Official title of study: Nicotinic Cholinergic Modulation as a Novel Treatment Strategy for Aggression Associated With Autism

NCT number: 02552147

Document date: 11/29/2017
Please refer to the HIC website for application instructions and information required to complete this application. The Instructions are available at http://www.yale.edu/hrpp/forms-templates/biomedical.html
Submit the original application and one (1) copy of all materials including relevant sections of the grant which funds this project (if applicable) to the HIC.

### SECTION I: ADMINISTRATIVE INFORMATION

<table>
<thead>
<tr>
<th>Title of Research Project:</th>
<th>Nicotinic cholinergic modulation as a novel treatment strategy for aggression associated with autism</th>
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<tbody>
<tr>
<td>Principal Investigator:</td>
<td>Alan S. Lewis, MD, PhD</td>
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<tr>
<td>Yale Academic Appointment:</td>
<td>Lecturer in Psychiatry</td>
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<tr>
<td>Department:</td>
<td>Psychiatry</td>
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<td>Fax:</td>
<td>203-737-2043</td>
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<td>Pager:</td>
<td>No pager</td>
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<tr>
<td>E-mail:</td>
<td><a href="mailto:alan.lewis@yale.edu">alan.lewis@yale.edu</a></td>
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<tr>
<th>Protocol Correspondent Name &amp; Address (if different than PI):</th>
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<tbody>
<tr>
<td>Campus Phone:</td>
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<tr>
<td>Yale Cancer Center CTO Protocol Correspondent Name &amp; Address (if applicable):</td>
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<tr>
<td>Campus Phone:</td>
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<tr>
<td>Business Manager:</td>
</tr>
<tr>
<td>Campus Phone:</td>
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<tr>
<th>Faculty Advisor: (required if PI is a student, resident, fellow or other trainee)</th>
<th>Yale Academic Appointment:</th>
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</thead>
<tbody>
<tr>
<td>Denis Sukhodolsky, PhD</td>
<td>Associate Professor, Child Study Center</td>
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<tr>
<td>Campus Address:</td>
<td>SHM IG-69, 230 S. Frontage Road</td>
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<td>Campus Phone:</td>
<td>(203) 785-</td>
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<tr>
<td>E-mail:</td>
<td><a href="mailto:denis.sukhodolsky@yale.edu">denis.sukhodolsky@yale.edu</a></td>
</tr>
</tbody>
</table>
Investigator Interests:

Does the principal investigator, or do any research personnel who are responsible for the design, conduct or reporting of this project or any of their family members (spouse or dependent child) have an incentive or interest, financial or otherwise, that may affect the protection of the human subjects involved in this project, the scientific objectivity of the research or its integrity? Note: The Principal Investigator (Project Director), upon consideration of the individual’s role and degree of independence in carrying out the work, will determine who is responsible for the design, conduct, or reporting of the research.

See Disclosures and Management of Personal Interests in Human Research
[link]

☐ Yes ☐ No

Do you or does anyone on the research team who is determined by you to be responsible for the design, conduct or reporting of this research have any patent (sole right to make, use or sell an invention) or copyright (exclusive rights to an original work) interests related to this research protocol?

☐ Yes ☐ No

If yes to either question above, list names of the investigator or responsible person:

The Yale University Principal Investigator, all Yale University co-investigators, and all Yale University individuals who are responsible for the design, conduct or reporting of research must have a current financial disclosure form on file with the University’s Conflict of Interest Office. Yale New Haven Hospital personnel who are listed as co-investigators on a protocol with a Yale University Principal Investigator must also have a current financial disclosure form on file with the University’s Conflict of Interest Office. If this has not been done, the individual(s) should follow this link to the COI Office Website to complete the form:
[link]

NOTE: The requirement for maintaining a current disclosure form on file with the University’s Conflict of Interest Office extends primarily to Yale University and Yale-New Haven Hospital personnel. Whether or not they are required to maintain a disclosure form with the University’s Conflict of Interest Office, all investigators and individuals deemed otherwise responsible by the PI who are listed on the protocol are required to disclose to the PI any interests that are specific to this protocol.

SECTION II: GENERAL INFORMATION

1. Performing Organizations: Identify the hospital, in-patient or outpatient facility, school or other agency that will serve as the location of the research. Choose all that apply:
a. Internal Location[s] of the Study:
- Magnetic Resonance Research Center (MR-TAC)
- Yale University PET Center
- YCCI/Church Street Research Unit (CSRU)
- Yale Cancer Center/Clinical Trials Office (CTO)
- YCCI/Hospital Research Unit (HRU)
- Yale Cancer Center/Smilow
- YCCI/Keck Laboratories
- Yale-New Haven Hospital
- Yale-New Haven Hospital—Saint Raphael Campus
- Cancer Data Repository/Tumor Registry
- Specify Other Yale Location: Yale Child Study Center

b. External Location[s]:
- APT Foundation, Inc.
- Haskins Laboratories
- Connecticut Mental Health Center
- John B. Pierce Laboratory, Inc.
- Clinical Neuroscience Research Unit (CNRU)
- Veterans Affairs Hospital, West Haven
- Other Locations, Specify: Services for the Underserved (SUS), 3580 Netherland Ave, Bronx, NY 10463, 718-885-8179 (please see accompanying SUS documentation)
- International Research Site

(Specify location(s)):

c. Additional Required Documents (check all that apply):
- N/A
- *YCCI-Scientific and Safety Committee (YCCI-SSC) Approval Date:
- *Pediatric Protocol Review Committee (PPRC) Approval Date:
- *YCC Protocol Review Committee (YRC-PRC) Approval Date:
- *Dept. of Veterans Affairs, West Haven VA HSS Approval Date:
- *Radioactive Drug Research Committee (RDRC) Approval Date:
- YNHH-Radiation Safety Committee (YNHH-RSC) Approval Date:
- Magnetic Resonance Research Center PRC (MRRC-PRC) Approval Date:
- YSM/YNHH Cancer Data Repository (CaDR) Approval Date:
- Dept. of Lab Medicine request for services or specimens form
- Imaging on YNHH Diagnostic Radiology equipment request form (YDRCTO request) found at http://radiology.yale.edu/research/ClinTrials.aspx

*Approval from these committees is required before final HIC approval is granted. See instructions for documents required for initial submission and approval of the protocol. Allow sufficient time for these requests. Check with the oversight body for their time requirements.

2. Probable Duration of Project: State the expected duration of the project, including all follow-up and data analysis activities. 2 years

3. Research Type/Phase: (Check all that apply)
   a. Study Type
      - Single Center Study
      - Multi-Center Study
      - Does the Yale PI serve as the PI of the multi-site study? Yes □ No □
      - Coordinating Center/Data Management
      - Other:
b. **Study Phase** □ N/A
   • Pilot □ Phase I □ Phase II □ Phase III □ Phase IV
   □ Other (Specify)

4. **Area of Research: (Check all that apply)** Note that these are overlapping definitions and more than one category may apply to your research protocol. Definitions for the following can be found in the instructions section 4c:
   □ Clinical Research: Patient-Oriented
   □ Clinical Research: Epidemiologic and Behavioral
   • Translational Research #1 (“Bench-to-Bedside”)
   □ Translational Research #2 (“Bedside-to-Community”)
   □ Clinical Research: Outcomes and Health Services
   □ Interdisciplinary Research
   □ Community-Based Research

5. Is this study a clinical trial? Yes ☒ No □
   
   **NOTE the current ICMJE (International Committee of Medical Journal Editors) definition of a clinical trial: “any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes.” Health-related interventions include any intervention used to modify a biomedical or health-related outcome (for example, drugs, surgical procedures, devices, behavioral treatments, dietary interventions, and process-of-care changes). Health outcomes include any biomedical or health-related measures obtained in patients or participants, including pharmacokinetic measures and adverse events”**
   
   If yes, where is it registered?
   Clinical Trials.gov registry ☒
   Other (Specify)

**Registration of clinical trials at their initiation is required by the FDA, NIH and by the ICMJE.**

*If this study is registered on clinicaltrials.gov, there is new language in the consent form and compound authorization that should be used.*

For more information on registering clinical trials, including whether your trial must be registered, see the YCCI webpage, [http://ycci.yale.edu/researchers/ors/registerstudy.aspx](http://ycci.yale.edu/researchers/ors/registerstudy.aspx) or contact YCCI at 203.785.3482)

6. Does the Clinical Trials Agreement (CTA) require compliance with ICH GCP (E6)?
   Yes □ No ☒

7. Will this study have a billable service? A Billable Service is defined as a service or procedure that will be ordered, performed or result in charging in EPIC for individuals who are enrolled in a clinical research study, regardless if the charge is intended to be paid by the subject/their insurance or the research study.
Yes □ No ☒

If you answered "yes", this study will need to be set up in OnCore Support
http://medicine.yale.edu/ymg/systems/ppm/index.aspx

8.. Are there any procedures involved in this protocol that will be performed at YNHH or one of its affiliated entities? Yes ____ No  ☒ If Yes, please answer questions a through c and note instructions below. If No, proceed to Section III.
a. Does your YNHH privilege delineation currently include the specific procedure that you will perform?
b. Will you be using any new equipment or equipment that you have not used in the past for this procedure?
c. Will a novel approach using existing equipment be applied?

