

**AWARD NUMBER:** W81XWH-17-1-0253

**TITLE:** Cannabidiol (CBDV) Versus Placebo in Children with Autism Spectrum Disorder (ASD)

**PRINCIPAL INVESTIGATOR:** Eric Hollander, MD

**CONTRACTING ORGANIZATION:**  
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| <b>4. TITLE AND SUBTITLE</b><br>Cannabidiol (CBDV) versus placebo in children with Autism Spectrum Disorder   |                                 | <b>5a. CONTRACT NUMBER</b>                          |
|   |                                 | <b>5b. GRANT NUMBER</b><br>W81XWH-17-1-0253         |
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**14. ABSTRACT**

The CDC currently estimates 1 in 59 children have Autism Spectrum Disorder (ASD). Children with ASD have problems with social communication, irritability, repetitive behaviors, impulsivity, temper tantrums, and a high caregiver burden. The only medications approved by the FDA for symptoms of ASD are aripiprazole and risperidone. Both of these are used to reduce irritability but have short-term and long-term side effects.

During year one of this project, we obtained OPR HRPO, New York State Department of Health, Bureau of Narcotic Enforcement (BNE) Class 7 Individual Researcher and Class 9 Importer licenses, DEA Schedule I license, IND study may proceed status, Albert Einstein College of Medicine Institutional Review Board Einstein IRB #1, East and New York University Langone Medical Center IRB #6 regulatory approvals to conduct this study. We prepared all necessary assessments and source documents and advertisement materials. We conducted raters training. We identified 28 patients interested to be enrolled in the study, once contract signature with CBDV supplier is finalized.

This double-blind randomized placebo-controlled study will test the efficacy and safety of a new medication, cannabidivarin (CBDV), to treat autism in children ages 5-18. CBDV is non-psychoactive, is derived from the cannabis plant, but has effects opposite to THC. Approximately 100 patients will be enrolled at Montefiore-Einstein and NYU sites during the duration of the study. The study lasts up to 16 weeks, and during this time, patient's will come 9 times for study visits. Mood, social and cognitive functions will be assessed by the means of research questionnaires. All adverse effects will be reported. We will assess the effects of CBDV versus placebo on irritability and social functions in patients with ASD.

**15. SUBJECT TERMS**

|  |                    |                     |                                   |                            |   |
|--|--------------------|---------------------|-----------------------------------|----------------------------|---|
| <b>16. SECURITY CLASSIFICATION OF:</b> |                    |                     | <b>17. LIMITATION OF ABSTRACT</b> | <b>18. NUMBER OF PAGES</b> | <b>19a. NAME OF RESPONSIBLE PERSON</b><br>USAMRMC       |
| <b>a. REPORT</b>                       | <b>b. ABSTRACT</b> | <b>c. THIS PAGE</b> |                                   |                            | <b>19b. TELEPHONE NUMBER</b> <i>(include area code)</i> |
|  |                    |                     | Unclassified                      |                            |   |

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**1. INTRODUCTION:** *Narrative that briefly (one paragraph) describes the subject, purpose and scope of the research.*

The CDC currently estimates 1 in 59 children have Autism Spectrum Disorder (ASD). Children with ASD have problems with social communication, irritability, repetitive behaviors, impulsivity, temper tantrums, and a high caregiver burden. The only medications approved by the FDA for symptoms of ASD are aripiprazole and risperidone. Both of these are used to reduce irritability but have short-term and long-term side effects. This double-blind randomized placebo-controlled study will test the efficacy and safety of a new medication, cannabidiol (CBDV), to treat autism in children ages 5-18. CBDV is non-psychoactive, is derived from the cannabis plant, but has effects opposite to THC. Approximately 100 patients will be enrolled at Montefiore-Einstein and NYU sites during the duration of the study. The study lasts up to 16 weeks, and during this time, patient's will come 9 times for study visits. Mood, social and cognitive functions will be assessed by the means of research questionnaires. All adverse effects will be reported. We will assess the effects of CBDV versus placebo on irritability and social functions in patients with ASD.

**2. KEYWORDS:** *Provide a brief list of keywords (limit to 20 words).*

Cannabidiol, Autism spectrum Disorders, irritability, cannabinoids, autism, repetitive behaviors

**3. ACCOMPLISHMENTS:** *The PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official whenever there are significant changes in the project or its direction.*

**What were the major goals of the project?**

*List the major goals of the project as stated in the approved SOW. If the application listed milestones/target dates for important activities or phases of the project, identify these dates and show actual completion dates or the percentage of completion.*

|   | <b>Timeline</b> | <b>AECOM/Monte</b>  | <b>NYU</b>                   |
|---|-----------------|---|------------------------------|
| <b>Major Task 1: Preparatory Stage</b>  | Months          |   |                              |
| <b>Subtask 1: Prepare and Submit Regulatory Documents</b>   |                 |   |                              |
| Coordinate with Sites and GW Pharma for clinical trial agreements (CTAs) submission   | 1-4             | 90%   | 90%                          |
| Coordinate with Sites and GW Pharma for nondisclosure agreements (NDAs).  | 1-4             | 06/03/2016  | 06/03/2016                   |
| Coordination with GW Pharma and other sites for the continued work on the submission or re-submission of an Investigational New Drug (IND) application to the U.S. Food and Drug Administration. The Investigators plan to submit the IND application prior to study start so that approval is underway when the funding period begins. | 1-4             | IND application submitted on 01/19/2018. IND may proceed status granted on 04/02/2018 | Same status as at AECOM/ MMC |
| Refine eligibility criteria, exclusion criteria, screening protocol   | 1-4             | 100%  | 100%                         |
| Finalize consent form & human subjects protocol   | 1-4             | 100%  | 100%                         |
| Finalize recruitment materials  | 1-4             | 100%  | 100%                         |
| Coordinate with Sites for the US Army Medical Research and Material Command Office of Research Protections (ORP) and the Human Research Protection Office (HRPO) Submission   | 1-4             | 100%  | 100%                         |

|  |           |                     |                     |
|--|-----------|---------------------|---------------------|
| Coordinate with Sites for IRB protocol submission  | 1-4       | 100%                | 100%                |
| Coordinate with Sites for CTSA sponsored Clinical Research Center (CRC) approval                           | 1-4       | 90%                 | 90%                 |
| Submit amendments, adverse events and protocol deviations as needed  | As Needed | As needed           | As needed           |
| Coordinate with Sites for annual IRB report for continuing review  | Annually  | Annually            | Annually            |
| <i>Milestone Achieved: Local IRB approval at AECOM/Monte and NYU</i>                                       | 4         | 05/15/2018          | 05/02/2018          |
| <i>Milestone Achieved: HRPO and ORP approval for protocol</i>  | 4         | 05/25/2018          |                     |
| <b>Subtask 2: Training of Study Staff</b>  |           |                     |                     |
| Coordinate with Sites for Coordinator training   | 4-6       | 100%,<br>06/01/2018 | 100%,<br>06/01/2018 |
| Coordinate with Sites for training Raters until 100% concordance   | 4-6       | 100%,<br>06/01/2018 | 100%<br>06/01/2018  |
| Complete Regulatory Binders  | 4-6       | 100%                | 100%                |
| Create Manual of Operations  | 4-6       | 100%                | 100%                |
| <i>Milestone Achieved: Research staff trained and Regulatory procedures set up</i>                         | 4-6       | 06/01/2018          | 06/01/2018          |
| <b>Subtask 3: Facilitate Communication Between Sites and Staff</b>   |           |                     |                     |
| Coordinate with Sites bi-weekly meetings to review study goals, recruitment and enrollment                 | 1-48      | 100%                | 100%                |
| <i>Milestone Achieved: Bi-weekly meetings completed throughout study</i>                                   | 1-48      | Study is ongoing    | Study is ongoing    |
| <b>Subtask 4: Assessments and Surveys Preparation</b>  |           |                     |                     |
| Finalize assessment measurements   | 4-6       | 100%                | 100%                |
| Order all assessments and distribute across sites  | 4-6       | 100%                | 100%                |
| Prepare Patient Study Binders including surveys and source documents                                       | 4-6       | 100%                | 100%                |
| <i>Milestone Achieved: All study materials prepared for patient enrollment</i>                             | 4-6       | 100%                | 100%                |
| <b>Subtask 5: Receipt of Study Drug</b>  |           |                     |                     |
| Develop protocol with pharmacy for storage and dispensing of study drug/placebo and randomization protocol | 1-4       | 08/01/2018          | 08/01/2018          |
| Work with GW Pharma to ship study drug and placebo to sites  | 6         | Pending             | Pending             |
| <i>Milestone Achieved: Receipt of Study Drug and Placebo</i>   | 6         | Pending             | Pending             |
| <b>Subtask 6: Data Management Preparation</b>  |           |                     |                     |
| Coordinate with Sites for flow chart for study steps, data collection and database requirements            | 4-6       | 100%                | 100%                |
| Develop and Maintain Electronic Database with the ICTR at AECOM  | 4-48      | 50%                 | 50%                 |
| <i>Milestone Achieved: Electronic database prepared and maintained throughout study</i>                    | 4-48      | Study is ongoing    | Study is ongoing    |
| <b>Major Task : Participant Recruitment and Enrollment</b>   |           |                     |                     |
| Subtask 1: Begin Subject Recruitment   |           |                     |                     |
| Contact patients in site databases   | 6-42      | 100%                | 100%                |
| Advertise using internet and radio advertisements and study  | 6-42      | 50%                 | 50%                 |

