A Randomized Controlled Trial of PCIT-ED for Preschool Depression

NCT02076425

January 13, 2014

PCIT-ED Study Protocol

Parent Child Interaction Therapy Emotion Development (PCIT-ED) will be conducted with a sample of preschoolers who exhibit symptoms of depression compared to a wait list (WL) control after which participants will receive the active treatment. PCIT-ED is an expansion of PCIT, a well-known, widely used and proven effective treatment for preschool disruptive disorders. To address early disturbances of mood and affect, a novel ED module was added based on empirical data in emotion development. The ED module targets parent emotion learning skills with the goal of training the parent to serve as a more effective emotion teacher and coach to the child. The goal of the ED module is to enhance the child's capacity for emotion recognition and regulation or "emotional competence." In order to test the efficacy of PCIT-ED, to estimate accurate effect sizes and to investigate mediators and moderators of treatment response participants will complete comprehensive pre-, interval, and post-assessments.

SCREENING
Prior to screening potential participants, a research team member will obtain verbal consent (see 'Initial Phone Screen'). Once this is complete and the team member answers parents' questions, the PFC (if not already completed) and then Initial Phone/Exclusion Screen will be administered. If team member suspects possibility of an ASD, the SRS will be administered to the parent. If eligible based on PFC and Initial Phone/Exclusion Screen (and possibly SRS), another phone interview will be scheduled and the team will administer the MDD Phone/Inclusion Screen which will be audio recorded. Research staff will utilize Washington University's Research Electronic Data Capture (REDCap) to administer and record information from potential participants. When potential subjects screen-out based on not meeting MDD eligibility criteria, the research team will send the 'PCIT-ED RCT Screen-Out Follow-Up Letter' to inform them of the possibility of re-screening if the child's moods and behaviors worsen.

BASELINE, POST 1 and POST 2 ASSESSMENTS:
-TAKE HOME:
If eligible based on the MDD Phone Screen, parents will receive several forms (BRIEF, ERC, My Child, Emotion Understanding Parent Questionnaire, BIS/BAS, Contact Information, Teacher Contact Information) in the mail or if families have internet access via REDCap to complete before the laboratory assessment. This will take approximately 1 hour to complete. A copy of the Consent Form and Consent Letter will be included in this take-home packet (sent via mail or email). At the Post 1 & Post 2 assessments, parents will receive this packet/REDCap link (BRIEF, ERC, My Child, Emotion Understanding Parent Questionnaire) prior to the in-office assessment to complete on their own.

-IN-OFFICE:
Parent and child will complete the Parent Child Interaction - DPCIS as well as Teaching Tasks (marble maze, etch-a-sketch, and prohibited toys) at Baseline, Teaching Tasks (magnet puzzle, team drawing and prohibited toys) at Post 1 and Waiting Task at Post 2. The PCI will be video recorded and take approximately 45 minutes to complete.

Then, a research team member will assist the child in completing Handedness, Height & Weight measurement, FACE - Blurry Face & Emotion Labeling, KIDSEDF, Emotion Understanding, KBIT-2, Narratives, Dot Probe task, Narratives for Suicidal Ideation, and Death Interview. All these tasks will be video recorded and take approximately 1.5-2 hours.

The parent will independently complete the BDI, PFC-Scale, ECBI, CBCL, PSI, CCNES, GPSQ, PSDQ, and OC-YC Screener. Another research team member will work with the parent to complete the KSADS-EC, Breastfeeding Questions, LEC-Child, PECFAS/CAFAS, FIGS, HBQ Medical & Peer Relationships sections, Asthma Questionnaire, Religion in Subject Family, and SES measures; this portion will be audio recorded. FIGS will be used to obtain information about the parent reporter; when parents report symptoms or diagnosis of specific disorders, the appropriate screener/checklist will be administered [MDD, Mania, and Anxiety (GAD, OCD, Panic Disorder); Alcohol, Drugs, Psychosis]. Research staff will utilize Washington University's Research Electronic Data Capture (REDCap) to administer and record information from parent participants. Parents will complete the MSCEIT online via a secure website. They will also complete the Parent-Child Conflict Tactics Scales and the Parental Survey of Media Exposure or Media Quotient - A Questionnaire for Parents via REDCap survey. The parent assessment will take approximately 4-5 hours. Clinicians will complete the CGAS following the assessment. Any self-report measures not completed in office may be completed via REDCap or paper copies at home.