If you answered “no” to question 7a, or "yes" to question 7b or c, please contact the YNHH Department of Physician Services (688-2615) for prior approval before commencing with your research protocol.

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**SECTION III: FUNDING, RESEARCH TEAM AND TRAINING**

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**SECTION IV:**

**PRINCIPAL INVESTIGATOR/FACULTY ADVISOR/ DEPARTMENT CHAIR AGREEMENT**

As the principal investigator of this research project, I certify that:

- The information provided in this application is complete and accurate.
- I assume full responsibility for the protection of human subjects and the proper conduct of the research.
- Subject safety will be of paramount concern, and every effort will be made to protect subjects’ rights and welfare.
- The research will be performed according to ethical principles and in compliance with all federal, state and local laws, as well as institutional regulations and policies regarding the protection of human subjects.
- All members of the research team will be kept apprised of research goals.
- I will obtain approval for this research study and any subsequent revisions prior to my initiating the study or any change and I will obtain continuing approval of this study prior to the expiration date of any approval period.
- I will report to the HIC any serious injuries and/or other unanticipated problems involving risk to participants.
- I am in compliance with the requirements set by the University and qualify to serve as the principal investigator of this project or have acquired the appropriate approval from the Dean’s Office or Office of the Provost, or the Human Subject Protection Administrator at Yale-New Haven Hospital, or have a faculty advisor.
- I will identify a qualified successor should I cease my role as principal investigator and facilitate a smooth transfer of investigator responsibilities.

Alan S. Lewis, MD, PhD
PI Name (PRINT) and Signature 8/5/2015
Date
As the **faculty advisor** of this research project, I certify that:

- The information provided in this application is complete and accurate.
- This project has scientific value and merit and that the student or trainee investigator has the necessary resources to complete the project and achieve the aims.
- I will train the student investigator in matters of appropriate research compliance, protection of human subjects and proper conduct of research.
- The research will be performed according to ethical principles and in compliance with all federal, state and local laws, as well as institutional regulations and policies regarding the protection of human subjects.
- The student investigator will obtain approval for this research study and any subsequent revisions Prior to initiating the study or revision and will obtain continuing approval prior to the expiration of any approval period.
- The student investigator will report to the HIC any serious injuries and/or other unanticipated problems involving risk to participants.
- I am in compliance with the requirements set forth by the University and qualify to serve as the faculty advisor of this project.

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Denis Sukhodolsky, PhD  
Advisor Name (PRINT) and Signature  
8/4/2015  
Date

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**Department Chair’s Assurance Statement**

Do you know of any real or apparent institutional conflict of interest (e.g., Yale ownership of a sponsoring company, patents, licensure) associated with this research project?

- [ ] Yes (provide a description of that interest in a separate letter addressed to the HIC.)
- [x] No

As Chair, do you have any real or apparent protocol-specific conflict of interest between yourself and the sponsor of the research project, or its competitor or any interest in any intervention and/or method tested in the project that might compromise this research project?

- [ ] Yes (provide a description of that interest in a separate letter addressed to the HIC)
- [x] No

I assure the HIC that the principal investigator and all members of the research team are qualified by education, training, licensure and/or experience to assume participation in the conduct of this research trial. I also assure that the principal investigator has departmental support and sufficient resources to conduct this trial appropriately.

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John H. Krystal, MD  
Chair Name (PRINT) and Signature  
2/23/2015  
Date

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**Psychiatry**

**Department**
YNHH Human Subjects Protection Administrator Assurance Statement
Required when the study is conducted solely at YNHH by YNHH health care providers.

As Human Subject Protection Administrator (HSPA) for YNHH, I certify that:

- I have read a copy of the protocol and approve it being conducted at YNHH.
- I agree to notify the IRB if I am aware of any real or apparent institutional conflict of interest.
- The principal investigator of this study is qualified to serve as P.I. and has the support of the hospital for this research project.

YNHH HSPA Name (PRINT) and Signature

<table>
<thead>
<tr>
<th>Date Approved</th>
<th>Human Investigation Committee Signature</th>
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</table>

This protocol is valid through ________________

SECTION V: RESEARCH PLAN

1. **Statement of Purpose**: State the scientific aim(s) of the study, or the hypotheses to be tested.

   The scientific aims of this pilot study are to determine the feasibility, tolerability, and efficacy of transdermal nicotine to treat irritability and aggression comorbid with Autism Spectrum Disorder in adults without intellectual disability.

2. **Background**: Describe the background information that led to the plan for this project.
   Provide references to support the expectation of obtaining useful scientific data.

   Autism spectrum disorder (ASD) is a heterogeneous disorder characterized by deficits in communication, social interactions, and behavior, presenting in the early developmental period that causes significant impairment in functioning[1]. The constellation of aggression and related behaviors, which include irritability, agitation, and aggression, are highly comorbid with ASD, with a large recent study reporting over two-thirds of children with ASD have demonstrated aggressive behaviors toward caregivers[2]. Aggression in ASD, both toward others or as self-injurious behavior, significantly increases the risk for acute hospitalization or residential placement[3], increases parent and/or caregiver stress[4], and places the patient at risk for abuse[5].
Current treatment options for aggression in ASD include behavioral approaches and pharmacotherapy[6-8]. Atypical antipsychotics, especially risperidone and aripiprazole, have emerged as the accepted first-line treatment of aggression in ASD and pervasive developmental disorders (PDD), and are complimented by other antipsychotics and mood stabilizers[7, 9]. Risperidone demonstrated a large effect on aggression in children with ASD [10]. Despite this, treatment-resistant cases are common, with one large recent study of individuals of all ages with ASD finding almost 40% were resistant to pharmacotherapy over a 3-5 year period[11]. Complicating this problem are significant side effects of these medications, particularly metabolic derangements, which appear to be even more significant in an ASD population[12]. For instance, children prescribed risperidone gained on average 5.6 kg (16.7%) over 6 months[10, 13], increasing the risk for obesity and diabetes. The reality of aggression and its consequent harms weighed against partially effective treatments with significant side effects is one faced every day for patients with ASD, their parents and caregivers, as well as healthcare providers.

None of the pharmacotherapies used for aggression in ASD are specific for treating aggression in ASD, and only a limited understanding exists regarding the neurobiological mechanisms driving aggression and irritability in ASD. The study of aggression in rodent models has benefited substantially from novel technologies such as rodent fMRI[14] and optogenetic techniques[15, 16], yet further knowledge of neurobiological mechanisms of aggression in general, as well as in ASD specifically, is critically needed. We rationalized that a logical foundation on which to design novel treatments for aggression in ASD is to identify systems important for modulating aggressive behavior that are also consistently misregulated in ASD cohorts. Modulation of nicotinic cholinergic signaling through nAChRs represents a novel strategy for influencing aggression in ASD. Multiple lines of evidence have identified abnormal cholinergic signaling and changes in nAChRs in patients with ASD[17]. Neuropathological studies from adults with ASD demonstrate significant misregulation of β2-containing and α7 nAChRs in diverse brain regions, including the cortex[18], cerebellum[19, 20], and thalamus[21], while studies of infantile autism identified abnormalities in basal forebrain cholinergic neuron development[22]. Genetic and epigenetic studies have also demonstrated that changes in nAChR subunits might contribute to ASD in humans, with the preponderance of evidence pinpointing changes in CHRNA7, the gene coding for the α7 subunit[23-25]. The 15q13.3 microdeletion syndrome results from a copy number variation encompassing roughly 6 genes, one of which is CHRNA7, and affected subjects can present with ASD, aggression, epilepsy, and schizophrenia[26, 27], which is replicated by a 15q13.3 mouse model[28]. Deletion of CHRNA7 itself is likely responsible for at least some of the phenotypic findings of 15q13.3 microdeletion syndrome[29], directly linking abnormal α7 expression and signaling with ASD and aggression. Commonly used mouse models of ASD and related neurodevelopmental disorders, including the BTBR mouse[30] and the Mecp2-null mouse[31] demonstrate reduced prefrontal cortical acetylcholine levels and altered nAChR currents, respectively. The BTBR mouse also shows increased impulsivity[30], which could predispose to aggression in ASD. Taken together, human neuropathological studies, genetic studies, and animal models implicate alterations of nAChRs and cholinergic signaling in ASD throughout the lifespan.
Pharmacological strategies designed to normalize or augment the cholinergic misregulation in ASD might be beneficial for treating its symptoms. Donepezil, an acetylcholinesterase inhibitor, improves cognitive rigidity and social deficits in the BTBR mouse model of ASD[30, 32] and has demonstrated encouraging, though as yet inconclusive, results for certain core symptoms in humans with ASD[33-35]. Despite these promising results, research on the use of cholinergic agents in ASD will have greater impact if experiments focus on specific ASD-related behaviors that are most likely to be improved by cholinergic modulation. Substantial evidence demonstrates that nAChR agonists, especially nicotine, reduce aggression in animal models with heightened aggression, including cats, rats, and mice[36-41], thereby acting as a serenic agent[42]. The pharmacological or neural circuit mechanisms underlying such serenic effects are unknown. Given the cholinergic changes in ASD and the ability of nAChR agonists to act as serenic agents, we hypothesize that nicotinic pharmacotherapies will be specifically therapeutic for aggression in ASD. Other disorders with cholinergic dysfunction and persistent aggression have been successfully treated with transdermal nicotine, including dementia[43, 44] and schizophrenia[45]. Nicotinic AChR agonist therapy has not been systematically described to treat ASD, however use of varenicline, an α7 par agonist with activity at α7, was reported in a 9-year old boy with ASD, with good tolerability and efficacy for social, communication, and repetitive behavior measures[46].