|   |       |                       |                       |
|---|-------|-----------------------|-----------------------|
| flyers  |       |                       |                       |
| <i>Milestone Achieved: All patients in databases contacted</i>                                    | 6     | 100%, ongoing         | 100%, ongoing         |
| <i>Milestone Achieved: 1<sup>st</sup> Advertisements are placed</i>                               | 6     | 50%, study is ongoing | 50%, study is ongoing |
| Subtask 2: Conduct Study  |       |                       |                       |
| Consent and screen potential patients and review I/E criteria (n=100)                             | 6-42  | Pending               | Pending               |
| Evaluate and assign eligible participants to one of the two randomized groups                     | 6-42  | Pending               | Pending               |
| Participants complete assigned condition over 12 weeks  | 6-42  | Pending               | Pending               |
| Assess all participants at the appropriate study visits   | 6-42  | Pending               | Pending               |
| <i>Milestone Achieved: Study Begins</i>   | 6     | Pending               | Pending               |
| <i>Milestone Achieved: 1<sup>st</sup> Patient Consented and Enrolled</i>                          | 6     | Pending               | Pending               |
| <i>Milestone Achieved: Last Patient Consented and Enrolled</i>                                    | 42    | Pending               | Pending               |
| <b>Major Task : Data Analysis and Publication</b>   |       |                       |                       |
| Subtask 1: Coordinate with Sites for monitoring data collection rates and data quality            |       |                       |                       |
| Perform all analyses according to specifications, share output and finding with all investigators | 42-48 | Pending               | Pending               |
| Work with data core and dissemination of findings (abstracts, presentation, publications, DOD)    | 42-48 | Pending               | Pending               |
| Share data with NDAR  | 42-48 | Pending               | Pending               |
| <i>Milestone Achieved: Report results from data analyses</i>                                      | 42-48 | Pending               | Pending               |
| <i>Milestone Achieved: Share results with NDAR</i>  | 42-48 | Pending               | Pending               |

## What was accomplished under these goals?

### Major Task 1: Preparatory Stage.

#### **Subtask 1: Prepare and Submit Regulatory Documents.**

*-Coordinate with Sites and GW Pharma for Clinical Trial Agreements (CTA) Submission.*

We regularly discussed all contract-related issues with Dr. Dhanonjoy C. Saha, Director of Office of Grant Support at AECOM/MMC. Furthermore, we conducted a series of conference calls for CTA negotiation and revisions with Deirdre Flaherty, Head of Pipeline Programs at GW Pharma, which occurred on 9/11/17, 10/20/17 and 10/23/17.

On 01/22/2018 we conducted a meeting between Dr. Eric Hollander (AECOM/MMC), Dr. Vera Nezgovorova (AECOM/MMC), Deirdre Flaherty (GW Pharma) and James Ryan (GW Pharma Contract Specialist) to finalize terms of statistical support for the project and discuss study drug dispense questions. Same day, a revised draft of the CTA was received for review by Dr. Dhanonjoy C. Saha, Director of Office of Grant support at AECOM/MMC. On 02/07/2018 we conducted a meeting with Attorney Laura Wilson-Youngblood, Assistant Counsel at AECOM/MMC, to review the terms before she could proceed for further negotiation of final details with GW Pharma.

On 03/16/18 a call between Attorney Laura Wilson-Youngblood, Assistant Counsel at AECOM/MMC, Deirdre Flaherty (GW Pharma), James Ryan (GW Pharma Contract Specialist), Dr. Eric Hollander (AECOM/MMC) and Dr. Vera Nezgovorova (AECOM/MMC) occurred to further negotiate details of the CTA with GW Pharma with an emphasis on Steering Committee charter development. It was decided that AECOM/MMC will

proceed with CTA signature with GW Pharma, and a subcontract will be than issued between AECOM/MMC and NYU to document the terms of collaboration for this study. Subcontract between AECOM/MMC and NYU is currently being finalized.

Following that call, CTA updated by GW Pharma was reviewed by Einstein legal team, which included Lara Jean Ancona, Esq., Partner at Garfunkel Wild firm. Feedback on breaking the blind for the analyses; rights and liabilities of GW Pharma and feedback on publications committee has been incorporated. CTA and Steering Committee Charter were submitted for GW Pharma review on 03/30/18. To further address final terms of the agreement, a call between Dr. Volker Knappertz (Chief Medical Officer at GW Pharma), Deirdre Flaherty (GW Pharma) and Dr. Eric Hollander (AECOM/MMC) occurred on 05/03/18, where key points of the CTA were reviewed prior to its execution by legal teams on both sides. On 05/10/2018 Einstein legal team, comprising Attorney Laura Wilson-Youngblood, Assistant Counsel at AECOM/MMC and Lara Jean Ancona, Esq., Partner at Garfunkel Wild firm, had a call with James Ryan (GW Pharma Contract Specialist) to finalize terms of the CTA. Revisions to the contract in regards to IP and data analysis provisions were incorporated by GW Pharma contract department and Einstein legal team and sent to GW Pharma contract division for approval on 06/13/2018. GW Pharma contract division completed review of the revised contract terms on 07/18/2018. Dr. Eric Hollander (AECOM/MMC), Dr. Orrin Devinski (NYU) and Dr. Volker Knappelz (Chief Medical Officer at GW Pharma) had a call on 07/20/2018 to discuss IP provisions for the CTA finalization. Einstein legal team had a series of calls with Cynthia Clark, attorney from Greenwich Biosciences (US subsidiary of GW Pharmaceuticals) on 07/18/2018 and 08/07/2018 to discuss IP provisions.

Legal team of AECOM/MMC is currently finalizing signature of the CTA contract with GW Pharma.

- *Coordinate with Sites and GW Pharma for Nondisclosure Agreements (NDA).*

Two-way confidentiality agreement between Montefiore Medical Center and GW Pharma has been signed as of June 3 2016, and the copy of the executed CDA is on file.

-*Coordinate with GW Pharma and other sites for the continued work on the submission or resubmission of an Investigational New Drug (IND) Application to the U.S. Food and Drug Administration.*

During current reporting period, we obtained a study May proceed letter from an Investigational New Drug (IND) Application to the U.S. Food and Drug Administration.

This work was preceded by a series of email communications and phone calls organized by Kevin Hong (AECOM/MMC) and Karen Twigden (GW Pharma), which took place on 7/26/17, 7/28/17, 8/7/17, 8/10/17, and 8/16/17. Dr. Hollander and Kevin Hong organized and participated in a meeting with Dr. Orrin Devinsky, Latoya King, and Anjanette Burns at NYU to review logistic obstacles and regulatory challenges associated with IND submission. Following that meeting on 9/11/2017, Dr. Hollander and GW Pharma agreed to delay IND application submission. It was suggested to wait until release of Edition 6 of the Investigator's Brochure (IB), as it would include updated pharmacokinetics and dosage regimen data pertinent to the upcoming IND submission. Upon release of IB edition 6 by GW Pharmaceuticals in preparation of our IND submission, we conducted a series of meetings with Dr. Michelle Wellborn (GW Pharma consultant) and Deirdre Flaherty (GW Pharma), which occurred on 11/22/2017, 11/27/2017 and 01/17/2018. Investigational New Drug Application to the U.S. Food and Drug Administration was submitted by us on 01/19/2018. It was received into Neurology Division Office on 02/01/2018 with assigned IND # 138371. Study may proceed letter from Department of Health and Human services, Food and Drug Administration, Division of Psychiatry Products, Office of Drug Evaluation I, Center for Drug Evaluation and Research was received on 04/02/18 with non-hold comments. These non-hold clinical and clinical pharmacology comments were incorporated in the study protocol. On 04/13/18 a call between Deirdre Flaherty (GW Pharma), Carole Baker (GW Pharma), Daniel Checketts (statistician, GW Pharma) Dr. Eric Hollander (AECOM/MMC) and Dr. Vera Nezgovorova (AECOM/MMC) occurred, where FDA may proceed letter comments with an emphasis on a strategy of incorporation of statistical feedback received were discussed. Non-hold statistical comments from the FDA Study May proceed letter are currently being incorporated in the protocol.



*-BNE application submission.*

On 10/9/17, Dr. Eric Hollander and Kevin Hong consulted Dr. Sheryl Haut, Director of the Adult Epilepsy Program and Chief of Neurology Service at AECOM/MMC, who had worked with a Cannabidiol containing compound from GW Pharma in the past to inquire about unanticipated challenges for the study implementation and were advised on importance of tandem submission to the Institutional Review Board and to the New York State Department of Health, Bureau of Narcotic Enforcement (BNE) for the timely BNE inspection scheduling and application processing.

