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TITLE: **Behavior Therapy for Irritability and Aggression in Adolescents with Autism**

PRINCIPAL INVESTIGATOR: **Denis Sukhodolsky**

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14. ABSTRACT

Approximately 50 percent of children with Autism Spectrum Disorder (ASD) exhibit irritability and disruptive behaviors such as tantrums, noncompliance, and aggression. If present in childhood, aggression tends to persist into adolescence and adulthood and contribute to disability over and above the core ASD symptoms. The purpose of this study is to investigate the clinical efficacy of a novel intervention, Behavior Therapy for Irritability in Adolescents with ASD (BTIA). Specifically, this is a 4-year, randomized controlled trial of BTIA vs. Psychoeducation and Supportive Therapy (PST) control condition in adolescents, ages 12 to 18, with ASD and significant levels of disruptive behavior. During the first year of the project period, the study was successfully launched, and it is currently conducted in accordance with the study protocol.

15. SUBJECT TERMS Autism Spectrum Disorder; Adolescents; Irritability; Disruptive Behavior; Treatment; Cognitive-Behavior Therapy; Behavior Therapy for Irritability in Adolescents; Randomized Controlled Trial

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1. INTRODUCTION

This is a 4-year randomized controlled trial of Behavior Therapy for Irritability (BTIA) in 12 to 18-year-old adolescents with autism spectrum disorder. There are four primary goals in this study. Goal 1 is to evaluate the efficacy of BTIA vs. Psychoeducation and Supportive Therapy (PST) for reduction of irritability and disruptive behavior in adolescents with ASD in a randomized controlled trial. Goal 2 is to test the effects of BTIA on adaptive behavior using the Vineland Adaptive Behavior Scales-3 edition (Vineland-3) administered at baseline, endpoint, and 6-month follow-up. Goal 3 is to test durability of treatment gains over a 6-month follow-up period. And goal 4 is to explore the moderating effects of subject demographic and clinical characteristics at baseline on response to BTIA vs PST. BTIA consists of 15 ninety-minute weekly sessions that are delivered by behavioral therapists using a detailed manual that targets both common and ASD-specific mechanisms of irritability. It includes structured, illustrated activities for teaching emotion regulation and problem-solving skills to the adolescent; a functional assessment to identify unique triggers of disruptive behavior; and a parent component that teaches antecedent management and reward strategies. PST is used as a control condition because during adolescence, many individuals with ASD may become more acutely aware of their differences from peers and may benefit from psychological support. PST also consists of 15 weekly sessions and will be conducted by experienced therapists using a structured manual. Regarding potential clinical impact of this study, irritability and disruptive behavior are common in children and adolescents with ASD, tend to persist into adulthood, and contribute to disability over and above the core ASD symptoms. There is also a major gap in treatments for adolescents on the autism spectrum. This study is conducted to evaluate the clinical effects of a novel intervention, Behavior Therapy for Irritability in adolescents with ASD (BTIA). If proven effective, BTIA will provide a useful treatment option for adolescents with ASD complicated by behavioral problems.

2. KEYWORDS

Autism Spectrum Disorder; Adolescents; Irritability; Disruptive Behavior; Treatment; Cognitive-Behavior Therapy; Behavior Therapy for Irritability in Adolescents; Randomized Controlled Trial

3. ACCOMPLISHMENTS

What were the major goals of the project?

The major goals of the project during the first year were accomplished in accordance with the approved SOW and included the following tasks: 1) Obtaining human subjects review and approvals; 2) Preparing to launch the study; 3) Conducting subject recruitment; 4) Conducting study assessments; 5) Delivery of study interventions; and 6) Conducing data and safety monitoring.

What was accomplished under these goals?

The first task of the project included obtaining initial approvals by the Yale Institutional Review Board (IRB) and by the U.S. Army Medical Research and Development Command (USAMRDC), Office of Research Protections (ORP), Human Research Protection Office (HRPO). The protocol was approved on 3 September 2020 by the USAMRDC ORP HRPO. The Yale IRB and the USAMRDC ORP HRPO also conducted continuing reviews of this protocol on 31 January 2021.