3. Research Plan: Summarize the study design and research procedures using non-technical language that can be readily understood by someone outside the discipline. Be sure to distinguish between standard of care vs. research procedures when applicable, and include any flowcharts of visits specifying their individual times and lengths. Describe the setting in which the research will take place.

The study will take the form of a small, randomized-controlled trial with a cross-over design. The basic study design is as follows:

1. Participants: Participants will be recruited through the Yale Child Study Center (YCSC) Autism Program, local support and advocacy groups for young adults with Autism Spectrum Disorder (ASD), local therapeutic schools, and local mental health providers who work with individuals with ASD. We will invite these entities to inform their patients/students about our study, and invite them or their parents (if legal guardians) to contact the PI (Alan Lewis) if they are interested in learning more about the study, and potentially participating, or having their adult children participate. Pamphlet advertisements with contact information will be placed at the meeting sites of these groups, with permission. Clinicians or group leaders will also offer the participants the option of submitting their telephone numbers in order for us to contact them directly.

2. Consent: After telephonic contact is made, participants or parents who express interest in participation will be invited for an initial screening visit. At this point it will be determined whether the participants are able to give informed consent in accordance with the inclusion criteria of the study. Once this is established,
informed written consent will be obtained. Participants will be invited to attend the screening visit with a primary caregiver. If participants are unable to provide consent, a parent, if still their legal guardian, will be allowed to provide informed consent on their behalf. In the case where the participant is unable to provide informed consent and it is provided by the participant’s parent, assent will be obtained from the participant and the participant will still sign the consent form to confirm willingness to participate. Once participants are enrolled, this contact will be considered Visit 1, and relevant behavioral baseline data will be obtained, as discussed under study design.

3. Study design: This is a double blind study such that subjects and all investigators will be unaware of treatments during the data collection phase of the study. It will be placebo controlled using identical appearing transdermal patches that either contain or do not contain nicotine. After informed consent is obtained, participants will be scheduled for a total of three visits with a member of the study team at the YCSC or at Services for the Underserved (SUS), Bronx, NY, as noted above. The purpose of conducting the study at SUS is to enable a subject who would otherwise meet criteria for the study but clinical considerations make the logistics of transportation to YCSC unacceptably challenging.

a. Visit 1: As described above, informed consent will be obtained from participants or their legal guardian parent on meeting inclusion criteria and without exclusion criteria. Assent will be obtained from the participant in cases where informed consent is provided by a parent. Baseline behavioral rating scales will be performed. Specifically, we will obtain the Aberrant Behavior Checklist (ABC), State/Trait Anxiety Inventory (STAI), and Social Responsiveness Scale-Adults (SRS-A). These will be obtained from patients and primary caregivers as appropriate. Vital signs will be obtained. All participants will be given three weeks of identical appearing transdermal patches. Participants are randomized into two groups, one of which receives nicotine patches first and the other receives placebo patches first. Randomization will be performed by block randomization using blocks of 4 subjects, and allocation concealment performed via the use of sequentially numbered, sealed opaque envelopes, on which the participant’s identifying information is written prior to opening the envelope. In collaboration with the Investigational drug service at YNHH, we will link the allocation to a set of patches that are numbered in a simple fashion to help participants use the correct patch on the correct day. The first group will receive 7 days of nicotine patches, dose = 7 mg patches followed by 14 days of identically appearing placebo patches. The second group will receive 14 days of placebo patches, followed by 7 days of 7 mg nicotine patches. This design allows each participant to serve as his/her own control, with a seven-day washout period, which will eliminate carryover effects for those subjects receiving nicotine during the first 7 days of the study. Subjects will be asked to place the nicotine patch on their skin in the morning and remove the patch prior to sleep at night prior
to sleep. This counter-balanced design is aimed to control for expectation bias and maximize validity. *Duration of visit: 90 minutes.*

b. **Visit 2:** Participants will return for a subsequent visit at day 8, at which point the above rating scale data will again be collected to measure both primary and secondary outcomes. Tolerability will be assessed as determined by vital signs, open-ended inquiry, and screening for common adverse effects of transdermal nicotine as observed in previous studies with non-smoking subjects. Open-ended inquiry for tolerability will be performed by asking subjects “What types of side effects or discomfort did you experience while wearing the patch during the preceding week?” and subject responses will be recorded by detailed notes. This approach may allow the investigators to gain a better understanding of the experience of the patch in individuals with ASD who might experience side effects differently than neurotypical individuals. Brief qualitative reports of the patient’s subjective experience will be recorded by asking “In what ways did you find the patch helpful or harmful during the past week, if at all?”. Detailed notes of responses will be written. *Duration of visit: 60 minutes*

c. **Visit 3:** Participants will return for a third and final visit at day 22, at which point data will again be collected to measure primary and secondary outcomes, tolerability, and subjective experience (as detailed in Visit 2, above). *Duration of visit: 60 minutes*

4. **Data analysis:** Study results will be tabulated and subjected to statistical analysis to determine the presence of significant differences in primary and secondary outcomes between control and intervention. Statistical methods are outlined under ‘statistical considerations’ and performed by a trained statistician the YCCI and Yale Center for Analytical Sciences. Data regarding tolerability will be compared between control and interventions arms.

5. **Deviations from standard of care:** Current pharmacological standard of care for treatment of agitation and irritability in the population from which we are recruiting include mood stabilizers and antipsychotics[7, 9]. Patients currently taking these agents will not be required to discontinue this treatment, and the intervention is not expected to interfere with this treatment. Therefore, during the placebo period patients will not experience treatment below the standard of care, and during the active period they will continue to receive the standard of care, plus the active agent with its potential positive and negative effects.

4. **Genetic Testing**  N/A  ☒
   A. Describe
      i. the types of future research to be conducted using the materials, specifying if immortalization of cell lines, whole exome or genome sequencing, genome wide association studies, or animal studies are planned
ii. the plan for the collection of material or the conditions under which material will be received
iii. the types of information about the donor/individual contributors that will be entered into a database
iv. the methods to uphold confidentiality

B. What are the conditions or procedures for sharing of materials and/or distributing for future research projects?
C. Is widespread sharing of materials planned?
D. When and under what conditions will materials be stripped of all identifiers?
E. Can donor-subjects withdraw their materials at any time, and/or withdraw the identifiers that connect them to their materials?
   i. How will requests to withdraw materials be handled (e.g., material no longer identified: that is, anonymized) or material destroyed)?

F. Describe the provisions for protection of participant privacy
G. Describe the methods for the security of storage and sharing of materials

5. **Subject Population:** Provide a detailed description of the types of human subjects who will be recruited into this study.

Our study population will consist of adult subjects with ASD who have primary caregivers. Specifically, our population is individuals over the age of 18 participating, or with parents participating in local support and advocacy groups for ASD. Participants in this study will have prior, confirmed diagnoses of ASD in order to be considered for inclusion. In this pilot study we will include both higher functioning individuals with ASD (who will provide their own consent), as well as less cognitively able individuals (who will have consent provided by a guardian parent). All participants will be living with or closely engaged with a primary caregiver, and are expected to have at least moderate impairment related to social and communication deficits. Please see the study inclusion and exclusion criteria for a quantitative description of the study subjects.