-TEACHER:
We will also ask parents to give permission to contact their child's teacher to complete a questionnaire regarding his/her behaviors and development. Teachers will receive the C-TRF/TRF in the mail or a REDCap link via email with a copy of the permission letter and brief description of the study/measure to be completed and returned via mail/electronically via REDCap.

After completing the Baseline assessment, if the participant child continues to meet DSM MDD criteria (adjusted for development) families will be randomly assigned to receive immediate treatment or be placed on an 18-week wait list after which they will receive treatment.

TREATMENT (Immediate Treatment Randomization: ~Week 1-18 or Wait List Randomization: ~Week 18-36) During the treatment, parent and child will work with a therapist at the Early Emotional Development Program each week for 18 weeks. Each session will last approximately 1 hour, although there are a few weeks when sessions will last approximately 1.5-2 hours. During these sessions, parent and child will work with a therapist to improve their relationship, learn safe and effective disciplinary techniques, as well as both learn strategies to deal with a range of emotions. (See attached Sessions Manual) The therapist will assign homework and activities on a weekly basis. Parents will complete the ECBI prior to each session. Therapists will complete the DPICS, EDCI, TIC, OC-YC Screener, and Acceptance Inventory throughout the course of treatment.

INTERVAL A, B, C & D ASSESSMENTS (~ Weeks 6, 12, 24, 30) Either over the phone, at the Early Emotional Development Program, or via REDCap, parents will complete the HBQ-P Peer & Medication section, CBCL, PFC-Scale, BDI, PSI, CCNES and TAI. This will take approximately 1-1.5 hours to complete.

DISCONTINUATION
If at any point in the study the family decides to discontinue their participation, the research team will ask the parent to complete an Exit Questionnaire and potentially the parent and child to complete the Post 1 or Post 2 assessment if families are willing to do so.

LONG TERM FOLLOW UP
After the completion of planned study visits (Baseline, Post 1, and Post 2 assessments), the research team will contact families via phone and/or email with the contact information they provided us. This will be done in order to ensure up-to-date contact information. The research team will update their contact information in the REDCap database for future follow-up studies with this population. Participants can let us know if they would no longer like to be contacted for future studies and we will note that in the REDCap database and cease contact.

PCIT-ED Statistical Analysis Plan

All measures will be collected at pre- and post-treatment assessments (except EI). In addition, the HBQ-P (measuring symptom severity of all Axis I disorders and impairment), PFC-Scale, parent BDI-II, PSI, EDCI (measuring ESL in both groups) and will be collected at the 6- and 12-week assessments in both groups. In the PCIT-ED group, these interval assessments correspond to completion of the CDI and PDI modules.

An intent-to-treat analytic approach will be employed. Multiple imputation will be utilized for subjects who discontinue during the study and do not complete the post-treatment assessment. Multiple imputation is desirable because instead of filling in a single value for each missing data point, each missing value is replaced with a set of plausible values, creating multiple imputed datasets. These datasets are then analyzed using standard procedures (that would be appropriate for a single, complete dataset), and results from the multiple data sets are combined into one set of results. The SAS procedures MI and MIANALYZE will be used for creating and analyzing multiple imputed data, resulting in statistically valid results that appropriately reflect the uncertainty due to missing values.

