

AWARD NUMBER: **W81XWH-20-1-0718**

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

PRINCIPAL INVESTIGATOR: **Denis Sukhodolsky**

CONTRACTING ORGANIZATION: **Yale University, New Haven, CT**

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<b>14. ABSTRACT</b>  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 19, with ASD and significant levels of disruptive behavior. During the second year of the project period, the study was successfully continued and it is currently conducted in accordance with the study protocol.					
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## TABLE OF CONTENTS

	<u>Page</u>
1. Introduction	4
2. Keywords	4
3. Accomplishments	4
4. Impact	7
5. Changes/Problems	7
6. Products	7
7. Participants & Other Collaborating Organizations	7
8. Special Reporting Requirements	9
9. Appendices	9

## 1. INTRODUCTION

This is a 4-year randomized controlled trial of Behavior Therapy for Irritability (BTIA) in 12 to 19-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 second year were accomplished in accordance with the approved SOW and included the following tasks: 1) Maintaining human subjects review and approvals; 2) Conducting community outreach and subject recruitment; 3) Conducting subject characterization and treatment-outcome study assessments; 4) Delivery of study interventions; and 5) Carrying out data and safety monitoring.

### What was accomplished under these goals?

Task 1, maintaining IRB approvals This protocol is approved 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). During the second year of the study, the Yale IRB has approved our amendment to increase the upper age-range for this study from 18 to 19 year on October 18, 2022, and to include a subject with autism complicated by language impairment on April 27, 2022. The Yale IRB also conducted continuing review and re-approved this protocol on January 6, 2022, and the USAMRDC ORP HRPO also conducted continuing review and reapproval of this protocol January 6, 2022.

Task 2, community outreach and subject recruitment. During this year, 25 subjects have been consented and 21 meet inclusion and were randomized. Of the four subjects who were not randomized, three declined participation due to scheduling consideration and one subject did not meet inclusion criterion for presence of irritability symptoms.

In the past year, we have continued active community outreach and recruitment efforts. From September 1, 2021 to August 31, 2022, we attended a total of 6 resource fairs to engage with stakeholders; gave 4 presentations and talks to community members; completed 7 mailouts to various stakeholder or community

organizations and individuals (including local schools, mental health professionals, and recreation/community centers); promoted our recruitment material through various forms of social media including Facebook, Instagram, and Twitter; and partnered with community organizations like ASRC and stakeholder groups like autism parent support groups to post our recruitment materials. Our recruitment numbers reflect this expanded recruitment outreach from this past year, with a 450% increase of phone calls inquiring about the study.

To expand our recruitment efforts to underserved populations within CT, we compiled a list of 68 local community, family, and recreation centers and emailed and mailed out flyers and brochures. Community centers included those within majority-Black and Latinx populations (i.e., The Hispanic Coalition, Burroughs Community Center), youth centers and organizations (i.e., Higher Heights Youth Empowerment Programs, Inc., Boys & Girls Club), religious and ethnic community centers (i.e., Bridgeport Islamic Community Center, Pontelandolfo Community Club), family organizations (i.e., Women and Family Life Center), and local sports and recreation centers (JCC, YMCAs, and Parks and Recreation departments).

Other recruitment efforts have included tabling at various community events, including the annual Connecticut Autism Speaks walk on 10/10/2021, and Autism Services & Resources Connecticut (ASRC)'s Benhaven Walk on 9/26/2021. Our recruitment flyer has also been featured on ASRC's fall newsletter and on our social media platforms, including Facebook, Instagram, and Twitter. To increase views of our study flyer on social media, we have also boosted our recruitment post with Facebook ads. Lastly, we have also physically posted recruitment flyers on bulletin boards of local grocery stores in New Haven and surrounding areas. Starting in the Spring of 2022 we have expanded our recruitment efforts to include attendance at both remote and in-person fairs and events. Our lab participated as an exhibitor for the Autism Connection's 2022 online Autism Conference on April 29; as an exhibitor, our lab had a virtual "booth" in an exhibitor hall that attendees could click and view our study information, our study information in the program booklet that all attendees received, and two live chat sessions in which attendees could speak directly with our study coordinators to learn more about our study. We also participated in the in-person Fairfield Special Education PTA (SEPTA)'s 2022 Special Needs Provider and Resource Fair on May 7, where we tabled and shared our study flyers with local families and other service providers. We also co-sponsored and attended the Autism Services & Resources Connecticut (ASRC)'s Connecticut Walk for Autism 2022 on May 22. As a co-sponsor, ASRC provided us with a booth at the exhibitor showcase at the walk, in which approximately 100 people stopped by our table and half of them took study flyers. Additionally, ASRC mailed out postcards with our recruitment flyer to their listserv of 13-14,000 people and featuring our lab for a Facebook live talk in June. Other in-person recruitment events included tabling at the STEM Career Showcase at the Connecticut Science Center on June 3, which will target 300 middle and high school students. We are also scheduled to participate in the Autism Speaks Westchester Greater Hudson Valley Walk on October 2; and co-sponsoring the Connecticut Association of School Based Health Centers' Fair on November 8.