6. **Subject classification:** Check off all classifications of subjects that will be specifically recruited for enrollment in the research project. Will subjects who may require additional safeguards or other considerations be enrolled in the study? If so, identify the population of subjects requiring special safeguards and provide a justification for their involvement.

- [ ] Children
- [ ] Non-English Speaking
- [ ] Decisionally Impaired
- [ ] Yale Students
- [ ] Healthy
- [ ] Prisoners
- [ ] Employees
- [ ] Fetal material, placenta, or dead fetus
- [ ] Economically disadvantaged persons
- [ ] Pregnant women and/or fetuses
- [ ] Females of childbearing potential
NOTE: Is this research proposal designed to enroll children who are wards of the state as potential subjects? ☐ Yes ☒ No (If yes, see Instructions section VII #4 for further requirements)

7. **Inclusion/Exclusion Criteria:** What are the criteria used to determine subject inclusion or exclusion?

**Inclusion criteria:**
- Age: 18-60
- Gender: All
- Language: Communicative in English
- Participants with a prior diagnosis of DSM-5 ASD at some point in their lifetime OR a DSM-4 diagnosis of Autism OR a DSM-4 diagnosis of Asperger’s syndrome OR a DSM-4 diagnosis of Pervasive Developmental Disorder Not Otherwise Specified.
- Symptoms of irritability, agitation or aggression as reported by parent and/or participant
- Aberrant behavior checklist – Irritability Subscale (ABC-I) score of 16 or higher
- No changes in psychotropic medications within the past 14 days.
- Either lives with a primary caregiver or closely engaged with a primary caregiver who interacts with the patient daily
- BMI > 17.5 and ≤ 45

**Exclusion criteria:**
- Age < 18 or > 60
- BMI < 17.5 or > 45
- Currently using tobacco or any nicotine products (transdermal, gum, e-cigarettes)
- Changes in psychotropic medication management within the past 14 days
- Previous allergy to transdermal patches
- Patients with heart rate > 100 or < 50 or known history of cardiac rhythm abnormalities
- Systolic blood pressure > 150 or < 95; diastolic blood pressure > 90 or < 50
- No symptoms of irritability, agitation, or aggression as reported by parent and/or participant
- ABC-I score of less than 16
- No primary caregiver, or primary caregiver unable to assist with rating scales

8. **How will eligibility** be determined, and by whom?

Eligibility will be determined by the investigators. Once potential participants or a parent makes contact telephonically, we will explain briefly some information about the study, and offer them the opportunity to present for a screening visit. We will explain that a diagnosis of ASD is required for participation in the study, and encourage participants or their parent to bring information about their prior diagnosis to the screening visit, but will
not request any PHI over the phone. At the screening visit, we will again explain the study procedures, and determine whether participants meet inclusion and exclusion criteria. In order to confirm diagnosis, we will require potential participants to provide evidence of a prior diagnosis done by a psychiatrist or clinical psychologist.

9. **Risks:** Describe the reasonably foreseeable risks, including risks to subject privacy, discomforts, or inconveniences associated with subjects participating in the research.

The study has a number of risks:

- **Medication related:** Side effects of transdermal nicotine exposure have been well studied, and participants may experience nausea, insomnia, headache, skin irritation, palpitations, and dizziness. These side effects were found to be dose related in healthy, non-smoking subjects, with 15 mg nicotine patch significantly less likely to cause side effects than higher dose such as 30 mg[49]. Specifically, in this study 8 non-smoking patients were given a 15 mg nicotine patch. Five of 8 patients experienced mild nausea and lightheadedness after one hour, while 3 of 8 did not have any side effects. Seven of 8 patients continued with the study. Studies of chronic transdermal nicotine in non-smoking populations are very encouraging regarding tolerability. In a large study of transdermal nicotine for treating mild cognitive impairment in older adults, tolerability was excellent in the over 30 subjects randomized to nicotine treatment [50]. It is not known whether subjects with ASD will be more or less susceptible to the common side effects of transdermal nicotine, however, transdermal nicotine use has been reported in case series or trials of patients with advanced dementia and age, a population that is likely to be increasingly sensitive to nicotine than younger, healthier subjects[43, 44, 50-52].

The question of development of physiological dependence or even nicotine use disorder secondary to patch exposure in non-smoking participants is an important one. We can base the likelihood on previous studies in non-smoking participants that were conducted for significantly longer periods of time than in the proposed study. Nicotine patch has been used for 4-weeks in patients with mild-moderate Alzheimer’s Disease for 16 hours per day, initially using 5 mg patches for 7 days, 10 mg patches for 14 days, and finally 5 mg patches for 7 days [51]. In general, patches were well tolerated, with only one of 8 subjects discontinuing. There were no observed nicotine withdrawal symptoms in these participants. Sleep interruption was not problematic as the patches were removed at bedtime. An almost identical study was performed with 15 subjects with age-associated memory impairment using the same nicotine patch dose[52]. Only one of 15 subjects withdrew from this study due to nicotine-related side effects, in this case, nausea. In this study, the most common side effects were local skin irritation, mild nausea and abdominal discomfort, and lightheadedness. Two subjects reported palpitations, but there was no change in body weight, blood pressure, or heart rate in subjects receiving nicotine compared to receiving placebo. No subjects appeared physiologically or psychologically dependent on the nicotine patches. In a 6-month trial of transdermal nicotine or placebo to treat mild cognitive impairment, no subjects (0 of 34 subjects) developed withdrawal or continued to use nicotine products following the study[50]. Data from studies of smokers, who might be predisposed to difficulty discontinuing
nicotine-containing products, demonstrated that difficulty with discontinuation of transdermal nicotine after use for smoking cessation was rare (2%), with the percentage of smokers continuing to use nicotine replacement products proportional to the rate of nicotine delivery[53]. Taken together, these previous studies are reassuring regarding the safety of nicotine products from an addiction potential standpoint in non-smoking subjects. Whether addiction potential differs in ASD populations remains to be seen, but epidemiological data demonstrating reduced smoking in ASD subjects argues that this group will not be predisposed to development of nicotine use disorder[54].

- **Inconvenience:** Participants with significant symptoms of irritability may be negatively affected by not being able to make other medication changes for the duration of the study unless they withdraw from the study. In this instance, subjects will be withdrawn from the study and instructed to seek further treatment from their medical providers.

10. **Minimizing Risks:** Describe the manner in which the above-mentioned risks will be minimized.

- **Dependance:** Please see above (#9) for a detailed discussion regarding the risk of development of dependence. To further reduce the risk in our study we will administer the active agent for no longer than one week, which is substantially shorter than the trials cited above that demonstrated no risk of dependence with transdermal nicotine. We chose transdermal delivery of nicotine because its slow rate of delivery significantly reduces the risk of dependence development[53]. Finally, our protocol involves removal of nicotine patch prior to sleep, which significantly reduces the total exposure to nicotine within the study.

- **Discomfort:** The potential for discomfort will be clearly explained to subjects and where appropriate and permissible, their caregivers. In order to minimize the risk of discomfort, participants will be provided a low dose of 7 mg patches to be used for 16 hours a day while the subjects are awake. Similar to a previous study[55], study subjects who experience unpleasant side effects above and beyond those on which subjects were counseled during the first visit will be asked to contact study staff and report their symptoms. Subjects experiencing expected, non-dangerous side effects such as moderate nausea will be instructed to remove the patch for that day and resume using the patch the next morning. Individuals experiencing side effects considered medically concerning, including severe headache, chest pain, or severe palpitations, will be instructed to discontinue patch use altogether and will be withdrawn from the study. Placebo patches will be handled in exactly the same manner, with the same ability to remove as described above. These data will be important for not only understanding tolerability of nicotine in subjects with ASD, but also tolerability of skin patches in populations with ASD, who are known to have altered somatic sensation.

It should be noted that nicotine patches have been used successfully in populations with cardiovascular disease [56]. Although subjects with known cardiovascular
disease, including hypertension, history of myocardial infarction, heart failure, or arrhythmia will be excluded, these data are reassuring given the possibility of enrolling a subject with a previously undiagnosed cardiovascular condition.

- **Inconvenience:** In order to be included in our study, participants should not be undergoing active changes in their psychotropic medications, reducing the likelihood that this may become a problem in the course of the study. We have limited the number of visits to three, which we believe to be the minimum number of visits yielding scientifically useful data.

11. Data and Safety Monitoring Plan:

**Greater Than Minimal Risk DSMP**

1. **Personnel responsible for the safety review and its frequency:**

   The principal investigator and the faculty advisor (Denis Sukhodolsky) will be responsible for monitoring the data, assuring protocol compliance, and conducting the safety reviews at the specified frequency, which must be conducted at a minimum of every 6 months (including when reapproval of the protocol is sought). During the review process, the principal investigator (monitor) and the faculty advisor will evaluate whether the study should continue unchanged, require modification/amendment, or close to enrollment. Either the principal investigator, the faculty advisor, the IRB or the Yale Child Study Center have the authority to stop or suspend the study or require modifications.