We submitted application to the New York State Department of Health, Bureau of Narcotic Enforcement (BNE) for Class 7 Individual Researcher and Class 9 Importer licenses approvals in tandem with our IRB submission. Our BNE application was received as of 11/7/2017. Soon after AECOM/MMC Investigational Drug Service Pharmacy received BNE inspection for GW Pharma safe, which was approved. On 01/16/2018 after submitting conditional IRB approval notice for AECOM/MMC site, we were advised by Michele Mulloy, Regulatory Compliance Section Manager, Bureau of Narcotic Enforcement (BNE), that we would need to provide final unconditional IRB approval letter and IND approval letter from the FDA prior to the BNE final review and approval. Following FDA study may proceed letter receipt on 04/02/18, we received an IRB approval letter without IND clause, which satisfied Bureau of Narcotic Enforcement (BNE) requirements. Case number for BNE inspection was assigned. As we were moving forward with BNE inspection, we were advised that an independent safe designated only for Dr. Hollander study would be required as a condition for BNE approval. Reconditioned Amsec Plate Steel Safe Model 2230 (right swing) UL-TL-30 1 Group 1R radiological lock: SG560 UL group 1 lock, SGD550 dial w/ 10" spindle; SGR167 ring, SC, SPKL was successfully ordered and installed on 04/16/18. Inspector Johnson from the BNE completed site and safe inspection on 04/18/18. BNE review was completed on 04/25/18. Dr. Hollander received Class 7 Individual Researcher and Class 9 Importer licenses approvals on 05/11/2018.

*-DEA application submission.*

We communicated with Terrance Woodworth (GW Pharma consultant) and were advised to submit DEA application upon submission of our IND application prior to the IND approval by the FDA. Thus on 02/09/2018 we submitted DEA Schedule I application, which included the following items:

- DEA application form 225
- Certification that an IND application was submitted
- PI signed and dated CV
- Cover Letter
- Application Fee
- Copy of conditionally IRB approved study protocol
- IND acknowledgement letter

BNE approval and IND approval by the FDA are required for the subsequent DEA approval. IND approval by the FDA was received on 04/02/2018. However, in order to expedite DEA approval, we scheduled DEA Inspection on site. Inspector Rivera completed DEA inspection at AECOM/MMC on 04/11/18. Additional DEA inspection to approve reconditioned Amsec Plate Steel Safe Model 2230 (right swing) UL-TL-30 1 Group 1R radiological lock: SG560 UL group 1 lock, SGD550 dial w/ 10" spindle; SGR167 ring, SC, SPKL was conducted by Inspector Rivera on 05/18/2018. DEA Schedule I license was received on June 26 2018.

*-Finalize consent form and human subjects protocol*

After programmatic review and subsequent follow-up communications with Dr. Stan Niu, Science Officer at the Department of Defense, requested changes in the protocol have been incorporated. After a conference call on 10/20/17 between Dr. Eric Hollander (AECOM/MMC), Dr. Orrin Devinsky (NYU), Dr. Volker Knappertz (Chief Medical Office at GW Pharma), Deirdre Flaherty (GW Pharma), James Ryan (Contract specialist at GW Pharma), Dr. Vera Nezgovorova (AECOM/MMC), Kevin Hong (AECOM/MMC), Danya Schluskel (AECOM/MMC) and Dr. Bonnie Taylor (AECOM/MMC), language was added to eligibility criteria

regarding parent consent and child assent; exclusion criteria were specified regarding history of drug abuse. As the protocol was finalized, Dr. Hollander deemed that these additions were not substantive, and that they would not affect study recruitment process or statistical power.

Following a meeting on 11/22/17 between Dr. Eric Hollander (AECOM/MMC), Dr. Orrin Devinsky (NYU), Deirdre Flaherty (GW Pharma), Dr. Terrance Woodworth (GW Pharma), Dr. Michelle Wellborn (GW Pharma), Dr. Kenneth Sommerville (GW Pharma) Dr. Vera Nezgovorova (AECOM/MMC), Danya Schlusser (AECOM/MMC) and Dr. Bonnie Taylor (AECOM/MMC), language was added to human subjects protocol to include safety assessments. It was concluded that Columbia Suicide Severity Rating Scale will be administered in the beginning of each study visit. Following this meeting schedule of events was updated to include safety labs. As an additional statistical analysis not affecting statistical power, age of subject was proposed to be a covariate. Appendix A on P450 Drug Interactions, Flockchart table and Appendix B on U91A9 or U9T2B7 potential interactions were added to the human subjects protocol. Informed consent was revised to include language specifying potentials benefits to the study participant. IDSMC (Independent Data Safety Monitoring Committee) charter was developed and its members were confirmed. As the protocol and informed consent were finalized, Dr. Hollander deemed that these additions were not substantive, and that they would not affect study recruitment process or statistical power.

Following changes were made to the study protocol and ICF following HRPO ORP comments received on 02/13/18, and were IRB approved on 03/28/18:

1. Protocol: Section L: As required by the Human Research Protections Office (HRPO)/U.S. Army Medical Research and Materiel Command (USAMRMC) the role and responsibilities of the Research Monitor have been modified and now include: May discuss the protocol with the investigators, interview subjects, and consult with others outside the study about the research; Shall have the authority to stop the protocol, remove subjects from the protocol, and take any necessary steps to protect the safety and well-being of subjects until the IRB can assess the Monitor's report; Shall have the responsibility to promptly report their observations and findings to the IRB or other designated official; Is required to review all unanticipated problems involving risks to subjects or others, serious adverse events and all subject deaths associated with the protocol and provide an unbiased written report of the event. At a minimum, the research monitor must comment on the outcomes of the event or problem and in the case of a serious adverse event or death, comment on the relationship to participation in the study. The research monitor must also indicate whether he/she concurs with the details of the report provided by the principal investigator. Reports for events determined by either the investigator or research monitor to be possibly or definitely related to participation and report of events resulting in death must be promptly forwarded to the USAMRMC ORP HRPO.
2. Protocol: Section C7: As required by the Human Research Protections Office (HRPO)/U.S. Army Medical Research and Materiel Command (USAMRMC), the protocol must describe how participation in the research is intended to be beneficial to each subject participating in the study and the benefit(s) must apply to both the treatment and placebo groups. This section has been modified accordingly.
3. Consent Form: Page 7: The "Benefits" section of the ICF has been modified according to #2 above

*-Finalize recruitment materials.*

Drafting of recruitment materials, including flyers, advertisements, and referral solicitations was completed.

*-Coordinate with sites for the US Army Medical Research and Materiel Command Office of Research Protections (ORP) and the Human Research Protection Office (HRPO) Submission.*

HRPO received our initial submission on 10/31/17. The following items were included:

- HRPO Protocol Submission Form
- Principal Investigator CV, Independent Medical Monitor bio-sketch
- Documentation of Human Subjects Training for all the Investigators at the Einstein site
- Updated FDA Form 1572

- Informed Consent, Assent, HIPAA forms
- Letters of Support from Collaborating Institutions (NYU, GW Pharma)
- Updated Research Protocol
- Peer and Programmatic Review of Protocol
- Email Correspondence with Protocol Changes
- Study Instruments and Data Collection Forms. The following items were included:
  - Aberrant Behavior Checklist (ABC) – Irritability, Social Withdrawal
  - Repetitive Behavior Scale – Revised (RBS-R)
  - Pediatric Quality of Life Inventory (PedsQL) Family Impact Module
  - Vineland Adaptive Behavior Scale – II (VABS-II)
  - Clinical Global Impression Scale – Improvement, Severity (CGI-I, CGI-S)
  - IQ Test: Stanford-Binet Intelligence Scales, 5e
  - Autism Diagnostic Observation Schedule – II (ADOS-II)
  - Social Responsiveness Scale (SRS)

On 02/08/2018 upon request we submitted to Dr. Margaret Frederick additional items from AECOM/MMC site, and then our application was routed by her to the Approval Authority by COB for HRPO pre-review. Following items were included in this additional submission:

- Investigators Brochure Edition 6, GW Pharmaceuticals
- Einstein IRB conditional approval notice
- Conditionally IRB approved Research Protocol
- Conditionally IRB approved Informed Consent, Assent and informed consent feedback tool.
- IND acknowledgement letter
- CITI GCP certificate of Dr. A. Djukic (medical monitor)
- Human subject's protection training of Dr. A.Djukic (medical monitor)

On 02/13/18 we received following comments from HRPO:

A. Required Information/Documents.

1. Provide the final IRB submission package, approval memo, and stamped consent and assent forms when available.
2. Ensure that the IRB approval memo or other communication from the IRB states the risk category for the inclusion of children (either 45 CFR 46.404, 45 CFR 46.405, or 45 CFR 46.406).