Task 2, preparing to launch the study, has been accomplished. We have assembled assessment and treatment materials, trained personnel, and randomized four subjects who are currently receiving study interventions. Of note, all study procedures have been updated in compliance with the Yale School of Medicine COVID-19 safety requirements including face covering and social distancing during assessments of autism that have to be conducted in person. We also developed online assessments for clinical interviews that can be conducted remotely, by telehealth, and these will be conducted by the Yale approved and HIPAA compliant Zoom platform.

Task 3, subject recruitment. Six subjects have been consented and four meet inclusion and were randomized. Of the two subjects who were not randomized, one declined participation and the second subject did not meet

inclusion criterion for presence of irritability symptoms. As of this writing, two subjects are also scheduled for their baseline evaluation, and we are optimistic that they will meet study inclusion criteria and will be randomized.

As we noted in our quarterly progress reports, the recruitment efforts have been slowed down, unfortunately, by the realities of the COVID-19 pandemic. Most of our recruitment procedures had to be modified from in-person and paper-and-pencil formats to email, media, and online formats. We maintain both the Sukhodolsky lab website on the Yale School of Medicine platform and the Sukhodolsky Lab Facebook page with current and regularly updated information about the study. We also recently created a lab Twitter and Instagram account to expand our recruitment outreach to all social media platforms. The study is also advertised in the monthly online issues of Connecticut Parent magazine, the biweekly Connecticut Parent e-newsletter, and on the websites of local autism associations. We also carry out regular mailouts to local pediatricians, schools, mental health providers, and community centers.

Furthermore, Dr. Sukhodolsky maintains regular contact with the Autism Services and Resources Center of Connecticut, including participation in the annual conference in November 2020, which was virtual this year. In addition, in May 2021, the Yale Child Study Center sponsored a booth at the Annual Autism Walk that displayed study flyers and brochures that was attended by several hundred people. In July 2021, the Yale Autism Program hosted an outreach event for families at the Connecticut comics book convention. We also have scheduled outreach events including Dr. Sukhodolsky's presentations at the Connecticut Association of School Based Health Centers in October 2021 and at the annual ASRC conference in November 2021.

Task 4, conducting study assessments. The study's clinical characterization and outcome assessment visits are conducted by a team of highly trained clinicians who are supervised by Dr. Sukhodolsky. There are two 3-hour pre-treatment assessment visits for clinical characterization of ASD, co-occurring psychiatric disorder, IQ, language, and adaptive functioning. Repeated clinical outcome measures of irritability are collected at baseline, mid-point, endpoint and six-month follow up and are conducted by an independent evaluator ("blinded rater"), Mrs. Heidi Grantz, who is not involved in any aspects of treatment delivery in order to protect her blind. Scheduling and running assessment visits on a pre-determined timeline are key to successful administration of any clinical trial. During this year, Ms. Rebecca Jordan has served as a primary study coordinator and we have also successfully recruited and trained a new study coordinator, Ms. Julia Zhong, who will serve as the study coordinator next year. Ms. Jordan and Ms. Zhong have a challenging task of coordinating multi-team assessment efforts and they both have been remarkably effective in this role.

Task 5, delivery of study interventions. The study currently includes three behavioral therapists (Karim Ibrahim, Carla Kalvin, and Abigail Reed) who have been trained by Dr. Sukhodolsky to conduct both study interventions (BTIA and PST) reliably and in accordance with detailed manuals. We are also in the process of training additional therapists to allow us the flexibility to offer families evening appointments. All four randomized subjects are currently receiving study therapy (two subjects were randomized to BTIA and two to PST). Study therapists and Dr. Sukhodolsky have weekly, one-hour supervision meetings dedicated to discussing therapy progress, adherence to treatment manuals, and troubleshooting clinically relevant issues that might be brought up by study participants. All BTIA and PST sessions are videotaped and reviewed for adherence to treatment protocols. There were no unexpected, serious adverse events in this study.

Task 6, conducing data and safety monitoring. Dr. Sukhodolsky carries out clinical monitoring of the study to ensure compliance with the protocol; good clinical practice guidelines; federal, state, and local regulations and institutional policies and procedures; that data are of high quality and integrity; and that the facilities and staffing are adequate for continued study participation.