2. **The risks associated with the current study are deemed greater than minimal for the following reasons:** (choose those that apply)

   1. We do not view the risks associated with the nicotine as minimal risks.

   Although we have assessed the proposed study as one of greater than minimal risk, the potential exists for anticipated and/or unanticipated adverse events, serious or otherwise, to occur since it is not possible to predict with certainty the absolute risk in any given individual or in advance of first-hand experience with the proposed study methods. Therefore, we provide a plan for monitoring the data and safety of the proposed study as follows:

3. **Attribution of Adverse Events:**

   Adverse events will be monitored for each subject participating in the study and attributed to the study procedures / design by the principal investigator Alan Lewis according to the following categories:

   a.) Definite: Adverse event is clearly related to investigational procedures(s)/agent(s).
   b.) Probable: Adverse event is likely related to investigational procedures(s)/agent(s).
   c.) Possible: Adverse event may be related to investigational procedures(s)/agent(s).
   d.) Unlikely: Adverse event is likely not to be related to the investigational procedures(s)/agent(s).
e.) Unrelated: Adverse event is clearly not related to investigational procedures(s)/agent(s).

4. Plan for Grading Adverse Events:

The following scale will be used in grading the severity of adverse events noted during the study:

1. Mild adverse event
2. Moderate adverse event
3. Severe

5. Plan for Determining Seriousness of Adverse Events:

**Serious Adverse Events:**
In addition to grading the adverse event, the PI will determine whether the adverse event meets the criteria for a Serious Adverse Event (SAE). An adverse event is considered serious if it results in any of the following outcomes:

1. Death;
2. A life-threatening experience in-patient hospitalization or prolongation of existing hospitalization;
3. A persistent or significant disability or incapacity;
4. A congenital anomaly or birth defect; OR
5. Any other adverse event that, based upon appropriate medical judgment, may jeopardize the subject’s health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

An adverse event may be graded as severe but still not meet the criteria for a Serious Adverse Event. Similarly, an adverse event may be graded as moderate but still meet the criteria for an SAE. It is important for the PI to consider the grade of the event as well as its “seriousness” when determining whether reporting to the IRB is necessary.

6. Plan for reporting UPIRSOs (including Adverse Events) to the IRB

The principal investigator will report the following types of events to the IRB:

Any incident, experience or outcome that meets ALL 3 of the following criteria:

1. Is unexpected (in terms of nature, specificity, severity, or frequency) given (a) the research procedures described in the protocol-related documents, such as the IRB-approved protocol and informed consent document and (b) the characteristics of the subject population being studied; AND
2. Is related or possibly related to participation in the research (*possibly related* means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); AND
3. Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, legal, or social harm) than was previously known or recognized.
Unanticipated Problems Involving Risks to Subjects or Others (UPIRSOs) may be medical or non-medical in nature, and include – but are not limited to – serious, unexpected, and related adverse events and unanticipated adverse device effects. Please note that adverse events are reportable to the IRB as UPIRSOs only if they meet all 3 criteria listed above.

These UPIRSOs/SAEs will be reported to the IRB in accordance with IRB Policy 710, using the appropriate forms found on the website. All related events involving risk but not meeting the prompt reporting requirements described in IRB Policy 710 should be reported to the IRB in summary form at the time of continuing review. If appropriate, such summary may be a simple brief statement that events have occurred at the expected frequency and level of severity as previously documented. In lieu of a summary of external events, a current DSMB report can be submitted for research studies that are subject to oversight by a DSMB (or other monitoring entity that is monitoring the study on behalf of an industry sponsor).

7. Plan for reporting adverse events to co-investigators on the study, as appropriate the protocol’s research monitor(s), e.g., industrial sponsor, Yale Cancer Center Data and Safety Monitoring Committee (DSMC), Protocol Review Committee (PRC), DSMBs, study sponsors, funding and regulatory agencies, and regulatory and decision-making bodies.

For the current study, the following individuals, funding, and/or regulatory agencies will be notified (choose those that apply):

- [X] All Co-Investigators listed on the protocol.
- [□] Yale Cancer Center Data and Safety Monitoring Committee (DSMC)
- [□] National Institutes of Health
- [□] Food and Drug Administration (Physician-Sponsored IND #_______)
- [□] Medical Research Foundation (Grant______)
- [□] Study Sponsor
- [□] Other Data Safety Monitoring Board (DSMB) or Committee (DSMC)

The principal investigator (Alan Lewis, MD, PhD) will conduct a review of all adverse events upon completion of every study subject. The principal investigator will evaluate the frequency and severity of the adverse events and determine if modifications to the protocol or consent form are required.

12. Statistical Considerations: Describe the statistical analyses that support the study design.

a) We plan to enroll approximately 16 subjects in this pilot study.
b) The major hypothesis of the study is that transdermal nicotine will reduce symptoms of aggression as quantified by the Aberrant Behavior Checklist (ABC) – irritability subscale. For comparison, risperidone in a large clinical trial (n=63) had a large effect size of d>1.0 as determined by an ABC-irritability subscale reduction from a mean baseline score of 26.6 to a score of 9.5 after 8 weeks of medication exposure[10]. To determine power estimates for our study, we used 26.6 as our mean estimate for the placebo group. Based on a literature review, we conservatively estimated a standard deviation of 10. We then calculated power for a range of effect sizes, estimating a correlation of 0.70 for repeated measures. Alpha was set at 0.05. The power estimates are displayed in Table 1.

Table 1: Power estimates

<table>
<thead>
<tr>
<th>Placebo Mean (SD)</th>
<th>Treatment Mean (SD)</th>
<th>Effect size (d)</th>
<th>Power</th>
</tr>
</thead>
<tbody>
<tr>
<td>26.6 (10)</td>
<td>22 (10)</td>
<td>0.59 (small-medium)</td>
<td>0.57</td>
</tr>
<tr>
<td>26.6 (10)</td>
<td>20 (10)</td>
<td>0.85 (medium)</td>
<td>0.86</td>
</tr>
<tr>
<td>26.6 (10)</td>
<td>15 (10)</td>
<td>1.27 (large)</td>
<td>0.99</td>
</tr>
</tbody>
</table>

These figures demonstrate our study is highly powered to detect medium and large-sized differences between placebo and treatment groups.

c) For the major hypothesis we will collect ABC rating scale data as well as at both baseline as well as at two other timepoints: after 7 days of transdermal nicotine treatment as well as after 7 days of placebo patch. Repeated measures analysis of variance (ANOVA) will be used with treatment (nicotine or placebo) as within-subjects factor and order of treatment (nicotine-placebo-placebo or placebo-placebo-nicotine) as a between-subjects factor. We will first test models with between and within subjects factors only. We will then test the interaction between treatment and order, in order to test whether treatment effects varied by administration order. McNemar’s test or similar will be used for categorical variables such as whether or not a common, pre-defined side effect is reported. We will collect and report subjective experiences from patients and their caregivers but these will not be subjected to statistical analysis.

Section VI: Research Involving Drugs, Biologics, Radiotracers, Placebos and Devices

If this section (or one of its parts, A or B) is not applicable, state N/A and delete the rest of the section.

A. Drugs, Biologics and Radiotracers

1. Identification of Drug, Biologic or Radiotracer: What is (are) the name(s) of the drug(s) biologic(s) or radiotracer(s) being used? Identify whether FDA approval has been granted and for what indication(s).
Transdermal nicotine patch. This product is FDA approved for the indication of smoking cessation in persons 18 years of age and older.

All protocols which utilize a drug, biologic or radiotracer not approved by, but regulated by, the FDA, or a radiotracer regulated by the RDRC, must provide the following information:
   a. What is the Investigational New Drug (IND) number assigned by the FDA?
   b. Who holds the IND?
   c. All protocols which utilize a radiotracer not approved by, but regulated by the FDA must provide the IND number: __________________

Alternatively, use of the investigational radiotracer may be under RDRC/RSC oversight: (check if appropriate)_____________

For all investigational radiotracers, attach a copy of the RDRC/RSC application (for radioisotopes used in the PET Center, PET Center personnel may complete this step)
Go to http://rsc.med.yale.edu/login.asp?url=myApps.asp. When you have logged in, complete the application and attach a copy to this submission.

Alternatively, an exemption from IND filing requirements may be sought for a clinical investigation of a drug product that is lawfully marketed in the United States. If there is no IND and an exemption is being sought, review the following categories and complete the category that applies (and delete the inapplicable categories):

We are seeking an exemption from IND filing requirements.

