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General Information

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Are external grants or funds being used to support this research?: No external grants or funds are being used to support this research.

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Certification

Certification: All information is complete; I (PI) am responsible for the research; data will not be used to support litigious/commercial aims.
Data Use Agreement Training: As the Principal Investigator of this study, I certify that I have completed the YODA Project Data Use Agreement Training

Associated Trial(s): NCT00250354 - The Safety And Efficacy Of Risperidone Versus Placebo In Conduct Disorder In Mild, Moderate And Borderline Mentally Retarded Children Aged 5 To 12 Years
NCT00266552 - The Safety And Efficacy Of Risperidone Versus Placebo In Conduct Disorder and Other Disruptive

Behavior Disorders In Mild, Moderate And Borderline Mentally Retarded Children Aged 5 To 12 Years
What type of data are you looking for?: Individual Participant-Level Data, which includes Full CSR and all supporting documentation

Research Proposal

Project Title

RISPERIDONE FOR CONDUCT PROBLEMS: DO IMPROVED INDICATORS OF EMOTIONAL DYSREGULATION MEDIATE IMPROVED BEHAVIORAL OUTCOMES?

Narrative Summary:
National medical care data show that the treatment of childhood-onset conduct disorder (CD) with risperidone has increased markedly in the past 10 years. Existing studies show risperidone to be inconsistent in treating CD, leaving uncertainty of how the drug improves CD. To date, no study accounts for the distinct emotional temperaments associated with CD, obscuring a potential source of these varied outcomes. By reanalyzing data from a randomized, placebo-controlled study, we will investigate if risperidone treats CD by improving functional impairments of one of these temperaments. Results may further our understanding of how risperidone benefits CD, and improve psychiatric care for youth.

Scientific Abstract:
Background. Previous randomized, placebo-controlled trials of risperidone for conduct disorder (CD) show the drug to yield significantly improved behavioral outcomes as well as a high rate of treatment non-responders. These trials ignore the two disparate emotional temperaments that developmental research shows to contribute to CD. In addition to key cognitive and behavioral differences between the emotionally dysregulated (ED) and callous unemotional (CU) temperaments of CD, there is also a potentially meaningful difference in their neurobiological underpinnings. While ED is thought to arise, in part, from an ontogenetic excess of serotonin, research on CU has shown normatively diminished levels of the neurotransmitter within cerebrospinal fluid samples. This difference aligns with risperidone's pharmacodynamics as a serotonin antagonist, and may suggest that the drug's differential effectiveness stems from a treatment mechanism of improving ED symptoms.

Objectives. To test if risperidone effectiveness for conduct problems is mediated by improved ED symptoms.

Study Design. Reanalysis of individual participant-level data (IPD) from two trials of risperidone for conduct problems. Data were collected using a 6-week randomized, double-blind, placebo-controlled, intent-to-treat design.

Participants. Males or females, < 18 years old, and receiving risperidone treatment for a diagnosis of CD or Disruptive Behavior Disorder – Not Otherwise Specified.

Main Outcome Measure(s). Nisonger Child Behavior Rating Form

Statistical Analyses. Latent Growth Curve Modeling

Brief Project Background and Statement of Project Significance:
The National Ambulatory Medical Care Survey shows that risperidone has become a popular outpatient treatment of childhood-onset Conduct Disorder (CD) over the past fifteen years (1). In that time research has shown risperidone to be inconsistently effective when used for this purpose, yielding both significant treatment effects and a high rate of non-responders (2,3,4). Research on the emotional temperaments that lead to CD may provide a potential explanation for this differential treatment response.

Developmental psychopathology research shows CD to comprise two disparate emotional temperaments, each with distinct neurobiological correlates. One temperament is typified by intense negative affect, heightened interpersonal sensitivity, reactive aggression, and an ontogenetic excess of serotonin (emotional dysregulation; ED). The other is defined by diminished affectivity, lack of empathy, proactive forms of aggression, and diminished serotonin levels (Callous and Unemotional Traits; CU). The validity of these CD temperaments has been noted within the scientific literature (3,5), leading to the codification of CU Traits within the DSM-V (6). Research contrasting the serotonergic profiles of ED and CU is particularly suggestive when considering risperidone's

inconsistency when treating CD. Current gene-environmental theory of ED suggests that the low-expressing variant of the monoamine oxidase A (MAOA) allele yields serotonin excess in neural circuitry vital to socio-cognitive functioning (7), predisposing youth to develop ED deficits and related CD behaviors when exposed to early childhood trauma (8,9). Conversely, cerebrospinal fluid samples from incarcerated adults have shown individuals exhibiting CU traits to possess significantly diminished serotonin levels (10,11,12). This serotonergic difference, and the purported role of excess serotonin in the ED temperament aligns with risperidone's pharmacodynamics as a primary serotonin antagonist (13,14). This provides a testable explanation for the inconsistent effectiveness found in previous risperidone-CD trials, and suggests that the drug may affect CD behaviors by treating the functional deficits of the ED temperament.

This project will investigate if risperidone-CD effectiveness is mediated by improved indicators of ED. Research in developmental psychopathology and child and adolescent psychiatry supports the validity of this objective, underscoring tangible benefits to the study and treatment of CD. Empirically, the proposed analyses amounts to the first test of a potential treatment mechanism underlying risperidone-CD effectiveness. This may directly inform future investigations of risperidone-CD effectiveness and incrementally expand science's understanding of CD etiology. Clinically, this project may raise ED symptoms as important markers of risperidone-CD effectiveness, thereby promoting the judicious use of this increasingly popular psychiatric practice.