Multiple imputation is a useful method for analysis of datasets with data that are plausibly missing at random (MAR). Missing values rarely occur completely at random (MCAR). Instead, missing values are typically based on other variables, so they are MAR. During the multiple imputation process, the analyst should use all observed variables available in predicting missing values (even variables not used in analysis). If these variables are useful for predicting missing values, the multiple imputation increases power. Furthermore, by using an exhaustive set of predictor variables, the multiple imputation process creates a largely MAR dataset. Thus, multiple imputation can convert missing not at random (MNAR) data to MAR.

Simulation was used to determine sample size needed for analyzing multiple imputed datasets. We assume N=90 completers in each group, so a simulated dataset with N=180 subjects was created. Change in PAPA MDD severity sum scores were generated assuming normally distributed scores with a SD of 4.69 (pooled SD from our pilot RCT) and a mean difference in change scores in the two groups of 2.5. The demographic variables gender, age, race, family income, parental education level, and parental marital status were also included in this dataset. To simulate demographic characteristics, complete demographic profiles from the subjects in our pilot RCT were drawn with replacement 180 times and randomly assigned to the 180 simulated cases. A general linear model of change in PAPA MDD severity sum score by group was conducted for this simulated dataset.

To address differential dropout and its impact on power, we assume a 25% drop-out rate in the PCIT-ED group and a 30% drop-out rate in the WL group. So 25% and 30% of the simulated PCIT-ED and WL subjects' MDD severity sum change scores were set to missing, respectively, using a random number generator. Because the simulated missingness was random, missing values are not predicted by anything, so data are missing completely at random (MCAR). This should be realistic for the multiple imputation power analysis that follows.

The SAS v9.2 MI procedure was used to create multiple imputed datasets with MDD severity sum change scores based on the simulated demographic variables in the dataset. Multiple imputation was conducted 10 times, with 10 imputed datasets created. The SAS v9.2 MIANALYZE procedure was then used to run a general linear model of change scores by group for each set of multiple imputed datasets. Table 5 shows the results of the general linear model in the complete simulated dataset and then each of the 10 multiple imputed datasets.

Dataset	Estimate	SE	SE^2	t	p
Complete Simulated Dataset	-2.278	0.729	0.532	-3.12	0.0021
Multiple Imputed Dataset 1	-2.307	0.745	0.555	-3.10	0.0020
Multiple Imputed Dataset 2	-1.951	0.855	0.731	-2.28	0.0241
Multiple Imputed Dataset 3	-2.090	0.569	0.756	-2.40	0.0182
Multiple Imputed Dataset 4	-2.121	0.848	0.718	-2.50	0.0137
Multiple Imputed Dataset 5	-2.063	0.816	0.666	-2.53	0.0122
Multiple Imputed Dataset 6	-1.894	0.796	0.633	-2.38	0.0178
Multiple Imputed Dataset 7	-2.220	0.824	0.679	-2.69	0.0078
Multiple Imputed Dataset 8	-2.079	0.846	0.715	-2.46	0.0152
Multiple Imputed Dataset 9	-2.121	0.850	0.723	-2.49	0.0141
Multiple Imputed Dataset 10	-2.124	0.845	0.714	-2.51	0.0128
Mean	-2.097		0.689		
Variance	0.014				

Rubin's method for determining the uncertainty of the imputed estimate was employed. Following this method, the total variance from the imputed datasets is T = (mean within-imputation variance) + (1 + 1/(N sets of imputed datasets))*(between-imputations variance)

= 0.689 + 1.1*0.014 = 0.704. The SE^2 of the model conducted on the complete simulated dataset is 0.532. The ratio of these two values is 0.704/0.532 = 0.32.

So, the relative increase in variance due to missing values is 32%, indicating that 1.32*180 subjects = 238 subjects are required to attain the same power that would be attained in a sample of 180 subjects who all complete the study. In other words, 238 subjects must be enrolled in the study, with 180 completing, to achieve the same power when using multiple imputation as would be achieved if 180 subjects were enrolled and all completed. If multiple imputation were not used, and only complete cases were analyzed, approximately 238 subjects would have to be enrolled to produce 180 complete cases. Thus, multiple imputation is more efficient than complete-case analysis, in addition to avoiding bias due to MAR missingness.