What opportunities for training and professional development has the project provided?

All postbaccalaureate and postdoctoral trainees at Yale University are required to create an individual development plan (IDP) and to provide annual progress reports for review by, and discussion with, the faculty mentor. Progress reports are then submitted to the Yale Office of Postdoctoral Affairs as a condition of the trainee's reappointment by this Office. All graduate students in the Combined Program in the Biological and Biomedical Sciences as well as all other graduate students supported by federal awards at Yale University are required to create an individual development plan. Students provide updates on their IDP activities as a part of their annual thesis committee meetings, and documentation is retained by the students' graduate programs.

How were the results disseminated to communities of interest?

Denis Sukhodolsky and his lab regularly present at national and local meetings on the topic of treatment of irritability and disruptive behavior in children on the autism spectrum, including:

National Conference Presentations

2021 Presentation, the 20th annual conference of the International Society for Autism Research (INSAR), Virtual meeting. *Neural mechanisms of emotion regulation in children with ASD*.

2020 Presentation, the 54th annual convention of the Association for Behavioral and Cognitive Therapies (ABCT), Virtual Convention. *Adaptive functioning in children with ASD complicated by anxiety and aggressive behavior.* (Poster with lab members: Jordan, Kalvin, Rowley, and Ibrahim).

2020 Presentation, the 54th annual convention of the Association for Behavioral and Cognitive Therapies (ABCT), Virtual Convention. *Tantrum tool: Using digital parent training with videoconferencing to improve access to treatment for pediatric irritability.* (Poster with lab members: Rowley, Diaz Stransky, and Grodberg).

Yale University Lectures

2020 Grand Rounds, Yale Child Study Center, *CBT for pediatric irritability: From efficacy and biomarkers to personalized interventions.*

2020 Lecture, Dr. Charles Carl Conference sponsored by the Yale CSC Center for American Indian Health and The Native Services Branch of the Boys & Girls Club of America. *Promoting on-task, positive behavior in Boys & Girls Clubs*. (Presented with Yann Poncin and Mary Gunsalus).

2020 Lecture, Yale Child Study Center, T32 training program, *Experimental therapeutics and biomarkers in evidence-based psychosocial interventions for neurodevelopmental disorders.*

Local Workshops and Presentations

2021 Lecture. *Pediatric irritability: assessment and behavioral interventions.* Academics West, New York, NY.

2020 Presentation. *Helping children on the autism spectrum and their families to cope with anxiety and challenging behavior.* Meet the expert series of the Autism Services and Resources Center of Connecticut (ASRC), Wallingford, CT.

2020 Presentation. *Treatment of anxiety and disruptive behavior in children and adolescents with autism.* Annual meeting of the Autism Services and Resources Center of Connecticut (ASRC), Wallingford, CT.

What do you plan to do during the next reporting period to accomplish the goals?

This is a 4-year project. We will continue to run the study in accordance with the study protocol. The key activities of the next, 2nd year will include subject recruitment, clinical characterization assessment, treatment delivery, and collection of clinical outcome data.

4. IMPACT

Nothing to report

5. CHANGES/PROBLEMS

Actual or anticipated problems or delays and actions or plans to resolve them:

Our recruitment efforts have been slower than anticipated, unfortunately, by the realities of the Covid-19 pandemic. Human subjects research has been slow across all studies at the Yale Child Study Center. We are optimistic that we will be able to increase our enrollment as the rates of COVID decline and that recruitment for clinical trials such as our study of behavior therapy for irritability will return to the pre-pandemic level.

In order to increase study enrollment, we continue to ramp up recruitment efforts based on the experiences we have had thus far while recruiting during the COVID-19 pandemic. We maintain active online outreach via Facebook Twitter, and Instagram posts, the Sukhodolsky lab website, and ads in the online edition of Connecticut Parent magazine as well as emails to local schools, pediatricians, and community centers. We continue to develop ways of having our digital posts reach the most accurately targeted audience of parents within our catchment area who have children in the age range required by the study. As noted above, we were able to have two in-person outreach events this summer and we are optimistic that other in-person events such as presentations at local schools, community clinics, and parent advocacy groups will become available in the near future. For context, in the two years preceding COVID-19 pandemic, we have taken part in more than 20 local resource fairs and given more than 15 talks at community outreach events

Additionally, we increased the number of email contacts and mailouts to the local, non-Yale-affiliated mental health providers, pediatricians, principals, and special education coordinators with information about the study and ask them to pass along our information to families they think might be a good fit. Referral from other clinicians within the Yale Child Study Center, in particular, has been a very large source of study participants in the past. We will continue to make sure that these clinicians are aware of our study and have our recruitment materials on hand to pass the information about the study along to interested families.

