Contact: Developing New Clinical Management Strategies

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Statistical Analysis Plan

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Study Design

To examine the influence of visit frequency on antidepressant medication (ADM) and placebo response, we will conduct a prospective study, randomizing patients to Research Frequency Management (RFM, weekly study visits) vs. Community Frequency Management (CFM, monthly study visits), and double-blind escitalopram vs. placebo. The United States Principal Investigator (US PI) will be responsible for clinical trial operations at the Adult and Late Life Depression Research Clinic (ALLDRC), in the New York State Psychiatric Institute (NYSPI). One hundred and four participating patients will be equally randomized to the four treatment cells, stratifying for demographic, clinical, and attachment factors: RFM-escitalopram (n = 26), RFM-placebo (n = 26), CFM-escitalopram (n = 26), and CFM-placebo (n = 26). The primary experimental manipulation is visit frequency, which will be weekly in the RFM and monthly in the CFM group. This regime approximates practice in randomized control trials (RCTs) (RFM) and open clinical treatment (CFM), and it represents a balance between closely monitoring the patients, sufficiently differentiating the experimental groups, and generating results relevant to clinicians treating major depressive disorder (MDD) in the community both in Israel and the US (e.g., Stettin, Yao, Verbrugge, & Aubert, 2006).

Sample Size Calculation

The sample size was chosen to provide adequate power to test our hypotheses. The power calculation was based on effect sizes calculated using the meta-analyses by Posternak and Zimmerman (2007), and on previous studies by the applicants. *First hypothesis*. Based on Faul, Erdfelder, Lang, and Buchner, (2007), a minimum of 72 subjects is required to achieve a power of 0.8, using an error of 0.05 and an effect size of f = 0.15. *Second hypothesis*. To calculate the required sample size for the moderated mediation model, we used an approach based on Monte Carlo simulations, which produce more accurate results for power estimates than other methods when the sample size is relatively small (Zhang, 2014). The required sample size for significant moderated mediation was 99. Taking into account attrition (estimated from an RCT based on the same population, recruited from the same geographic area, conducted by Rutherford et al., 2013), the sample size was increased to 104. *Third hypothesis*. The required sample size was estimated using R code generated from the MLPowSim Software Package, applying 10,000 Monte Carlo simulations. Assuming alpha = 0.05 for pairwise interactions with the visit frequency, the simulations indicated a required sample size of 73 participants to ensure a power of at least 0.80. Subsequent exploratory analyses will include dose-effect analysis of visit frequency and the disentangling on the between- and within-patients effects of alliance on outcome (for more details, see Zilcha-Mano, 2017).

Aims and Objectives

The overarching objective of the present study is to explore the ingredients of the placebo effect, by offering and testing a theoretical model of a differential effect of visit frequency on treatment outcome in placebo vs. medication, mediated by the therapeutic alliance and supportive techniques. We propose to achieve this objective in three steps: (a) explore the differential effect of visit frequency on placebo vs. ADM response for patients with MDD; (b) examine the mechanisms underlying the expected effect, focusing on therapeutic alliance and the supportive techniques used in the sessions as potential mechanisms behind placebo and ADM response; and (c) identify MDD patient characteristics that moderate the effect of visit frequency on outcome.

Outcomes

On all accounts of data collection, the Israeli PI will examine all variables at all time points for illegitimate values, outliers, and inconsistencies. Analyses will be conducted on the intent-to-treat sample, with the therapist as a random effect.

Primary Outcome

First aim: Main outcomes. We will predict changes in HRSD as well as secondary outcomes across treatment as a function of visit frequency (0 = CFM, 1 = RFM) and medication (0 = placebo, 1 = escitalopram). Enrolled patients will be considered to have dropped out if they decide to discontinue participation in the study or if they miss a telephone assessment or clinic visit, and cannot be contacted afterwards. To fully adhere to the study visit schedule, RFM patients must attend all 9 in-person clinic visits, and CFM patients must attend the 3 in-person clinic visits, 6 phone interviews, and not have extra-protocol visits. Medication adherence will be measured for each patient as the self-reported number of pills taken over the 8 weeks. *Expected findings*: we expect a significant 2-way interaction, representing visit effects as a function of treatment on HRSD, demonstrating that increased visit frequency results in better outcome for patients assigned to placebo, while patients receiving medication will be less affected. Based on the literature, CFM will not be inferior to RFM in drop-out rates, medication adherence, and adverse events.

Secondary Outcomes

Second aim: Moderated-mediation model. Following Preacher and Hayes (2004), we will examine mediation in a series of three models. The first model will test the moderation effect of treatment on the association between the predictor (visit frequency) and the outcome (HRSD as well as secondary outcomes); the second model will test the associations between the predictor and the mediator (alliance,

evaluated by patients' and therapists' self-report and by trained coders, and the use of techniques, evaluated by trained coders on the two subscales); finally, the full mediated model will regress the outcome on the mediator, moderated by treatment effect and adjusted for the predictor-treatment interaction. We will explore whether adding another moderating path to the effect of visit frequency on the process mechanisms will improve the fit of the model. *Expected findings*: The potential mechanisms will partially mediate the effect of visit frequency on outcomes in placebo more than in ADM: the predictor will be associated with the mediator, the mediator will be significantly moderated by treatment (controlling for the predictor-treatment interaction), and the interaction between the predictor and treatment on outcome will be reduced after the interaction between the mediator and treatment is entered. A significant indirect effect is expected (using the Sobel test and the bootstrapping method). We predict that this mediation model shows a greater effect in the placebo than in the medication condition.