A secondary analytic approach will be to use mixed models on non-imputed data. Mixed models can be used to analyze repeated measures data without discarding subjects with missing data. Mixed models will be used for measures only obtained at pre- and post-assessment and on measures with interval assessments. Analytic approaches for each set of specific aims and hypotheses are detailed below.

Specific Aim 1: To conduct an RCT of an early dyadic intervention for PO-MDD, PCIT-ED, compared to a WL control condition.

Hypothesis 1A: Compared to those randomized to the WL, preschoolers who are first randomized to PCIT-ED will show significantly increased rates of remission, greater reductions in MDD symptoms, and decreases in impairment.

Hypothesis 1B: Compared to those randomized to the WL, preschoolers who are first randomized to PCIT-ED will show significantly greater increases in emotional competence measured by the ability to accurately identify emotions in themselves and others and the ability to effectively regulate intense emotions.

Hypothesis 1C: Compared to those on the WL, parents who are first randomized to PCIT-ED will show significantly greater increases in emotion skill learning (ESL) and reductions in MDD symptoms and parenting stress.

Analytic Approach: Continuous post-assessment scores will be compared between PCIT-ED and WL groups using analysis of covariance, covarying for pre-assessment scores. The stratification variables, gender and externalizing comorbid diagnoses, will also be included as covariates in the models.

PFC-Scale and PAPA MDD severity sum scores will be used to assess differences in depressive symptoms; HBQ and PAPA impairment scores will be analyzed to determine differences in functional impairment. Differences in emotion regulation (as an executive function) in the two groups will be examined using scores from the BRIEF-P; emotion development will be analyzed using scores from the ERC, Emotion Understanding, FACE, KIDSEDF, and the "Waiting" and "Puzzle" tasks. Post-assessment EDCI, BDI-II, and PSI scores will be compared between PCIT-ED and WL groups to determine differences in increases in Emotion Skill Learning and reduction of parental depressive symptoms and parenting stress.

Rates of remission (defined by 50% reduction in MDD severity and not meeting diagnostic criteria) will be compared in the PCIT-ED and WL subjects using logistic regression.

Interval assessment scores will also be analyzed across PCIT-ED and WL groups in repeated measures mixed models. In these models, repeated measures of PFC-Scale, HBQ MDD and externalizing co-morbidity severity and impairment, PSI and ESL (measured by EDCI) at pre-assessment, 6-week assessment, 12-week assessment, and post-assessment will be compared between the PCIT-ED and WL groups.

In addition to the analyses described above, pre-assessment variables that could possibly be associated with outcome, such as subject age and maternal depression, will be investigated as potential predictors of outcome.

Specific Aim 2: To investigate mediators and moderators of treatment effects.

Hypothesis 2A: Parental emotion skill learning (ESL) will mediate treatment effects. Child depression outcomes will be mediated by parental ESL.

Hypothesis 2B: Parental Emotional Intelligence (EI, a stable trait measured at baseline by MSCEIT) will be a moderator of ESL and child outcome. Parents with higher EI will show better ESL, and as a result, children of parents with high EI will show better outcomes than children of parents with low EI.

Analytic Approach: Parental ESL will be measured with the Emotion Development Coding instrument. This is an itemized assessment of parents' emotion skill learning. Each item is rated as 3=satisfactory, 2=needs practice, or 1=not evident. The total ESL score will be calculated as the mean of these items.

To assess parental ESL as a potential mediator of the relationship between treatment group and child treatment response, a macro (for SAS or SPSS) developed by Hayes will be utilized. For mediation analyses, the PROCESS macro estimates path coefficients in a mediation model and generates bootstrap confidence intervals for the indirect effects of the independent variable on the dependent variable through a mediator variable. It is also possible to include covariates not proposed to be mediators in the model. Paternal ESL will be evaluated by entering post ESL score into the model as a potential mediator, with treatment group as the independent variable and change in PAPA MDD severity sum score as the dependent variable.