B. Revisions to be made to the protocol.

1. The role and responsibilities of the Research Monitor, Dr. Djukic, must include the following.
  - a) May discuss the protocol with the investigators, interview subjects, and consult with others outside the study about the research.
  - b) Shall have the authority to stop the protocol, remove subjects from the protocol, and take any necessary steps to protect the safety and well-being of subjects until the IRB can assess the Monitor's report.
  - c) Shall have the responsibility to promptly report their observations and findings to the IRB or other designated official.
  - d) Is required to review all unanticipated problems involving risks to subjects or others, serious adverse events and all subject deaths associated with the protocol and provide an unbiased written report of the event. At a minimum, the research monitor must comment on the outcomes of the event or problem and in the case of a serious adverse event or death, comment on the relationship to participation in the study. The research monitor must also indicate whether he/she concurs with the details of the report provided by the principal investigator. Reports for events determined by either the investigator or research monitor to be possibly or definitely related to participation and report of events resulting in death must be promptly forwarded to the USAMRMC ORP HRPO.

2. BENEFITS to subjects - The protocol states in Section C7 that "It may or may not directly benefit the subjects." The consent form states on page 7 that "There may or may not be a direct medical benefit to you from being in this research study." As this protocol involves an experiment where the primary purpose is to determine the effect of the intervention, the requirements under 10 USC 980 apply. Since the protocol requires the informed consent from a legally authorized representative or parent, the protocol must describe

how participation in the research is intended to be beneficial to each subject participating in the study. This cannot include monetary compensation or possible benefit from the study drug, as the benefit is not yet known and not all subjects will receive the study drug. The benefit(s) must apply to both the treatment and placebo groups. The benefit(s) can take many forms. The protocol could possibly include providing education to the families on strategies to handle irritability or other symptoms of ASD, or providing feedback to the families on the results from the behavioral testing that may help them handle symptoms of ASD. These are just suggestions. The PI must revised Section C7 to describe the benefit(s) to the subjects.

C. Revisions to be made to the consent form (Version dated 9 February 2017).

1. BENEFITS to subjects - Once the protocol has been updated to describe the benefit to the subjects, the description of this benefit must be added to the consent form page 7.

They were addressed as summarized above and approved by HRPO for the IRB submission.

On 03/23/18 revised protocol and ICF were submitted to IRB and were approved on 03/28/18. After obtaining FDA study May Proceed letter on 04/02/18, we then submitted it to HRPO as well on 04/03/2018. On 04/13/18 we confirmed with Dr. Gloria Lawrence, Dr. Margaret Frederick successor from ORP HRPO, that the only outstanding item for HRPO approval is unconditional IRB approval (pending BNE and DEA approval).

We submitted NYU IRB approval to HRPO ORP on 05/02/2018 as it was received.

On 05/16/2018 we submitted to ORP HRPO Albert Einstein College of Medicine Institutional Review Board (Einstein IRB #1, East) Approval letter #035849. ORP HRPO approval for AECOM/MMC site HRPO Log Number A-20351.a was granted on 05/25/2018

*-Coordinate with sites for IRB protocol submission.*

Albert Einstein College of Medicine Institutional Review Board (Einstein IRB #1, East) received our initial IRB submission on 11/1/17. The following items were included: research protocol, parent consent/HIPAA forms, child assent form.

On 12/13/2017 Dr. Eric Hollander (AECOM/MMC) participated in Einstein IRB review meeting of the study protocol. Questions on frequency of Independent Data Safety Monitoring Committee (IDSMC) meetings, benefits to the child and psychoactive properties of CBDV have arisen, and were addressed during the meeting and in following the meeting correspondence.

On 01/08/2018 AECOM/MMC site received conditional IRB approval pending IND approval from the FDA, DEA license for schedule I substance, approval from Bureau of Narcotics, DEA approval to Pharmacy for additional storage space.

On 04/03/2018 AECOM/MMC site received conditional IRB approval pending approval from Bureau of Narcotics, DEA license for schedule I substance and DEA approval to Pharmacy for additional storage space.

On 05/11/2018 AECOM/MMC site received conditional IRB approval pending DEA license for schedule I substance and DEA approval to Pharmacy for additional storage space.

**On 05/15/2018 AECOM/MMC site received Albert Einstein College of Medicine Institutional Review Board (Einstein IRB #1, East) Approval letter #035849.**

In accordance with 45 CFR 46.110(b)(2) and 21 CFR 56.110(b)(2) it was approved with the following stipulations:

Enrollment of human subjects cannot begin until after the IRB receives:

DEA license for schedule I substance, and

DEA approval to Pharmacy for additional storage space (please contact Clemencia Solorzano from Pharmacy)

Written approval from collaborating research site(s) must be obtained and forwarded to the Einstein IRB prior to beginning the research at those sites.

Use only IRB stamped copies of the consent form(s) in your research. Do not use expired consent forms.

The risk/benefit category is 45 CFR 46.405.

Permission from one parent is sufficient.

A waiver of assent is granted for children under 7 years of age, and for children who do not have capacity to assent.

Parental consent can override child dissent.

The HIPAA Authorization was incorporated into the approved consent.

DEA license for Schedule I substance and DEA approval to Pharmacy for additional storage space (letter from Clemencia Solorzano) were submitted as amendment and acknowledged by Albert Einstein College of Medicine Institutional Review Board (Einstein IRB #1, East).

Dr. Orrin Devinsky submitted to the New York University Langone Medical Center IRB #6 on 02/16/2018. His submission was delayed by the requirement to obtain IND # prior to the submission. AECOM/MMC site shared all IRB approved documents with NYU site to facilitate their submission, as we obtained IND#138371 as of 02/07/2018 in the mail. NYU site subsequently amended their IRB submission once HRPO comments were addressed by AECOM/MMC site and FDA study May Proceed letter was received on 04/02/2018. NYU site received IRB approval on 05/02/2018. This approval was submitted as amendment and acknowledged by Albert Einstein College of Medicine Institutional Review Board (Einstein IRB #1, East).

*Coordinate with sites for CTSA-sponsored Clinical Research Center (CRC) approval.*

Application for Einstein-Montefiore CTSA-sponsored ICTR Clinical Research Center (CRC) was received on 11/10/2017. The following items were included: research protocol, parent consent form, child assent form, PI bio-sketch, study budget, projected use of CRC resources. We obtained ICTR approval notice on 11/28/2017 pending unconditional IRB approval. Dr. Orrin Devinsky completed submission for NYU CTSA-sponsored CRC. His submission was delayed by the requirement to obtain IND # prior to the submission. NYU site IRB approval was granted on 05/02/2018.

*Submit amendments, adverse events, and protocol deviations as needed.*

All amendments, adverse events, and protocol deviations will be reported and documented as they arise.

*Coordinate with sites for annual IRB report for continuing review.*

As the study progressed, investigators and coordinators at AECOM/MMC, NYU, and GW Pharma communicated regularly in regard to initial IRB submissions and remain accountable for timely review of all regulatory activities relevant to annual IRB reporting.

### **Subtask 2: Training of Study Staff**

Rater training was conducted on 06/01/2018. We completed regulatory binders and created manual of operations and IDSMC charter.

### **Subtask 3: Facilitate Communication between Sites and Staff**

We coordinate with NYU site weekly to review study goals and status of regulatory documents submission

#### **Subtask 4: Assessments and Surveys Preparation**

We finalized assessment measurements. We ordered study assessments and currently distribute them across sites.

We prepared patient study binders including surveys and source documents.

#### **Subtask 5: Receipt of Study Drug**

We finalized with pharmacy protocol for storage and dispensing of study drug/placebo and randomization. On 01/31/2018 Dr. Eric Hollander (AECOM/MMC) and Dr. Vera Nezgovorova (AECOM/MMC) met with Manager of Investigational Pharmacy at AECOM/MMC Dr. Clemencia Solorzano and Dr. Mark Sinett, Director of Clinical Services at AECOM/MMC to review dispensing of study drug/placebo strategy and confirmed storage space in GW designated safe, which is currently BNE and DEA approved.

As we were moving forward with BNE inspection, we were advised that an independent safe designated only for Dr. Hollander study would be required as a condition for BNE approval. Reconditioned Amsec Plate Steel Safe Model 2230 (right swing) UL-TL-30 1 Group 1R radiological lock: SG560 UL group 1 lock, SGD550 dial w/ 10" spindle; SGR167 ring, SC, SPKL was successfully ordered and installed on 04/16/18. We completed randomization protocol preparation on 08/01/2018.

We work with GW Pharma to schedule shipping of study drug and placebo to sites upon contract finalization for the IP provisions.

#### **Subtask 6: Data Management Preparation**

We coordinated with sites for flow chart of study steps, data collection and database requirements. We finalized Excel spreadsheets for data entry, which we will share with NYU site. We finalized discussions about electronic database with GW Pharma and agreed to maintain it in form of Excel spreadsheets.

#### **Major Task: Participant Recruitment and Enrollment**

##### **Subtask 1: Begin Subject recruitment.**

Currently, patients have been contacted in site databases, and 28 patients were identified and put on wait list until we finalize a contract with CBDV supplier.