Exempt Category 1
The clinical investigation of a drug product that is lawfully marketed in the United States can be exempt from IND regulations if all of the following are yes:

i. The intention of the investigation is NOT to report to the FDA as a well-controlled study in support of a new indication for use or to be used to support any other significant change in the labeling for the drug. ☒ Yes ☐ No

ii. The drug that is undergoing investigation is lawfully marketed as a prescription drug product, and the intention of the investigation is NOT to support a significant change in the advertising for the product. ☒ Yes ☐ No

iii. The investigation does NOT involve a route of administration or dosage level or use in populations or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product. ☒ Yes ☐ No

iv. The investigation will be conducted in compliance with the requirements for institutional (HIC) review and with the requirements for informed consent of the FDA regulations (21 CFR Part 50 and 21 CFR Part 56). ☒ Yes ☐ No

v. The investigation will be conducted in compliance with the requirements regarding promotion and charging for investigational drugs. ☒ Yes ☐ No
2. **Background Information:** Provide a description of previous human use, known risks, and data addressing dosage(s), interval(s), route(s) of administration, and any other factors that might influence risks. If this is the first time this drug is being administered to humans, include relevant data on animal models.

Transdermal nicotine has a lengthy history of use for the purpose of smoking cessation in people 18 years and older. This medication was approved by the FDA in the late 1980s-early 1990s[57] and in 1996 became available as an over-the-counter medication[58]. For use in smoking cessation, dosing of transdermal nicotine is well established and stratified by number of cigarettes smoking daily (For >10 cigarettes daily: 21 mg patch/day transdermally for 4-6 weeks, then 14 mg patch/day for 2 weeks, then 7 mg patch/day for 2 weeks; For < 10 cigarettes daily: 14 mg patch/day transdermally for 6 weeks, then 7 mg patch/day for 2 weeks). Patches are generally placed on non-hairy skin upon awakening and then removed prior to bed, although they may be left on overnight if tolerated. In our study patches will be removed prior to sleep.

Transdermal nicotine has been studied in non-smoking humans in a number of paradigms both acutely and chronically, generally well tolerated at low to moderate doses, and without evidence of nicotine dependence [43, 44, 50-52, 55, 59]. Please see above (#9) for a discussion of these studies.

3. **Source:** a) Identify the source of the drug or biologic to be used. Drug will be obtained through the Investigational Drug Service at Yale-New Haven Hospital.

   b) Is the drug provided free of charge to subjects? ☒ Yes ☐ No
   
   If yes, by whom?

4. **Storage, Preparation and Use:** Describe the method of storage, preparation, stability information, and for parenteral products, method of sterilization and method of testing sterility and pyrogenicity.

   Check applicable Investigational Drug Service utilized:
   
   ☒ YNHH IDS ☐ Yale Cancer Center
   ☐ CMHC Pharmacy ☐ West Haven VA
   ☐ PET Center ☐ None
   ☐ Other:

   Note: If the YNHH IDS (or comparable service at CMHC or WHVA) will not be utilized, explain in detail how the PI will oversee these aspects of drug accountability, storage, and preparation.

5. **Use of Placebo:** ☐ Not applicable to this research project
   
   If use of a placebo is planned, provide a justification which addresses the following:
   
   a. Describe the safety and efficacy of other available therapies. If there are no other available therapies, state this.
During the placebo period of this trial, participants will continue to take non-study medications as prescribed. Therefore, although there are currently available evidence based treatments for the symptom targets of this study, participants will not be deprived of these medications during the placebo phase owing to the study design.

b. State the maximum total length of time a participant may receive placebo while on the study.

2 weeks

c. Address the greatest potential harm that may come to a participant as a result of receiving placebo.

If the active study agent, transdermal nicotine, proves to be therapeutic, participants will be deprived of this benefit while on placebo.

d. Describe the procedures that are in place to safeguard participants receiving placebo.

Our trial design ensures that no one is receiving placebo only in lieu of nicotine patch therapy. All participants will ultimately receive nicotine patch, and thus all have the possibility of benefiting from the treatment. All study participants exposed to nicotine will be evaluated by study staff within seven days. Participants will have ability to reach study staff at any time during the trials. Furthermore, in case of severe or intolerable side effects, the transdermal route allows patients to remove the nicotine patch if instructed, with cessation of unwanted side effects within minutes to hours. Finally, participants who are undergoing active medication changes are excluded from this study. This will safeguard patient’s whose non-study medication choices might be influenced by enrollment within this study.

6. Use of Controlled Substances:
Will this research project involve the use of controlled substances in human subjects?
☐ Yes  ☒ No  See HIC Application Instructions to view controlled substance listings.

If yes, is the use of the controlled substance considered:
☐ Therapeutic: The use of the controlled substance, within the context of the research, has the potential to benefit the research participant.
☐ Non-Therapeutic: Note, the use of a controlled substance in a non-therapeutic research study involving human subjects may require that the investigator obtain a Laboratory Research License. Examples include controlled substances used for basic imaging, observation or biochemical studies or other non-therapeutic purposes. See Instructions for further information.

7. Continuation of Drug Therapy After Study Closure  ☐ Not applicable to this project
Are subjects provided the opportunity to continue to receive the study drug(s) after the study has ended?
☒ Yes  If yes, describe the conditions under which continued access to study drug(s) may apply as well as conditions for termination of such access.
Subjects will not be provided with transdermal nicotine from the study after completion. However, transdermal nicotine is available as an over-the-counter medication to adults age 18 and over. It will be explained to the patient that the evidence base for long-term transdermal nicotine have not been established, and that they should consult their physician if considering using this agent.

☐ No If no, explain why this is acceptable.

B. DEVICES

1. Are there any investigational devices used or investigational procedures performed at YNHH, e.g., YNHH Operating Room or YNHH Heart and Vascular Center? Yes ☐ No ☒

   If Yes, please be aware of the following requirements:
   a. A YNHH New Product/Trial Request Form must be completed;
   b. Your request must be reviewed and approved by a Hospital Committee before patients may be scheduled; and
   c. The notice of approval from YNHH must be submitted to the HIC for the protocol file.

   Please contact Gina D’Agostino, gina.d’agostino@ynhh.org or 203-688-5052, to initiate the process.

2. What is the name of the device to be studied in this protocol?

   Has this device been FDA approved? ☐ Yes ☐ No
   If yes, state for what indication.

3. **Background Information:** Provide a description of previous human use, known risks, and any other factors that might influence risks. If this is the first time this device is being used in humans, include relevant data on animal models.

4. **Source:**
   a) Identify the source of the device to be used.
   
   b) Is the device provided free of charge to subjects? ☐ Yes ☐ No

5. What is the PI’s assessment of risk level (significant or non-significant) associated with the use of the device?
**Significant Risk (SR) Device Study:** A study of a device that presents a potential for serious risk to the health, safety, or welfare of a participant and 1) is intended as an implant; 2) is used in supporting or sustaining human life; or otherwise prevents impairment of human health; 3) is of substantial importance in diagnosing, curing, mitigating or treating disease, or otherwise prevents impairment of human health; or 4) otherwise presents a potential for serious risk to the health, safety, or welfare of a participant.

Significant Risk Devices require an Investigational Device Exemption (IDE) issued by the FDA.

What is the **IDE number** assigned by the FDA?

Did the FDA approve this IDE as **Category A** (experimental/investigational) or as **Category B** (non-experimental/investigational)?

Who holds the IDE?

**Non-Significant Risk (NSR) Device Study:** A study of a device that does not meet the definition for a significant risk device and does not present a potential for serious risk to the health, safety, or welfare of participants. Note that if the HIC concurs with this determination, an IDE is not required.

6. **Abbreviated IDE or Exempt IDE:** There are abbreviated requirements for an IDE and there also are exemptions to the requirement for an IDE. See the criteria in the HIC Application Instructions, Section VI.B.4 at [http://www.yale.edu/hrpp/resources/docs/100FR1aHICProtocol_Application_Instructions5-25-11.pdf](http://www.yale.edu/hrpp/resources/docs/100FR1aHICProtocol_Application_Instructions5-25-11.pdf) to determine if these pertain to this study.

**Abbreviated IDE or Exempt IDE** – If criteria set forth in the HIC Application Instructions are met, copy and paste the completed relevant section from the Instructions into this application.