Other Pre-Specified Outcomes

Third aim: Identifying moderators. To test the potential moderators, we will examine the interactive influence of patients' demographics, clinical characteristics, and attachment orientations (anxiety and depression) on the effect of visit frequency on outcome. Each potential moderator will be examined using a 2-way interaction (visit frequency × moderator). A higher-level 3-way interaction (visit frequency × medication vs. placebo × moderator) will not be examined because according to the literature there is no strong basis to argue for a differential effect between placebo and medication in this moderation model. *Expected findings*: Increased attachment security and more severe symptoms will be associated with increased symptom change for patients in the RFM arm. We will repeat all analyses controlling for potential confounders previously identified in the literature (such as treatment expectancy).

Expected Results

First, we anticipate that increased visit frequency will contribute more to placebo response than to medication response. Such a finding will support our first hypothesis that increased visit frequency results in better outcome for the whole cohort, but this effect is stronger for patients assigned to placebo. Second, we anticipate that the effect of clinic visits on treatment outcome will be mediated by the proposed mechanisms (alliance and supportive techniques). Third, we expect to find variability in patients' ability to benefit from frequent visits, and that this variability can be predicted based on patients' pretreatment demographic and interpersonal characteristics. Thus, supporting the importance of optimizing psychopharmacologic management through personalized medicine, in which the number of visits is tailored to individual patient needs and characteristics.

Risk analysis and alternative paths. First, because one of the hypotheses may not be supported, each hypothesis was conceptualized as statistically independent and can be tested irrespective of the others (e.g., a significant differential effect of visit frequency on outcome in ADM vs. PBO is not mandatory for the mediation analyses; Preacher, Zyphur, & Zhang, 2010). If we fail to find a *general* differential effect of visit frequency on medication vs. placebo (Hypothesis 1) or a *general* moderation effect of visit frequency on outcome (Hypothesis 2), exploring a potential higher level 3-way interaction (visit frequency × medication vs. placebo × moderator) will help us understand for whom such effect of visit frequency on treatment condition (placebo, ADM) may exist and under what circumstances (for similar analyses, see Zilcha-Mano & Errázuriz, 2015, 2016). Interactions of each potential moderator with the dummy variable of treatment condition, with visit frequency, and with the lower-level effects will be included in the model. Given the large number of predictors in such analysis, its exploratory nature, and the relatively small sample size, we will adopt rigorous systematic machine learning approaches to subgroup analysis, as implemented by us previously (Zilcha-Mano, Roose, Barber, & Rutherford, 2017). Specifically, following Zilcha-Mano, Keefe, et al. (2016), we will apply decision tree analyses with the R package "party" (Hothorn, Hornik, & Zeileis, 2006), using random forest variable selection (Strobl, Malley, & Tutz, 2009) and Monte Carlo simulation for multiple testing adjustment (Strasser & Weber, 1999) (for the implementation of a similar procedure in ADM, see also Zilcha-Mano, Roose, Brown, & Rutherford, 2017). Second, it may be argued that rating supportive techniques is not feasible in clinical management sessions (e.g., low frequency in the use of techniques). The CSPRS, however, was specifically built for coding clinical management based on the exact manual used in the proposed study. Additionally, the adequacy of this rating system was evaluated in our research group. A pilot study (N = 43, 20 received medication and 23 placebo) based on audio tape coding of clinical management sessions using the same manual (Fawcett, 1987) taken from an RCT for MDD (Barber, Barret, Gallop, Rynn, & Rickels, 2012) indicated that in clinical case management, clinicians use many distinct types of supportive interventions (coded using the clinical management and facilitative conditions techniques of the CSPRS), with great variability between patients. Third, because the videotapes will originate from a different geographic and cultural area (NYC, US) than that of the coders (Haifa, Israel), this diversity may affect the quality of coding. In the last two years, material taped at a psychotherapy research lab in NYC, US, was coded in the Israeli PI's lab at the University of Haifa, Israel. All the coders except one (whose English was not adequate) produced high-quality coding, demonstrating high reliability with the group of NYC coders. Therefore, coders will be chosen not only based on the regular protocol but also taking into account their level of English and familiarity with cultural and social issues relevant to NYC. The experience of the last two years in the Israeli lab suggests that recruiting coders with adequate background is highly feasible. Fourth, as any method for studying the relationship with the therapist has strengths and

weaknesses, the use of multiple methods in the proposed study (both patient and therapist self-report, behavioral observations with each session coded by two independent coders) will compensate for any specific methodological weakness.

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