##### **(a) Human Use Regulatory Protocols**

**TOTAL PROTOCOLS:** One human subject research protocol will be required to complete the Statement of Work.

##### **PROTOCOL (1 of 1 total):**

Protocol [HRPO Assigned Number]: TBD

Title: Cannabidiol (CBDV) vs. Placebo in Children with Autism

Spectrum Disorder (ASD) Target required for clinical significance: TBD

Target approved for clinical significance: TBD

##### **SUBMITTED TO AND APPROVED BY:**

- ORP HRPO, initial submission 10/31/17, documents submitted by Dr. Margaret Frederick (HRPO) to the Approval Authority by COB for pre-review on 02/08/2018. Comments received on 02/13/18, addressed and approved by HRPO and Einstein IRB (03/28/18). NYU IRB approval submitted to ORP

HRPO on 05/02/2018. Einstein IRB#1 Approval letter #035849 submitted to ORP HRPO on 05/16/2018. ORP HRPO approval for AECOM/MMC site HRPO Log Number A-20351.a granted on 05/25/2018.

Albert Einstein College of Medicine Institutional Review Board (Einstein IRB #1, East), initial submission 11/1/17.

On 01/08/2018 AECOM/MMC site received conditional IRB approval pending IND approval from the FDA, DEA license for schedule I substance, approval from Bureau of Narcotics, DEA approval to Pharmacy for additional storage space.

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On 05/11/2018 AECOM/MMC site received conditional IRB approval pending DEA license for schedule I substance and DEA approval to Pharmacy for additional storage space.

**On 05/15/2018 AECOM/MMC site received Albert Einstein College of Medicine Institutional Review Board (Einstein IRB #1, East) Approval letter #035849.**

- New York University Langone Medical Center IRB #6, initially submitted 02/16/18 and amended after HRPO and IND non-hold comments. Approval letter received on 05/02/2018.
- New York State Department of Health, Bureau of Narcotic Enforcement (BNE), initial submission received 11/7/17, currently under review. BNE inspection (including safe and site inspection) completed on 04/18/18 by Inspector Johnson. Class 7 Individual Researcher and Class 9 Importer licenses approvals received on 05/11/2018.
- Drug Enforcement Administration (DEA), Drug and Chemical Evaluation Section, initial submission for Schedule I license received on 02/13/18. DEA inspection completed on 04/11/2018 by Inspector Rivera. Additional inspection for the new safe is scheduled for 05/18/2018 with Inspector Rivera. DEA schedule I license was granted on June 26 2018.

**STATUS:**

- (i) Number of subjects pre-screened in year one: 28 patients
- (ii) Number of patients enrolled/original planned target for year one: 0/16 patients
- (iii) Report amendments submitted to the IRB and USAMRMC HRPO for review: Nothing to report.
- (iv) Adverse event/unanticipated problems involving risks to subjects or others and actions or plans for mitigation: Nothing to report.

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

Nothing to report

**How were the results disseminated to communities of interest?**

Nothing to Report

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

During next reporting period upon finalization of a CTA with CBDV supplier, enrollment of study subjects will start. 28 subjects are currently waiting for study to begin enrollment. Study outline will be presented at the Autism Speaks conference in the end of November 2018 in New York. Study outline will be presented at American College of Neuropsychopharmacology conference panel entitled "No Longer Tarred With the Same Brush? Evidence for the Therapeutic Potential of Cannabidiol: Implications for Regulatory Policy," in December 2018 in Florida, US.

4. **IMPACT:** Describe distinctive contributions, major accomplishments, innovations, successes, or any change in practice or behavior that has come about as a result of the project relative to:

**What was the impact on the development of the principal discipline(s) of the project?**

If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how findings, results, techniques that were developed or extended, or other products from the project made an impact or are likely to make an impact on the base of knowledge, theory, and research in the principal disciplinary field(s) of the project. Summarize using language that an intelligent lay audience can understand (Scientific American style).

Nothing to report

**What was the impact on other disciplines?**

If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how the findings, results, or techniques that were developed or improved, or other products from the project made an impact or are likely to make an impact on other disciplines.

Nothing to report

**What was the impact on technology transfer?**

Nothing to report

**What was the impact on society beyond science and technology?**

Nothing to report

5. **CHANGES/PROBLEMS:** The PD/PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official whenever there are significant changes in the project or its direction. If not previously reported in writing, provide the following additional information or state, "Nothing to Report," if applicable:

We have continued discussions with GW Pharmaceuticals in regards to IP provisions

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

Describe problems or delays encountered during the reporting period and actions or plans to resolve them.

We have continued discussions with GW Pharmaceuticals in regards to IP provisions.



**Changes that had a significant impact on expenditures**

*Describe changes during the reporting period that may have had a significant impact on expenditures, for example, delays in hiring staff or favorable developments that enable meeting objectives at less cost than anticipated.*

We have continued discussions with GW Pharmaceuticals in regards to IP provisions

**Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents**

**Significant changes in use or care of human subjects**

Nothing to Report

**Significant changes in use or care of vertebrate animals**

Nothing to Report

**Significant changes in use of biohazards and/or select agents**

Nothing to Report

**6. PRODUCTS:** *List any products resulting from the project during the reporting period. If there is nothing to report under a particular item, state “Nothing to Report.”*

**Publications, conference papers, and presentations**

*Report only the major publication(s) resulting from the work under this award.*

**Journal publications.**

Vera Nezgovorova, Casara Jean Ferretti, Danya Schlusel, Bonnie Paige Taylor, Genoveva Uzunova, Kevin Hong, Orrin Devinsky and Eric Hollander. “Cannabinoids in autism spectrum disorders”. *Frontiers in Neuroscience*. Submitted, under review. Acknowledgement of federal support

**Books or other non-periodical, one-time publications.**

Nothing to report

**Other publications, conference papers and presentations.**

Nothing to report

**Website(s) or other Internet site(s)**

<https://www.autismeye.com/us-army-cannabis/> Autism Eye publication  
<https://www.childrenshospitals.org/newsroom/childrens-hospitals-today/articles/2018/03/military-funds-research-of-cannabis-based-autism-treatment-for-kids>  
Children’s Hospital association newsroom  
<http://www.montefiore.org/body.cfm?id=1738&action=detail&ref=1375>  
Montefiore news release  
<https://www.newsweek.com/2018/02/23/really-good-weed-why-cannabis-may-be-worlds-most-effective-remedy-core-806758.html>  
Newsweek magazine publication  
<https://nypost.com/2018/05/02/clinical-trials-will-test-if-cannabis-compound-can-treat-autism/> NY post publication

**Technologies or techniques**

Nothing to report

**Inventions, patent applications, and/or licenses**

Not applicable at this point

Not applicable at this point

**7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS**

**What individuals have worked on the project?**

Funding support:

Name: Eric Hollander

Project Role: Principal Investigator (AECOM/MMC Site):

Nearest Person Month Worked: 1.8 months, 15%

Contribution to Project: Dr. Hollander has performed work in monitoring study progress and development, protocol finalization. He oversaw regulatory documents submissions and assured that award reporting requirements are met.

Funding support: no change

Name: Bonnie Taylor, PhD  
Project Role: Study Coordinator/Rater Researcher Identifier:  
Nearest Person Month Worked: 1.8 months, 15%  
Contribution to Project: Dr. Taylor has performed work in the areas of regulatory and source documents preparation and protocol development.  
Funding support: no change

Name: Casara Ferretti  
Project Role: Study Coordinator/Rater  
Nearest Person Month Worked: 0.6 months, 5%  
Contribution to Project: Ms. Ferretti has performed work in the areas of grant writing, protocol drafting, and advertising materials preparation  
Funding support: no change

Name: Vera Nezgovorova, MD  
Project Role: Study/Regulatory Coordinator:  
Nearest Person Month Worked: 3 months, 25%  
Contribution to Project: Dr. Nezgovorova has performed work in the areas of regulatory documents preparation, protocol development, NYS BNE/DEA licensure, inter-sites communication and report writing.  
Funding support: AECOM/MMC

Name: Danya Schlusel  
Project Role: Study Coordinator:  
Nearest Person Month Worked: 0.6 months, 5%  
Contribution to Project: Ms. Schlusel has performed work in the areas of advertising materials preparation, regulatory documents preparation and submission.  
Funding support: AECOM/MMC

Name: Kevin Hong  
Project Role: Study Coordinator:  
Nearest Person Month Worked: 0.6 months, 5%  
Contribution to Project: Mr. Hong has performed work in the areas of advertising materials preparation, regulatory documents preparation and submission.  
Funding support: no change

Name: Asif Rahman  
Project Role: Study Coordinator:  
Nearest Person Month Worked: 0.6 months, 5%  
Contribution to Project: Mr. Hong has performed work in the areas of advertising materials preparation and contacting subjects in the patients databases.  
Funding support: no change

Name: Orrin Devinsky  
Project Role: Principal Investigator (NYU Site) :  
Nearest Person Month Worked: 1.2 months, 10%  
Contribution to Project: Dr. Devinsky has performed work in monitoring study progress and development, protocol finalization. He oversaw regulatory documents submissions and assured that award reporting requirements are met.  
Funding support: no change

Name: Latoya King

Project Role: Study Coordinator (NYU Site):

Nearest Person Month Worked: 3 months, 25%

Contribution to Project: Ms. King has performed work in the areas of regulatory documents preparation and submission.