Power for Mediation: To estimate power for this mediation analysis, the following steps were taken. First, we expect the difference in MDD severity sum change score in the two groups to be approximately 2.5, with a SD of 4.69 (based on our pilot study). With 90 subjects per group, an alpha of 0.05, and a 1-sided test, power=0.97. Next, we expect the correlation of change in MDD severity sum score and ESL score to be approximately 0.25. Using Fisher's Z transformation with a sample size of 180, the correlation of 0.25 transforms to Z = tanh(0.25)*SQRT(180-3) = 3.398. Subtracting 1.96 gives 1.438, corresponding to power=0.92. Thus, we will be well-powered to detect a mediation effect.

To assess parental emotional intelligence (EI) as a potential moderator of treatment response, the PROCESS macro will be used. For moderation analyses, the PROCESS macro

estimates a moderation model with the effect of the independent variable on the dependent variable moderated by a proposed moderator variable. The independent variable (ESL score) and proposed moderator variable (pre-assessment parental EI) are centered to eliminate any multicollinearity effects. The macro generates the conditional effects of ESL score on the dependent variable (MDD severity sum score) at values of EI score equal to selected percentiles (e.g., 10^{th}, 25^{th}, 50^{th}, 75^{th}, and 90^{th} percentiles) of the distribution in the sample. The Johnson-Neyman technique will be used to identify the values of EI score at which point the effect of ESL score changes from statistically significant to statistically non-significant. If EI score is found to be a significant moderator, the independent and moderator variables (ESL score and pre-assessment EI score) will be dichotomized so that all subjects fall into 1 of 4 categories (low ESL with low parental EI, low ESL with high parental EI, high ESL with low parental EI, and high ESL with high parental EI). Post-hoc pair-wise comparisons of treatment outcome in these 4 groups will be conducted.

Power for Moderation: To estimate power for this moderation analysis, a simulated dataset of 90 PCIT-ED subjects was created. This dataset contained variables for parental ESL, parental EI, and change in MDD severity sum score. Random data was generated for 45 "high EI" subjects and 45 "low EI" subjects assuming normally distributed data for each of these variables, with SD's based on our pilot study (SD=0.22 for ESL, SD=15.6 for EI, SD=4.69 for MDD change score). The mean scores for the random normally distributed data varied in the two groups as we expect it to in the proposed study. For the "high EI" group, assumed means were 2.1 for ESL, 118 for EI, and -6.5 for MDD change. For the "low EI" group, assumed means were 2.5 for ESL, 99 for EI, and -1 for MDD change. Running the PROCESS macro on the simulated dataset yielded a significant interaction of ESL and EI, with a coefficient=0.2440 and SE=0.0758. Subtracting 1.96 from the corresponding t score (3.219) gave Z=1.259, which corresponds to power=0.90.

Specific Aim 3: To investigate whether reductions in depressive symptom severity and diagnostic remission is sustained 18 weeks after treatment has ended in those randomized to PCIT-ED first.

Hypothesis 3: MDD remission (not meeting diagnostic criteria for $\geq$ 2 weeks) will be sustained at the 18 week follow-up in 80% of subjects who were in remission at the post-treatment assessment.

Analytic Approach: Rate of 18 week remission in subjects who met remission requirements at the post assessment will be calculated and compared to the 80% expected rate using a Chi-square goodness-of-fit test.

General Data Analysis Considerations: All outcome measures other than MDD diagnosis are continuous. The PFC-Scale and MDD severity scores from our pilot PCIT-ED and DEPI subjects were approximately normally distributed, as determined by the Shapiro-Wilk test. However, if these scores or other outcome scores are found to be from non-normal distributions, the data will be log- or power-transformed prior to analysis. Bonferroni correction will be used to limit the possibility of Type I errors for the main outcomes. A less conservative correction, such as the Bonferroni-Holm correction, will be applied for tests of other outcomes.