7. **Investigational device accountability:**

a. State how the PI, or named designee, ensures that an investigational device is used only in accordance with the research protocol approved by the HIC, and maintains control of the investigational device as follows:

   Maintains appropriate records, including receipt of shipment, inventory at the site, dispensation or use by each participant, and final disposition and/or the return of the investigational device (or other disposal if applicable):

Documents pertinent information assigned to the investigational device (e.g., date, quantity, batch or serial number, expiration date if applicable, and unique code number):

Stores the investigational device according to the manufacturer's recommendations with respect to temperature, humidity, lighting, and other environmental considerations:

Ensures that the device is stored in a secure area with limited access in accordance with applicable regulatory requirements:
Distributes the investigational device to subjects enrolled in the IRB-approved protocol:

**SECTION VII: RECRUITMENT/CONSENT AND ASSENT PROCEDURES**

1. **Targeted Enrollment: Give the number of subjects:**
   a. targeted for enrollment at Yale for this protocol _16_
   b. If this is a multi-site study, give the total number of subjects targeted across all sites ___

2. **Indicate recruitment methods below.** Attach copies of any recruitment materials that will be used.

   - [ ] Flyers
   - [ ] Internet/Web Postings
   - [ ] Radio
   - [ ] Posters
   - [ ] Mass E-mail Solicitation
   - [ ] Telephone
   - [ ] Letter
   - [ ] Departmental/Center Website
   - [ ] Television
   - [ ] Medical Record Review
   - [ ] Departmental/Center Research Boards
   - [ ] Newspaper
   - [ ] YCCI Recruitment database
   - [ ] Web-Based Clinical Trial Registries
   - [ ] Clinicaltrials.gov Registry (do not send materials to HIC)
   - [x] Other (describe): Individual email with general information about the study to targeted recipients

3. **Recruitment Procedures:**
   Potential subjects will be individuals, or children of individuals currently attending support or advocacy groups in greater New Haven for adults with ASD, patients of local providers working with individuals with ASD, and students at therapeutic schools or organizations for individuals with ASD. We will approach providers within these organizations using individual email, telephone, and/or mailing our study informational pamphlet.

   Providers/educators/support group workers will be educated and informed that their role is solely to identify individuals who may be eligible and interested in the study and that participation in the study is entirely voluntary with no repercussions on the therapeutic relationship. Individuals or parents interested in the study will be provided the opportunity to facilitate telephonic contact with the investigators. Specifically, contact information will be provided to potential participants or telephone numbers collected of participants who would like to be contacted by study investigators. Once telephone contact is made, the study procedure will be briefly explained to participants, including the requirement for a diagnosis of ASD. Potentially interested participants will be invited for a screening visit at the YCSC. It will be explained to participants or their parents that should they meet inclusion and exclusion criteria at the time of the study, and agree to further participation, that study procedures will commence at this visit.

   We will also recruit through study posting on national websites that promote the listing of studies. For instance, we plan to post our study on the websites of Autism Speaks and the National Alliance on Mental Illness (NAMI). Finally, our trial is listed on clinicaltrials.gov, which provides investigator contact information for individuals interested in learning more about our study.

4. **Screening Procedures**
   a. Will email or telephone correspondence be used to screen potential subjects for eligibility prior to the potential subject coming to the research office? [x] Yes  [ ] No
b. If yes, identify below all health information to be collected as part of screening and check off any of the following HIPAA identifiers to be collected and retained by the research team during this screening process.

**HEALTH INFORMATION TO BE COLLECTED:** Name, birth date, telephone number, diagnosis, symptoms, medication use (y/n), tobacco use (y/n), and high blood pressure status (y/n).

HIPAA identifiers:
- Names
- All geographic subdivisions smaller than a State, including: street address, city, county, precinct, zip codes and their equivalent geocodes, except for the initial three digits of a zip code if, according to the current publicly-available data from the Bureau of the Census: (1) the geographic unit formed by combining all zip codes with the same three initial digits contains more than 20,000 people, and (2) the initial three digits of a zip code for all such geographic units containing 20,000 or fewer people is changed to 000.
- Telephone numbers
- Fax numbers
- E-mail addresses
- Social Security numbers
- Medical record numbers
- Health plan beneficiary numbers
- Account numbers
- All elements of dates (except year) for dates related to an individual, including: birth date, admission date, discharge date, date of death, all ages over 89 and all elements of dates (including year) indicative of such age, except that such ages and elements may be aggregated into a single category of age 90 or older
- Certificate/license numbers
- Vehicle identifiers and serial numbers, including license plate numbers
- Device identifiers and serial numbers
- Web Universal Resource Locators (URLs)
- Internet Protocol (IP) address numbers
- Biometric identifiers, including finger and voice prints
- Full face photographic images and any comparable images
- Any other unique identifying numbers, characteristics, or codes

5. **Assessment of Current Health Provider Relationship for HIPAA Consideration:**
   Does the Investigator or any member of the research team have a direct existing clinical relationship with any potential subject?
   - Yes, all subjects
   - Yes, some of the subjects
   - No

   If yes, describe the nature of this relationship.
6. **Request for waiver of HIPAA authorization:** (When requesting a waiver of HIPAA Authorization for either the entire study, or for recruitment purposes only. Note: if you are collecting PHI as part of a phone or email screen, you must request a HIPAA waiver for recruitment purposes.)

**Choose one:** For entire study: _____ For recruitment purposes only: __X__
- i. Describe why it would be impracticable to obtain the subject’s authorization for use/disclosure of this data;
- ii. If requesting a waiver of **signed** authorization, describe why it would be impracticable to obtain the subject’s signed authorization for use/disclosure of this data; We will recruit subjects via a phone screening, and thus it is impractical to obtain a signed authorization prior to recruitment.

By signing this protocol application, the investigator assures that the protected health information for which a Waiver of Authorization has been requested will not be reused or disclosed to any person or entity other than those listed in this application, except as required by law, for authorized oversight of this research study, or as specifically approved for use in another study by an IRB.

Researchers are reminded that unauthorized disclosures of PHI to individuals outside of the Yale HIPAA-Covered entity must be accounted for in the “accounting for disclosures log”, by subject name, purpose, date, recipients, and a description of information provided. Logs are to be forwarded to the Deputy HIPAA Privacy Officer.

7. **Required HIPAA Authorization:** If the research involves the creation, use or disclosure of protected health information (PHI), separate subject authorization is required under the HIPAA Privacy Rule. Indicate which of the following forms are being provided:
   - [ ] Compound Consent and Authorization form
   - [X] HIPAA Research Authorization Form

8. **Consent Personnel:** List the names of all members of the research team who will be obtaining consent/assent.
   - Alan Lewis

9. **Process of Consent/Assent:** Describe the setting and conditions under which consent/assent will be obtained, including parental permission or surrogate permission and the steps taken to ensure subjects’ independent decision-making.

Consent will be obtained from participants or a parent (if they are unable to provide consent, and a parent remains their legal guardian) in a private office at the Yale Child Study Center or the Connecticut Mental Health Center or SUS, Bronx, NY. If subjects are not already clients of Connecticut Mental Health Center, a new outpatient chart will be created at that time. The subject or the subject and their parent, and one of the investigators will necessarily be present for the consent process. Participants who are accompanied by a family member or caregiver will be allowed the option of having that person in the room if required. The inclusion and exclusion criteria will ensure that participants have capacity for informed consent, or that a parent guardian is available to provide consent in their stead. Participants and their parent guardian(s) will be
given ample time to ask questions during the consent procedure, and to consult family members or caregivers prior to making a decision. Participants will be informed during the initial telephonic contact that they will be paid for this initial visit whether or not they decide to participate in the study.

10. Evaluation of Subject(s) Capacity to Provide Informed Consent/Assent: Indicate how the personnel obtaining consent will assess the potential subject’s ability and capacity to consent to the research being proposed.

During the screening process, the details of the study will be explained carefully to the subject. After time has been for the participant to ask any clarifying questions, the subject will be asked to summarize their understanding of the procedures, risks and benefits of the study. The study personnel will address any inaccuracies, but after two attempts at clarification, if a subject is unable to give a reasonable account of the study procedures, risks and benefits, they will be considered to not have capacity for consent. In this instance, if the subject has a parent who is also their legal guardian, they will be invited to provide consent on the subject's behalf.

11. Documentation of Consent/Assent: Specify the documents that will be used during the consent/assent process. Copies of all documents should be appended to the protocol, in the same format that they will be given to subjects.

A detailed consent form will be provided, which participants and a study personnel member will be required to sign. Participants will also be required to sign a HIPAA Research Authorization Form. A separate consent form will be provided with revised language in the event that a parent guardian provides consent. See attached documents.

12. Non-English Speaking Subjects: Explain provisions in place to ensure comprehension for research involving non-English speaking subjects. Translated copies of all consent materials must be submitted for approval prior to use.

Our inclusion criteria require English fluency.

13. Consent Waiver: In certain circumstances, the HIC may grant a waiver of signed consent, or a full waiver of consent, depending on the study. If you will request either a waiver of consent, or a waiver of signed consent for this study, complete the appropriate section below.