Funding support: no change

**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?**

NYU Langone Comprehensive Epilepsy Center. Sub-contractor on the award as second site for the study (co-PI Dr. Orrin Devinsky).

GW Pharmaceuticals, UK Collaboration in regards to study medication

**8. SPECIAL REPORTING REQUIREMENTS**

Not applicable

- 9. APPENDICES:** *Attach all appendices that contain information that supplements, clarifies or supports the text. Examples include original copies of journal articles, reprints of manuscripts and abstracts, a curriculum vitae, patent applications, study questionnaires, and surveys, etc.*

# Cannabinoids in autism spectrum disorders

Vera Nezgovorova<sup>1</sup>, Casara J. Ferretti<sup>1</sup>, Danya Shlussel<sup>1</sup>, Bonnie P. Taylor<sup>1</sup>, Genevieve Uzunova<sup>1</sup>, Kevin Hong<sup>1</sup>, Orrin Devinsky<sup>2</sup>, Eric Hollander<sup>1\*</sup>, Vera Nezgovorova<sup>3</sup>

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In review

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### *Conflict of interest statement*

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest

### *Author contribution statement*

VN, CF, BL, BPT, OD, GU and EH contributed to conception and design of the manuscript; VN wrote the first draft of the manuscript; CF, BPT, DS, OD, GU, KH and EH wrote sections of the manuscript. All authors contributed to manuscript revision, read and approved the submitted version.

### *Keywords*

Endocannabinoids, autism, Autism Spectrum Disorder, Cannabidiol, cannabidivarin, CB1, anandamide, core symptom domain of ASD, ECS

### *Abstract*

Word count: 145

Current treatments for Autism Spectrum Disorders (ASD) are limited in efficacy and are often associated with debilitating side effects. These medications typically palliate ASD symptoms but do not target core symptom domains. Endocannabinoids are arachidonic acid-derived lipid neuromodulators, which, in combination with their receptors and associated metabolic enzymes, constitute the endocannabinoid (EC) system (Zamberletti, Gabaglio et al. 2017, Karhson, Krasinska et al. 2018). Cannabinoid signaling may be involved in social dysfunction in ASD (Foldy, Malenka et al. 2013, Karhson, Hardan et al. 2016). They also may upregulate cognitive functions via synaptic transmission (Kim and Li 2015, Silva-Cruz, Carlstrom et al. 2017). Novel treatments for the core ASD symptom domains of social communication and neurodevelopmental deficits are needed, and the EC system could be a target for those therapies.

Keywords Endocannabinoids, autism, autism spectrum disorder, cannabidiol, cannabidivarin, EC, CB1, CB1, anandamide, core symptom domain of ASD

### *Funding statement*

This work is supported by U.S. Department of Defense Award AR160104, award # W81XWH-17-1-0253.

## Cannabinoids in autism spectrum disorders

### Abstract

Current treatments for Autism Spectrum Disorders (ASD) are limited in efficacy and are often associated with debilitating side effects. These medications typically palliate ASD symptoms but do not target core symptom domains. Endocannabinoids are arachidonic acid-derived lipid neuromodulators, which, in combination with their receptors and associated metabolic enzymes, constitute the endocannabinoid (EC) system (Zamberletti, Gabaglio et al. 2017, Karhson, Krasinska et al. 2018). Cannabinoid signaling may be involved in social dysfunction in ASD (Foldy, Malenka et al. 2013, Karhson, Hardan et al. 2016). They also may upregulate cognitive functions via synaptic transmission (Kim and Li 2015, Silva-Cruz, Carlstrom et al. 2017). Novel treatments for the core ASD symptom domains of social communication and neurodevelopmental deficits are needed, and the EC system could be a target for those therapies.

**Keywords** Endocannabinoids, autism, autism spectrum disorder, cannabidiol, cannabidivarin, EC, CB1, CB1, anandamide, core symptom domain of ASD

### Overview of Autism Spectrum Disorder

The CDC estimates that 1 in 59 children have Autism Spectrum Disorders (Baio, Wiggins et al. 2018). ASD is characterized by deficits in two core symptom domains - social communication and restricted/repetitive behaviors, accompanied by irritability, , impulsivity, temper tantrums, and high caregiver burden (Lecavalier, Leone et al. 2006). Nearly 11% of youth with ASD undergo psychiatric hospitalization and 65% are treated with psychotropic medications, which only palliate ASD symptoms and frequently cause disabling side-effects (Wink, Pedapati et al. 2017). The etiology of ASD involves interactions of genetic (>250 genes), epigenetic, environmental, immune-inflammatory, and nutritional factors (Hsiao 2013) (Loke, Hannan et al. 2015). This complex mechanistic network constrains the development of targeted treatments that extend beyond small subgroups. Autism may be largely divided into idiopathic and non-idiopathic, that includes the syndromal forms of autism. The syndromal forms are characterized in most instances by a defined clinical syndrome and an identified genetic cause.

The DSM-5 diagnostic criteria for ASD list two core symptom domains: social communication and restricted and repetitive patterns of behavior (Doernberg and Hollander 2016, Mazurek, Lu et al. 2018, APA 2013). Deficits in social communication and social interaction occur in diverse contexts: social-emotional reciprocity, nonverbal communication and initiating, maintaining and understanding of interpersonal relationships. Symptoms can manifest as impaired verbal and non-verbal communication, delayed and reduced interactions with peers, lack of enjoyment and interest in experiences with peers and lack of social judgment and insight. Anxiety, which often increases with age, can exacerbate social communication deficits (Duvekot, van der Ende et al. 2018). No treatments for social communication are FDA approved. The second core symptom domain - restricted and repetitive patterns of behavior, interests or activities (RRB) - are stereotyped or repetitive motor movements, insistence on sameness and rigidity, highly fixated interests, and hypo- or hyper-reactivity to sensory input (Leekam, Prior et al. 2011, Harrop 2015, Harrop, Gulsrud et al. 2015, Doernberg and Hollander 2016, Mazurek, Lu et al. 2018). RRBs vary widely in frequency and intensity among children and adolescents with ASD (Scahill, Aman et al. 2015), and may or may not cause distress. RRBs include “*lower level*” repetitive sensory and motor behaviors (e.g., hand flapping, rocking, humming, motoric compulsions and some self-injurious behaviors), and “*higher-level*” behaviors (e.g., insistence on sameness, pursuit of narrow

circumscribed interests, insistence that routines), similar to repetitive language. Individuals with ASD may use RRBs for self-stimulation or to decrease arousal, or both. RRBs also occur in other neurodevelopmental and psychiatric disorders (Joseph, Thurm et al. 2013). Individuals with ASD frequently have serious behavioral disturbances including irritability, which may manifest as aggression, self-injurious behavior and tantrums. These behavioral problems can severely disrupt school and family environments, further impairing education and social interactions. Irritability is often defined as a “feeling state characterized by reduced control over temper which usually results in irascible verbal or behavioral outbursts,” resulting from emotion dysregulation or stimulus hyper-responsivity (Fung, Mahajan et al. 2016). Approximately 20% of ASD individuals have moderate to severe irritability (Lecavalier 2006, Marcus, Owen et al. 2009, Robb, Andersson et al. 2011, Anagnostou 2018). FDA-approved treatments for irritability in ASD (i.e., aripiprazole and risperidone), utilized the Aberrant Behavior Checklist – Irritability subscale (ABC-I) as the primary outcome measure. The ABC-I was successfully used as an outcome measure for other pharmacological studies, psychosocial studies, and as a part of large-scale ASD databases, such as those for the Autism Treatment Network (ATN) and Simons Foundation (Kaat, Lecavalier et al. 2014).