Finally, we have also connected with various community clinicians and organizations through social media and mailouts. This year, we conducted a mail-out to 352 pediatricians and child mental health professionals in Connecticut that included a packet of our IRB approved recruitment materials (a letter informing about the study along with flyers brochures that can be displayed in their offices. And the second large mail-out to 125 CT public and private middle and high school principals, school psychologists, social workers, and director of pupil or special education services in September and October. A total of 474 school professionals received a personalized envelope with a letter, flyer, and brochure of our study. Throughout mid-February, we completed a mailout to 115 Connecticut-based child psychiatrists; each individual received a personalized envelope with a letter informing them of the study, a flyer, and brochure to be advertised in their office. We also maintained an online presence through monthly, targeted Facebook ads in February, April, and May 2022. Furthermore, we reached out via email to Connecticut parent support groups such as *Welcome to My World Autism* and the *HF Autism & Developmental Delays Support Group*, and national organizations like the Autism Research Institute and Connecticut Psychiatrist Society.

Task 3, 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. Julia Zhong, has served as the study coordinator. We have also hired a new research assistant, Ms. Megan Rutten, who has been trained on all study procedures and will be available as a backup for Ms. Zhong as needed.

Task 4, delivery of study interventions. Of the total number of 25 randomized subject to-date, 15 have completed all study interventions and 10 are currently receiving therapy. 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 have also trained a new study therapist, Mr. Joshua Snyder, who has completed all didactic training procedures and served as a co-therapist with Drs. Kalvin and Ibrahim during this year. He will be able to carry his own study therapy cases next year under supervision of Dr. Sukhodolsky. This process of training additional therapists 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 5, conducting 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:

- 2022 Lecture, *Irritability and anxiety in adolescents on the autism spectrum*, Autism Summer Institute, Child Study Center, Yale School of Medicine, New Haven, CT, (July 28, 2022).
- 2022 Lecture, *Helping children on the autism spectrum build emotional resilience*, Cape Cod Autism Lecture Series, Riverview School, East Sandwich, MA, (July 19, 2022).
- 2022 Presentation, *Co-occurring disorders in children with autism, helping children cope with irritability and anxiety*. Autism Services and Resources Center of Connecticut (ASRC), Wallingford, CT, (Facebook Live Event, July 6, 2022).
- 2022 Lecture, Center of Excellence for Teaching and Learning, Southern Connecticut State University, *Mindfulness tools for teachers and learners: Neuroscience informed strategies for emotional resilience*. (Presented with Michael Crowley), March 31, 2022.
- 2022 Lecture, *Irritability and behavioral difficulties in adolescents on the autism spectrum*. Clifford Beers children's mental health clinic, Hamden, CT. (presented with trainee Suparna Kailash) April 15, 2022.
- 2021 Presentation, the 55<sup>th</sup> annual convention of the Association for Behavioral and Cognitive Therapies (ABCT), Virtual Convention. *Aggressive behavior is associated with reduced social adaptive functioning*

*in children with autism and anxiety.* (Presented with lab members: Calvin, Jordan, Rowley, and Ibrahim).

- 2021 Presentation, the 55<sup>th</sup> annual convention of the Association for Behavioral and Cognitive Therapies (ABCT), Virtual Convention. *Atypical neural mechanisms of emotion regulation in children with ASD and co-occurring anxiety disorders.* (Presented with lab members: Calvin, Jordan, Ibrahim, and Tseng).
- 2021 Presentation, the 55<sup>th</sup> annual convention of the Association for Behavioral and Cognitive Therapies (ABCT), Virtual Convention. *Amygdala-prefrontal connectivity in children with autism spectrum disorder and co-occurring anxiety and disruptive behavior.* (Presented with lab members: Ibrahim, Rowley, Jordan, and McCarthy).
- 2021 Workshop, Connecticut Association of School Based Health Centers. *Irritability and Anger: Helping Children Manage Emotions*, Southbury, CT, October 22, 2021.

### **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, 3<sup>d</sup> 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 in year 1 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. During the 2<sup>nd</sup> year, we have been able to maintain high levels of community outreach that resulted in sharp increase of subjects enrollment. We are optimistic that we will be able to meet our enrollment goals 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.

#### **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:	<b>Denis Sukhodolsky. Ph.D.</b>
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: **Julia Zhong, B.S.**  
Project Role: Study Coordinator  
Researcher Identifier (ORCID ID): 0000-0002-1809-0572  
Nearest person month worked: 3  
Contribution to Project: Ms. Zhong coordinated recruitment efforts, scheduling assessment visits, and guiding children and their families through characterization and outcome assessments. She prepares all study assessment materials and outreach efforts.

Name: **Megan Rutten**  
Project Role: Study Coordinator  
Researcher Identifier (ORCID ID): 0000-0002-3104-2508  
Nearest person month worked: 1  
Contribution to Project: Ms. Rutten joined Denis Sukhodolsky lab in July 2021, and she has been trained on all study procedures to serve as a backup for Ms. Zhong when needed.

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 second year of the study, he worked with Dr. Sukhodolsky and the study team to assure completeness all phenotyping assessments and he also carrying study therapy cases and participates in training new therapists. 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 assure fidelity of treatment implementation and she also participates in weekly supervision meetings.

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 during the first year of the study in accordance with the treatment manuals and during the second year she has provide behavior therapy to study participants. She also participates in weekly supervision meetings and in the weekly research meetings of the study team.

Name: **Joshua Snyder, M.A.**  
Project Role: Behavior therapist  
Researcher Identifier (ORCID ID): 0000-0001-7054-5733  
Nearest person month worked: 1  
Contribution to Project: Mr. Snyder has been trained to deliver study interventions during this year of the study in accordance with the treatment manuals and he will be able to provide behavior therapy to study participants. He 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