☐ Not Requesting a consent waiver
☒ Requesting a waiver of signed consent
☐ Requesting a full waiver of consent

A. Waiver of signed consent: (Verbal consent from subjects will be obtained. If PHI is collected, information in this section must match Section VII, Question 6)

☒ Requesting a waiver of signed consent for Recruitment/Screening only

If requesting a waiver of signed consent, please address the following:

a. Would the signed consent form be the only record linking the subject and the research?

☐ Yes  ☐ No
b. Does a breach of confidentiality constitute the principal risk to subjects?  
☐ Yes  ☐ No  

OR  

c. Does the research activity pose greater than minimal risk?  
☐ Yes  If you answered yes, stop. A waiver cannot be granted.  Please note: Recruitment/screening is generally a minimal risk research activity  
☒ No  

AND  

d. Does the research include any activities that would require signed consent in a non-research context?  
☐ Yes  ☒ No  

☐ Requesting a waiver of signed consent for the Entire Study  (Note that an information sheet may be required.)  
If requesting a waiver of signed consent, please address the following:  
a. Would the signed consent form be the only record linking the subject and the research?  
☐ Yes  ☐ No  
b. Does a breach of confidentiality constitute the principal risk to subjects?  
☐ Yes  ☐ No  

OR  

B. Full waiver of consent: (No consent from subjects will be obtained for the activity.)  
☐ Requesting a waiver of consent for Recruitment/Screening only  
a. Does the research activity pose greater than minimal risk to subjects?  
☐ Yes  If you answered yes, stop. A waiver cannot be granted.  Please note: Recruitment/screening is generally a minimal risk research activity  
☒ No  
b. Will the waiver adversely affect subjects’ rights and welfare?  
☐ Yes  ☐ No  
c. Why would the research be impracticable to conduct without the waiver?  
d. Where appropriate, how will pertinent information be returned to, or shared with subjects at a later date?  

☐ Requesting a full waiver of consent for the Entire Study  (Note: If PHI is collected, information here must match Section VII, question 6.)  
If requesting a full waiver of consent, please address the following:
a. Does the research pose greater than minimal risk to subjects?
   ☐ Yes  If you answered yes, stop. A waiver cannot be granted.
   ☐ No

b. Will the waiver adversely affect subjects’ rights and welfare? ☐ Yes ☐ No

c. Why would the research be impracticable to conduct without the waiver?

d. Where appropriate, how will pertinent information be returned to, or shared with subjects at a later date?

SECTION VIII: PROTECTION OF RESEARCH SUBJECTS

Confidentiality & Security of Data:

a. What protected health information (medical information along with the HIPAA identifiers) about subjects will be collected and used for the research?

   The subject’s diagnosis and details about symptomology will be collected at several points throughout the study. Details of the patients BMI and vital signs will also be collected. As part of consent procedures, participants’ names, date of birth, and contact information will be collected.

b. How will the research data be collected, recorded and stored?

   Data will be collected by research personnel at the Yale Child Study Center or the Connecticut Mental Health Center, who will complete rating scales on paper, as well as collect basic information as described under section VIII a. This information will be stored in an individual envelop for each patient in a locked filling cabinet in the office of Dr. Alan Lewis.

c. How will the digital data be stored? ☐ CD ☐ DVD ☐ Flash Drive ☑ Portable Hard Drive ☐ Secured Server ☑ Laptop Computer ☐ Desktop Computer ☐ Other

d. What methods and procedures will be used to safeguard the confidentiality and security of the identifiable study data and the storage media indicated above during and after the subject’s participation in the study?

   The storage media will be kept in a locked filling cabinet in Dr. Sukhodolsky’s research lab (rooms G-69 and G-67 in the I-wing of the Sterling Hall of Medicine). All devices will be encrypted and password protected. Only the investigators will have access to passwords. The identifying data will not be stored in the same database as the study data; study data will be coded and stored separately.

   Do all portable devices contain encryption software? ☑ Yes ☐ No
   If no, see [http://hipaa.yale.edu/guidance/policy.html](http://hipaa.yale.edu/guidance/policy.html)

e. What will be done with the data when the research is completed? Are there plans to destroy the identifiable data? If yes, describe how, by whom and when identifiers will be destroyed. If no, describe how the data and/or identifiers will be secured.

   Identifying information will be deleted. The non-identifying study data will be transferred to a portable hard drive and stored in a locked filling cabinet.
f. Who will have access to the protected health information (such as the research sponsor, the investigator, the research staff, all research monitors, FDA, Yale Cancer Center Data and Safety Monitoring Committee (DSMC), SSC, etc.)? (please distinguish between PHI and de-identified data)

All study personnel listed on this protocol.

g. If appropriate, has a Certificate of Confidentiality been obtained? NA

h. Are any of the study procedures likely to yield information subject to mandatory reporting requirements? (e.g. HIV testing – reporting of communicable diseases; parent interview - incidents of child abuse, elderly abuse, etc.). Please verify to whom such instances will need to be reported. No.

### SECTION IX: POTENTIAL BENEFITS

**Potential Benefits:** Identify any benefits that may be reasonably expected to result from the research, either to the subject(s) or to society at large. (Payment of subjects is not considered a benefit in this context of the risk benefit assessment.)

As described earlier in the application, aggression and irritability comorbid with ASD confers a heavy burden in the form of increased exposure to potentially harmful medications, increased risks of hospitalization and residential placement, and significantly increased caregiver burden, which translates to increased potential for patient abuse. Novel pharmacotherapy with a risk-benefit profile superior to those agents currently available will be of benefit to both subjects as well as society at large. Importantly, subjects within the trial stand to benefit directly from the pharmacotherapy within the trial, and as described previously, there is little if any barrier to continuing the treatment after the trial if they derive substantial symptomatic improvement.

### SECTION X: RESEARCH ALTERNATIVES AND ECONOMIC CONSIDERATIONS

1. **Alternatives:** What other alternatives are available to the study subjects outside of the research?

Pharmacotherapy and behavior therapies are available to subjects with aggression and irritability in the context of ASD. Individuals participating in the study are not asked to discontinue pharmacotherapy or behavior therapies they are engaged in prior to beginning the study. However, as described above, pharmacological agents carry with them significant side effect burdens.

2. **Payments for Participation (Economic Considerations):** Describe any payments that will be made to subjects, the amount and schedule of payments, and the conditions for receiving this compensation.

All subjects will be compensated for their participation in the trial. Participants who are identified as potential subjects will be invited for screening at visit 1. Those who appear
for this visit but do not qualify for the study will be compensated $15 for their time, which we expect will not exceed 15 minutes. Those who do qualify for the study but do not wish to participate or are unable to provide full informed consent will also be compensated $15. Those participants who qualify, agree to participate, provide informed consent, and complete the baseline behavioral ratings will be compensated $90, a visit which we anticipate will take 90 minutes. At subsequent visits number 2 and 3, which we anticipate will take 60 minutes, subjects will be compensated $60.

3. **Costs for Participation (Economic Considerations):** Clearly describe the subject’s costs associated with participation in the research, and the interventions or procedures of the study that will be provided at no cost to subjects.

   Costs associated with participation include transportation to the Yale Child Study Center or Connecticut Mental Health Center. All interventions or procedures performed during the study are provided at no cost to subjects.

4. **In Case of Injury:** This section is required for any research involving more than minimal risk.
   a. Will medical treatment be available if research-related injury occurs? There will be no additional medical treatment available to subjects above and beyond what was available prior to initiating the study. The study visits will be conducted by either licensed physicians or study staff working directly with licensed physicians. Emergency medical treatment is available at Yale-New Haven Hospital, less than one block from the Yale Child Study Center and Connecticut Mental Health Center. All study subjects will be able to contact study staff throughout their enrollment in the study. Study subjects will be informed that research-related injury will be covered by their pre-study healthcare plans.

   Study subjects will have the contact information of a licensed physician at all times and they will be available for consultation to determine whether the patient should seek medical treatment during the study.

   Subjects and legal guardians of subjects who will participate in the study at the Services for the Underserved site will acknowledge that medical care will be obtained as would be obtained prior to their study enrollment, however the study physician, Dr. Lewis, will be available at all times to provide consultation by phone.

   b. Where and from whom may treatment be obtained? Subjects will obtain treatment either from their current outpatient physicians or via emergency medical services, as recommended by the study physician.

   c. Are there any limits to the treatment being provided? There are no limits to the treatment provided. Treatment decisions will be made entirely by the patient’s outpatient physician or emergency medical provider and will not be affected by the individual's participation in the study.

   d. Who will pay for this treatment?
Subjects will be responsible to pay for any treatment required. This is clearly described in the consent form.

e. How will the medical treatment be accessed by subjects?
Treatment will be accessed in the same manner as if the subject were not enrolled in the study.

References