Changes that had a significant impact on expenditures

We reduced personnel effort in Year 1 to reflect slow recruitment due to the COVID-19 pandemic in the hope that we can carry-over the balance to the later study periods when we are able to increase subject recruitment.

6. PRODUCTS

Nothing to Report

7. PARTICIPANTS & OTHER COLLABORATING ORGANZATIONS

What individuals have worked on the project?

Name: **Denis Sukhodolsky. Ph.D.**
Project Role: PI
Researcher Identifier (ORCID ID): 0000-0002-5401-792X
Nearest person month worked: 3
Contribution to Project: Dr. Sukhodolsky oversees all aspects of the proposed study, including assurance of regulatory compliance and communication with the funding organization, as well as subject recruitment, clinical characterization. He also provides training and supervision on study interventions to study therapists.

Name: **Rebecca Jordan, B.A.**
Project Role: Study Coordinator
Researcher Identifier (ORCID ID): 0000-0002-6334-8552
Nearest person month worked: 3
Contribution to Project: Ms. Jordan coordinated recruitment efforts, scheduling assessment visits, and guiding children and their families through characterization and outcome assessments. She prepared all study assessment materials and launched digital outreach efforts.

Name: **Julia Zhong, B.S.**
Project Role: Study Coordinator
Researcher Identifier (ORCID ID): 0000-0002-1809-0572
Nearest person month worked: 1
Contribution to Project: Ms. Zhong joined Denis Sukhodolsky lab in July 2021, and she has assumed primary responsibilities of the study coordinator. During the past two month she has been trained by Dr. Sukhodolsky and Ms. Jordan on the study tasks and responsibilities.

Name: **Karim Ibrahim, Psy.D.**
Project Role: Clinical psychologist
Researcher Identifier (ORCID ID): 0000-0002-5401-792X
Nearest person month worked: 3
Contribution to Project: Dr. Ibrahim conducts structured assessments of autism, and he is available to deliver behavior therapy for irritability. During the first year of the study, he worked with Dr. Sukhodolsky and Ms. Jordan to assemble study assessment and intervention manuals and launching the study. He also participates in weekly clinical supervision meetings.

Name: **Carla Kalvin, Ph.D.**
Project Role: Clinical psychologist
Researcher Identifier (ORCID ID): 0000-0002-5775-0131
Nearest person month worked: 3
Contribution to Project: Dr. Kalvin conducts structured assessments of psychiatric disorders that may co-occur with autism, and she delivers study interventions. She worked closely with Dr. Sukhodolsky to assemble study intervention manuals and she also participates in weekly supervision meetings.
Funding Support: Dr. Kalvin has been supported by the T32 training grant MH18268.

Name: **Abigail Reed, M.A.**
Project Role: Behavior therapist
Researcher Identifier (ORCID ID): 0000-0002-2768-2158
Nearest person month worked: 1
Contribution to Project: Ms. Reed has been trained to deliver study interventions in accordance with the treatment manuals and she is now available to provide behavior therapy to study participants. She also participates in weekly supervision meetings and in the weekly research meetings of the study team.

Name: **Heidi Grantz, M.S.W.**
Project Role: Independent evaluator
Researcher Identifier (ORCID ID): 0000-0002-5401-792X
Nearest person month worked: 1
Contribution to Project: Mrs. Grantz conducts structured diagnostic interviews at baseline and administers clinical outcome measures including at all assessment points. She also participates in the weekly meetings of the study team.

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

Nothing to report

What other organizations were involved as partners?

Nothing to report

8. Special Reporting Requirements

N/A

9. Appendices

None