Specific Aims of the Project:
This project seeks to understand the role that improved ED indicators play when risperidone is used to treat conduct problems. Below are three specific research objectives and their associated hypotheses:

1.) Over 6 weeks, does treatment of conduct problems with risperidone yield parent-reports of conduct problems (i.e., Nisonger Child Behavior Rating Form [NCBRF]- Conduct Problems) that are significantly improved when compared to placebo? Hypothesis: Yes

2.) Over 6 weeks, does treatment of conduct problems with risperidone yield parent-reported indicators of emotional dysregulation (i.e., NCBRF Anxious/Insecure; NCBRF Overly-sensitive) that are significantly improved when compared to placebo?
Hypothesis: Yes

3.) Over 6 weeks, does the treatment of conduct problems with risperidone yield improvements in parent-reported conduct problems that are significantly mediated by improvements in parent-reported indicators of emotional dysregulation?
Hypothesis: Yes

What is the purpose of the analysis being proposed? Please select all that apply. New research question to examine treatment effectiveness on secondary endpoints and/or within subgroup populations

Research Methods

Data Source and Inclusion/Exclusion Criteria to be used to define the patient sample for your study:
This project will utilize individual-level participant data from already completed clinical trials (ClinicalTrials.gov ID: NCT00250354; NCT00266552). To be included in this reanalysis, data will come from individuals who 1.) Were <18 years of age at the start of the study, 2.) Diagnosed with DSM-IV-TR Conduct Disorder or Disruptive Behavior Disorder – Not Otherwise Specified. 3.) Took at least one dose of trial medication and had at least one post-baseline assessment.

Main Outcome Measure and how it will be categorized/defined for your study:
Both targeted datasets include weekly data from the parent version of the Nisonger Child Behavior Rating Form (NCBRF), which is a 66-item rating scale that assesses parent's perceptions of their child's emotional and behavioral status. Previous studies show the NCBRF to be a valid and reliable measure (16), and it is frequently used as an outcome measure for psychopharmaceutical research (2,3,4). This project will use data from three NCBRF scales to measure the dependent variable (Conduct Problems) and indicators of the studied mediator variable (Emotional Dysregulation; ED).

Dependent Variable: Conduct problems (CP) will be defined as:

- Weekly parent ratings on the NCBRF-CP scale.

Mediator Variables: Indicators of emotional dysregulation (ED) will be defined as:
- Weekly parent ratings on the NCBRF Anxious/Insecure scale
- Weekly parent ratings on the NCBRF Overly-Sensitive scale.

Main Predictor/Independent Variable and how it will be categorized/defined for your study:
Independent Variables:
Within subject variable – Time: Defined as the change in NCBRF data across weekly observations
Between subject variable – Treatment group: Defined as the participants' randomization to the Risperidone group or Placebo group

Other Variables of Interest that will be used in your analysis and how they will be categorized/defined for your study:
N/A

Statistical Analysis Plan:
Latent growth curve modeling (LGM) within a structural equation modeling (SEM) framework will be used (17). In LGM, repeated measures (Weekly NCBRF data) are used to indicate an individual's underlying trajectory ("latent growth curve") on 1 or more variables. Growth curves are defined by "growth factors" (i.e., Latent Intercept - Baseline NCBRF level; Latent Slope - Rate of NCBRF change from Baseline to Week 6). Estimates of the mean and variance for the sample's growth factors and covariates are used to predict individual growth factors. As such, LGM can examine how the rates of change in multiple longitudinal variables relate to each other, allowing for mediation tests. Model fitness for all models will be tested using the model chi-square test statistic and two fit indices: Root Mean Squared Error of Approximation (RMSEA) and Comparative Fit Index (CFI; 17). Below, specific LGM procedures are described by research question:

Questions 1 & 2: An unconditional growth model (i.e., no predictors) will be fit for weekly CP scale and ED indicator scales to determine the ideal fit for the data's growth trajectory for the whole sample. Follow up conditional model will test if treatment group significantly moderates the growth factors of CP scale and ED indicator scales.

Question 3: A final model will test if the slopes of either ED indicator mediates the relationship between treatment group and the slope of CP scale across the 7 weekly observations (Baseline to Week 6). Significance of mediated effects will be determined using asymmetric 95% confidence intervals obtained with the bias-corrected bootstrap procedure (18, 19).

Project Timeline:
Note: Timeline dates are subject to YODA's timeline for standard review process (and when data would become available).

Project Start Date: January 19, 2014

Analysis Completion Date: March 1, 2015. This estimate is based upon the anticipation that data will need to be cleaned, scaled, and recoded before proposed analyses could take place. This estimate could come down if these steps are unnecessary.

Manuscript Drafted: April 19, 2015. Literature review and method sections have been completed for this project, expediting this portion of the manuscript.

Submitted for Publication: May 1, 2015

Results Reported to YODA: May 1, 2015. Once a manuscript is drafted, project staff will submit a copy of the abstract and manuscript to the YODA Team to be reviewed and shared with the Data Holder.

Total Estimated Project Duration: 3.5 months

Dissemination Plan:
Presently, no clinical trials of risperidone for CD have analyzed effectiveness in manner that is sensitive to the ED/CU temperaments borne out of the developmental psychopathology literature. This project would be the first to

do this, making it an important contribution to the field of pediatric psychopharmacology. As such, target audiences for this work include scientists and practitioners who study and treat CD. To reach these audiences, we propose disseminating the results of this study in one of a variety of suitable biomedical journals, including:

• Journal of the American Academy of Child and Adolescent Psychiatry
• Journal of Child & Adolescent Psychopharmacology
• Psychopharmacology
• Journal of Clinical Psychopharmacology
• Archives of General Psychiatry
• Journal of Child Psychology & Psychiatry
• CNS Drugs

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