Seizures frequently occur among ASD children and can result from many genetic mutations, and are associated with immune dysfunction, inflammation and cytokine imbalance (Knuesel, Chicha et al. 2014, Blackmon 2015, Washington, Kumar et al. 2015). Epilepsy prevalence in ASD varies between 8% and 30% (Jokiranta, Sourander et al. 2014), with increasing prevalence over the course of childhood and adulthood. Patients with early childhood-onset epilepsy have 15–35% rates of ASD. Risk factors that increase the presence of both ASD and epilepsy/seizures include intellectual disability, female gender, and age (Jokiranta, Sourander et al. 2014, Lo-Castro and Curatolo 2014, Blackmon, Bluvstein et al. 2016, Blackmon, Thesen et al. 2018) (Jokiranta, Sourander et al. 2014). Intellectual disability increases the risk of epilepsy in ASD by ~3-5 fold (Strasser, Downes et al. 2018). Epilepsy is treatment-resistant in about 30% of cases, particularly in those with epileptic encephalopathies and females (Sansa, Carlson et al. 2011, O'Connell, Gloss et al. 2017). Additionally, seizures and interictal epileptiform activity may contribute to neurodevelopmental delays by impairing excitatory-inhibitory (E-I) balance and altering synaptic neuroplasticity. For example, ASD is a common comorbidity in Lennox-Gastaut syndrome (LGS), a severe epileptic encephalopathy, characterized by treatment-resistant tonic (and other) seizures, specific abnormal electroencephalogram (EEG) abnormalities (ie, slow spike-wave discharges, generalized paroxysmal fast activity) and cognitive impairment (He, Li et al. 2018). Risk for both epilepsy and ASD symptoms are also increased in patients with Rett syndrome, Dravet Syndrome, Tuberous Sclerosis Complex (TSC) and Fragile X syndrome, and many other genetic epilepsies (Strasser, Downes et al. 2018). The prevalence of ASD in TSC is 17-63% (Vignoli, La Briola et al. 2015). TSC is an autosomal-dominant disease, affecting 1 in 6000 patients, associated with cortical tubers and dysplasia, which could be related to ASD symptom severity, especially in the social communication domain (Mous, Overwater et al. 2017). ASD also occurs in 24% to 61% of children with Dravet Syndrome (DS), which is known as severe myoclonic epilepsy in infancy (SMEI) (Berkvens, Veugen et al. 2015), an epileptic encephalopathy presenting in the first year of life with multiple seizures febrile and afebrile types (Li, Liu et al. 2011). In sum, epilepsy and seizures commonly complicate ASD, or disorders that commonly feature co-morbid ASD symptoms, and contribute to intellectual ability and social communication and cognition. Sudden death in epilepsy (SUDEP) is the leading cause of death in ASD (Schendel, Overgaard et al. 2016). Thus, timely interventions addressing seizures and/or social-cognitive deficits could significantly improve outcomes, especially for young children with ASD and epilepsy (Tuchman 2017, Burns and Matson 2018).

Increased excitatory-inhibitory (E-I) ratio and excitation and inhibition imbalance. E-I imbalance due to abnormal GABAergic and glutamatergic neurotransmission may contribute to ASD and epilepsy pathogenesis (Uzunova, Pallanti et al. 2016). E-I imbalance can result in seizures, behavioral changes and social dysfunction, including irritability, repetitive and disruptive behaviors, and social avoidance and withdrawal. Immune dysfunction and inflammation are also believed to play a role in the development of ASD symptomatology. Individuals with ASD have marked immune dysfunction and heightened inflammatory responses, as evidenced by microglial activation (Vargas, Nascimbene et al. 2005, Onore, Careaga et al. 2012, Goines and Ashwood 2013, Hsiao 2013, Rose and Ashwood 2014, Masi, Quintana et al. 2015, Kalkman and Feuerbach 2017), and



abnormal cytokine levels. Elevated pro-inflammatory cytokines (IL-1 $\beta$ , IL-6, IL-8, IL-12p40) (Ashwood, Krakowiak et al. 2011, Tonhajzerova, Ondrejka et al. 2015) and IFN- $\gamma$  (Masi, Quintana et al. 2015), and decreased anti-inflammatory cytokines (IL-10 and TGF $\beta$ ) levels (Estes and McAllister 2015, Masi, Quintana et al. 2015) have also been observed. Increases in the pro-inflammatory cytokines IL-1 $\beta$ , IL-6, IL-8, IL-12p40 are associated with more regressive autism and more pronounced stereotypical behaviors. Further, in children with ASD and asthma IL-17 is elevated following T-cell stimulation (Akintunde, Rose et al. 2015). These changes in cytokines in ASD may be developmentally regulated as they differ when measured during the neonatal period compared to later developmental periods (Abdallah, Larsen et al. 2012, Estes and McAllister 2015). Further studies on immune dysregulation in ASD are needed, particularly looking at its impact on neural systems also impacted in ASD, such as the endocannabinoid (EC) system (Ashwood, Krakowiak et al. 2011, Ahmad, Nadeem et al. 2017).

## The Endocannabinoid (EC) System

Pathophysiological mechanisms, which are thought to underlie the neurobehavioral deficits present in ASD, include aberrant synaptic plasticity (Pardo, Vargas et al. 2005, Nelson and Valakh 2015, Liu, Li et al. 2017), immune dysfunction (Careaga, Van de Water et al. 2010), and metabolic disturbances (Frye and James 2014). Many of these mechanisms can be modulated by the endocannabinoid system (EC) (Pacher, Batkai et al. 2006, Chakrabarti, Persico et al. 2015, Zamberletti, Gabaglio et al. 2017). Here we provide a review of the endocannabinoid system and its dysfunction in the ASD population.

The EC system exerts its effects through multiple receptors and channels including the G-protein coupled (GPCR) CB<sub>1</sub> and CB<sub>2</sub> cannabinoid receptors, transient receptor potential (TRP) channels (Iannotti, Hill et al. 2014) that may modulate calcium flux (Ryan, Drysdale et al. 2009), the orphan G-protein-coupled receptor GPR55, the 5-HT<sub>1A</sub> receptor, the  $\alpha$ 3 and  $\alpha$ 1 glycine receptors (Li, Jones et al. 2011, Devinsky, Cilio et al. 2014), and nuclear PPARs (Battista, Di Tommaso et al. 2012). CB<sub>1</sub> receptors are among the most widely expressed GPCRs in the brain, and are most present in the forebrain including the allocortex, neocortex, thalamus, and basal ganglia areas, in addition to the peripheral nerves and non-neuronal tissues (Prenderville, Kelly et al. 2015). Generally, CB<sub>1</sub> receptors are expressed pre-synaptically on glutamatergic and GABAergic interneurons. CB<sub>1</sub> receptor activation results in glutamate release and inhibition of synaptic transmission (Perucca 2017). CB<sub>2</sub> receptors are predominantly expressed in cells of the immune system, but are also expressed in the adrenal gland, heart, lung, prostate, uterus, ovary, testes, bone and pancreas in a number of mammalian species (Siniscalco, Sapone et al. 2013, Turner, Williams et al. 2017). ECs are synthesized on demand and the EC system may be modulated by ligand binding to the CB<sub>1</sub> and CB<sub>2</sub> receptors, leading to AKT, mitogen activated protein kinase (MAPK) and mTORC (mammalian target of rapamycin complex) pathway activation, which is responsible for cell differentiation and proliferation (Prenderville, Kelly et al. 2015). This is schematically summarized in **Figure 1**, and also leads to the inhibition of cellular EC uptake or the modulation of the intracellular metabolism of EC by specific enzymes. These enzymes might include the DAG lipase alpha (DAGL $\alpha$ ), fatty acid amide hydrolase 1 (FAAH) and monoacylglycerol lipase (Battista, Di Tommaso et al. 2012), which in turn are responsible for the synthesis and degradation of endogenous cannabinoids such as arachidonoylglycerol (2-AG) and anandamide (arachidonylethanolamide, AEA) (Turner, Williams et al. 2017). **Table 1** summarizes key findings of the relationship between CB<sub>1</sub> and CB<sub>2</sub> receptor modulation and neurological and psychiatric conditions.

### *Role of the EC system in synaptic plasticity and neuronal processes relevant to ASD*

EC signaling in the brain is complex. The EC system has an important role in neurodevelopment (Basavarajappa, Nixon et al. 2009) and is transiently activated during stressful conditions (Steiner and Wotjak 2008). Additionally, ECs are key modulators of synaptic function, which is believed to be disrupted in ASD (Castillo, Younts et al. 2012). Numerous studies implicate the EC system in ASD (Chakrabarti, Persico et al. 2015). Disruption of this system may impair social communication, social play and reciprocity (Kerr, Downey et al. 2013). Polymorphisms in the CB<sub>1</sub> receptor gene may adversely affect social reward processing in ASD

(Chakrabarti and Baron-Cohen 2011). Additionally, the BTBR autism mouse model demonstrated upregulated CB2A gene expression in the cerebellum, and treatment with an EC reduces locomotor activity, suggesting an impact on irritability and repetitive behaviors that are commonly observed in those with ASD (Onaivi, Benno et al. 2011). Children with ASD are also shown to have increased CB<sub>2</sub> mRNA and protein levels in their peripheral blood compared to healthy subjects (Siniscalco, Sapone et al. 2013). Intriguingly, EC-mediated signaling at inhibitory synapses is dysregulated in mouse models of autism-associated Neuroligin 3 mutations (Foldy, Malenka et al. 2013). In another mouse model of autism, the Fragile X knockout mouse, there is an absence of an EC-mediated type of synaptic plasticity (long term depression) in the ventral striatum and prefrontal cortex. Pharmacological enhancement of the EC signaling normalizes this synaptic plasticity deficit and corrects the behavioral abnormalities, suggesting that the EC signalosome is a molecular substrate in Fragile X syndrome (Jung, Sepers et al. 2012).

