means that, potentially, temporal relations of higher resolution (e.g., day-by-day, hour-by-hour) that could explain mediation cannot be detected using this study design. Against this background, in this study, we do not regard a significant result from the test of temporal precedence to be a prerequisite for mediation.

Table 1. Overview of hypothesized mediators

Potential mediator	Hypothesis for Exp-CBT	Hypothesis for T-CBT
Avoidance behavior [a]	Yes, a reduction in the mediator is positively associated with reduction in fibromyalgia severity	Yes, a reduction in the mediator is positively associated with reduction in fibromyalgia severity
Catastrophizing	Yes, a reduction in the mediator is positively	Yes, a reduction in the mediator is positively

	associated with reduction in fibromyalgia severity	associated with reduction in fibromyalgia severity
Hypervigilance	Yes, a reduction in the mediator is positively associated with reduction in fibromyalgia severity	Exploratory only
Overdoing	Exploratory only	Yes, a reduction in the mediator is positively associated with reduction in fibromyalgia severity
Pacing	Exploratory only	Yes, an increase in the mediator is positively associated with reduction in fibromyalgia severity
Physical activity [b]	Yes, an increase in the mediator is positively associated with reduction in fibromyalgia severity	Yes, an increase in the mediator is positively associated with reduction in fibromyalgia severity

Exp-CBT: exposure-based cognitive behavior therapy; T-CBT: traditional cognitive behavior therapy.

[a] Because functional impairment is measured as part of the FIQ, and these items (1-11) could be argued to overlap with avoidance, a sensitivity analysis will be conducted using only those items of the FIQ that do not measure functional impairment.

[b] Will also be included in a multivariate model together with avoidance behavior, to control for the potential confounder that a mediating effect decreased avoidance can be explained by of increased physical activity.

Analytical framework

Initial inspection of variables
Baseline distributions, correlations, and development over time will be visually inspected with regard to all variables of interest.

Main mediation analysis
Because, in terms of mechanisms, we are primarily interested in the processes of Exp-CBT and T-CBT per se, as opposed to significant differences in processes between the treatments, the main analyses will be conducted within each group separately, i.e., the mediation analyses are strictly within-group analyses. For each treatment, we will test for mediation in a parallel process growth curve modelling framework. First, unconditional growth in the putative mediator and the outcome will be modelled separately, each with a random intercept and a random slope. Second, the role of the putative mediator as a predictor (not mediator) of change in the outcome will be tested by entering both variables in the same model and regressing the slope of the outcome on the random intercept of the putative mediator. Third, we will test for mediation based on bootstrapping. This is a test of the slope of the mediator (equivalent to the a-path, should time be conceptualized as independent variable of a traditional mediation model) multiplied by the effect of the mediator slope on the outcome slope (equivalent to the b-path, should time be conceptualized as the independent variable of a traditional mediation model).

Conditional indirect effects
Fourth, we will evaluate if the general level on the potential mediator (e.g., the general level of avoidance) is a moderator of mediation via the same variable (e.g., mediation via avoidance). In this step, we will test the indirect path from the random intercept of the potential mediator, to the slope of the potential mediator, to the slope in the outcome. This is not a test of moderation of the b-path (see above; [1]). Therefore, fifth, a moderating effect on the b-path will also be tested in a linear mixed model framework, where the outcome is regressed on the time-lagged potential mediator, the baseline value of the mediator, time, and all interactions. This will be a test of the baseline mediator × time-lagged mediator coefficient.

Week-by-week temporal ordering: random-intercepts cross-lagged panel models
The above analyses do not test whether change in the potential mediator systematically precedes change in the outcome. Therefore, for each treatment, we will test for temporal precedence using random-intercepts cross-lagged panel models.

Sensitivity analyses
As is specified above, two sensitivity analyses of the main test of mediation will be conducted with regard to avoidance behaviors. First, the analysis will be repeated without the use of functional impact items of the FIQ (item 1-11). Second, a multivariate model that includes physical activity will be fit to determine whether avoidance behavior has a specific effect beyond physical activity.

Secondary analyses

Pain intensity as a potential moderator of processes of change
In a previous trial, we found that the Brief Pain Inventory – Short form, severity subscale (BPI-SF) was a moderator of the effect of Exp-CBT versus a waitlist control. Though, in this trial, the BPI-SF was not a moderator of the between-group effect of Exp-CBT versus T-CBT, we intend to explore if BPI-SF is a moderator of the processes of change in Exp-CBT and T-CBT respectively. Therefore, the baseline BPI-SF value will be evaluated in a manner analogous to the intercept of the mediator in steps four and five above.

Count variables pertaining to treatment engagement in relation to the outcome
Three measures of treatment engagement were developed as count variables for this trial. In Exp-CBT, the number of conducted exposure exercises and mindfulness exercises were reported by the participants. In T-CBT, participants reported the number of conducted relaxation exercises. All were reported on a weekly basis. Overall correlations will be calculated between the total number of each respective treatment activity and the outcome (FIQ). Because we expect data to be non-normally distributed, Spearman correlations will be used. If model convergence can be achieved, these count variables will also be analyzed in cross-lagged panel models.

The item used for capturing work with exposure reads "*How many exposure exercises have you conducted during the last 7 days? If unsure, please try to estimate to the best of your ability*". Engagement with mindfulness exercises will be quantified by summarizing the responses on the following items: "*How many times have you conducted the exercise 'mindfulness through focus on breathing, the body and the surrounding environment', during the last 7 days? If unsure, please try to estimate to the best of your ability*"; "*How many times*

have you conducted the exercise 'everyday mindfulness', during the last 7 days? If unsure, please try to estimate to the best of your ability"; and "*How many times have you conducted the exercise 'mindfulness when experiencing symptoms', during the last 7 days? If unsure, please try to estimate to the best of your ability*". The item for capturing work with relaxation exercises reads "*How many times have you practiced relaxation during the last 7 days? If unsure, please try to estimate to the best of your ability*".

Avoidance as a potential mediator on catastrophizing and hypervigilance
In Exp-CBT, avoidance behavior will also be tested as a potential mediator of the effect on catastrophizing and hypervigilance.

References

1.   Muller D, Judd CM, Yzerbyt VY. When moderation is mediated and mediation is moderated. J Pers Soc Psychol. 2005;89(6):852-63. 10.1037/0022-3514.89.6.852