**Table 1** Select compounds affecting endocannabinoid system functioning in the brain

| Target   | Compound   | Citation  | Action   |
|--|--|---|--|
| monoacylglycerol lipase (MAGL) inhibitor                     | JZL184 (4-nitrophenyl 4-[bis(1,3-benzodioxol-5-yl)(hydroxy)methyl]piperidine-1-carboxylate)                                  | (Lee, Ledri et al. 2015)  | Increases 2-AG levels and concomitantly decreases GABAergic transmission in animal model   |
| inhibitor of fatty acid amide hydrolase (FAAH)               | URB597/KDS-4103 (cyclohexylcarbamic acid 3'-carbamoylbiphenyl-3-yl ester)  | (Piomelli, Tarzia et al. 2006, Fidelman, Mizrachi Zer-Aviv et al. 2018) | Long-term treatment could potentially improve PTSD symptoms, induce anxiolytic like behavior and antidepressant-like behavior in animal models |
| inhibitor of fatty acid amide hydrolase (FAAH)               | PF3845 (N-pyridin-3-yl-4-[[3-[5-(trifluoromethyl)pyridin-2-yl]oxyphenyl]methyl]piperidine-1-carboxamide)                     | (Chen, Spiers et al. 2018)  | Alleviates the proinflammatory response in rat hippocampus following acute stress  |
| cannabinoid type 1 (CB1) receptor antagonist/inverse agonist | Rimonabant   | (Gomis-Gonzalez, Busquets-Garcia et al. 2016)                           | Low doses (from 0.01mg/kg) normalize the cognitive deficit in the mouse model of Fragile X syndrome  |
| neutral CB1 receptor antagonist                              | NESS0327 (8-chloro-1-(2,4-dichlorophenyl)-N-piperidin-1-yl-5,6-dihydro-4H-benzo[2,3]cyclohepta[2,4-b]pyrazole-3-carboxamine) | (Gomis-Gonzalez, Busquets-Garcia et al. 2016)                           | Prevents the novel object-recognition memory deficit in Fmr1 KO mice   |
| CB1 receptor ligand  | Anandamide   | (Devane, Hanus et al. 1992,   | Children with low plasma levels are  |

|                |   |   |  |
|----------------|---|---|--|
|                |   | Karhson, Krasinska et al. 2018)   | more likely to develop ASD   |
| CB1 agonist    | Oleamide  | (Giulivi, Napoli et al. 2016)   | Lower plasma levels might be related to higher incidence of substance abuse, anxiety and sleep disturbances in 55-200 CGG expansion in the fragile X mental retardation 1 (FMR1) gene.                 |
| CB2 agonist    | JWH-133 (3-(1,1-dimethylbutyl)-6aR,7,10,10aR-tetrahydro-6,6,9-trimethyl-6H-dibenzo[b,d]pyran) | (Schmidt, Schafer et al. 2012, Aso, Juves et al. 2013)  | Might contribute to improvement in cerebral infarction; might lead to cognitive improvements in rodents models of Alzheimer disease  |
| CB2 antagonist | AM-630 (6-Iodopravadoline)  | (Arevalo-Martin, Garcia-Ovejero et al. 2012, Lopez-Rodriguez, Siopi et al. 2015, Haj-Mirzaian, Amini-Khoei et al. 2017) | Impairment of spontaneous locomotor recovery; prevention of neuroprotective effects of minocycline; reversal of antidepressant properties of WIN55, 212-2 (non-selective cannabinoid receptor agonist) |

#### *Role of the EC system on immune-inflammatory processes relevant to ASD*

ECs also have potent anti-inflammatory and immunosuppressive properties (Klein and Cabral 2006, Jean-Gilles, Gran et al. 2010, Devinsky, Cilio et al. 2014, Siniscalco, Bradstreet et al. 2014). ECs have been identified in immune cells, such as monocytes, macrophages, basophils, lymphocytes and dendritic cells (Cabral, Rogers et al. 2015). Reciprocal regulation has been described between ECs and the cytokine-mediated immune system (Jean-Gilles, Gran et al. 2010). Children with ASD have immune system dysfunction including marked microglial activation (Takano 2015), altered cytokine profiles (Masi, Quintana et al. 2015) with an elevation of pro-inflammatory cytokines in the postmortem brain and peripheral blood (McDougle, Landino et al. 2015), the presence of autoantibodies directed to brain and other antigens, and an association with MHC complex haplotypes (Gesundheit, Rosenzweig et al. 2013). From these immune system changes, peripheral blood cytokines are readily measurable and act as quantifiable biomarkers (Rose and Ashwood 2014). Elevated levels of the enzyme Nagalase, which is responsible for proper macrophage function (via Gc Protein-Derived Macrophage Activating Factor, GcMAF) (Bradstreet JJ 2012), and significantly upregulated CB<sub>2</sub> receptor

mRNA in peripheral blood mononuclear cells (PBMC) have been reported in children with ASD (Siniscalco, Sapone et al. 2013). These alterations indicate that the EC system is involved in ASD pathogenesis. Treatment with GcMAF ameliorates symptoms of ASD in some children (Siniscalco, Bradstreet et al. 2014) which may be due to effects on gene expression of the EC system and CB2R protein, and down-regulation of the over-activated blood monocyte-derived macrophages. Additionally, the endocannabinoid anandamide was shown to modulate social deficits observed in ASD rodent models (Servadio, Melancia et al. 2016, Wei, Dinh et al. 2016). Anandamide regulates ion-channel activity and neurotransmitter release via CB<sub>1</sub> cannabinoid receptors activation (Silva, Atchison et al. 2013). In a recent pilot study, plasma concentrations of anandamide were lower in children with ASD in comparison to healthy controls (Karhson, Krasinska et al. 2018). In sum, the multiple links between the EC system and ASD suggest both potential mechanisms and treatment targets.

## **Existing medications for treatment of ASD**

The current treatments for ASD symptoms are inadequate and tend to focus on palliating specific associated symptoms instead of the core symptom domains. Many patients are treated with a combination of applied behavioral analysis, medications, and occupational, physical and speech-language therapy. Currently, there are very few FDA-approved medications to treat ASD, and none that specifically target the core symptom domains. The atypical antipsychotics risperidone and aripiprazole are the only pharmacological interventions approved by the FDA to treat the aggression and irritability present in children and adults with ASD (Wink, Pedapati et al. 2017). These medications are effective, but are associated with considerable side effects, such as weight gain, metabolic syndrome, risk of onset of type 2 diabetes, prolactin elevation, development of breast tissue, and extrapyramidal/movement-related side effects. The need for long-term use of these treatments can exacerbate these side effects. The atypical antipsychotic lurasidone is also used to treat irritability in children with ASD, but its safety and tolerability has yet to be established, and it is currently used only as an off-label medication. It was also not shown to be efficacious during a 6-week long double-blind randomized placebo controlled study in children and adolescents with ASD (Loebel, Brams et al. 2016, McClellan, Dominick et al. 2017). Additionally, a 12-week, randomized, double-blind, placebo-controlled trial of divalproex sodium (valproate) vs. placebo was completed in 27 children and adolescents with ASD, aged 5 to 17, selected for high levels of irritability (ABC-I subscale score of 18 or higher) (Hollander, Chaplin et al. 2010). Ten of sixteen valproate treated subjects (62.5%) had an improvement of impulsive and aggressive symptoms, as measured by the Clinical Global Impressions Scale – Improvement (CGI-I), compared to only one of the placebo subjects (9.09%). This indicates that subjects receiving treatment with valproate are 16 times more likely to respond than the subjects receiving placebo (OR = 16.66; p = 0.008). There was also a significant weeks x condition interaction (p = 0.048) which suggests an additional drop of 0.53 points/week on the ABC-I ratings in the valproate treatment condition compared to the placebo condition (Hollander, Chaplin et al. 2010). Thus, the anticonvulsant drug divalproex sodium (valproate/VPA) significantly reduces irritability and repetitive behaviors (Hollander, Soorya et al. 2006, Hollander, Chaplin et al. 2010, King, Dukes et al. 2013). However, although VPA is efficacious for pediatric epilepsy and some symptoms of ASD, it also has disabling side effects, including weight gain, sedation, tremor and nausea. Pharmacogenomic testing may be useful to assess individualized antipsychotic medications drug metabolism profiles (Bose-Brill, Xing et al. 2017), and assist in treatment decisions for those with ASD, but overall there is an urgent need to develop new medications to treat the core symptoms of this disabling neurodevelopmental disorder.

## **Cannabinoids Therapeutic Potential for the ASD Population**

### *Potential Mechanisms*

Pathophysiological mechanisms underlying the neurobehavioral deficits present in ASD include aberrant synaptic plasticity (Pardo, Vargas et al. 2005, Nelson and Valakh 2015), immune dysfunction (Careaga, Van de Water et al. 2010), and metabolic disturbances (Frye and James 2014). Many of these mechanisms can be modulated by the endocannabinoid system (Pacher, Batkai et al. 2006, Chakrabarti, Persico et al. 2015). While the activity of phytocannabinoids (pCBs), such as cannabidiol (CBD) or cannabidivarin (CBDV), can be

discussed in terms of the endocannabinoid system ECS, it is clear that this can be achieved by mechanisms other than interaction with cannabinoid (CB) receptors (O'Connell, Gloss et al. 2017, Brodie and Ben-Menachem 2018). While  $\Delta(9)$ -tetrahydrocannabinol (THC) is responsible for most of the psychoactive effects of marijuana (Brodie and Ben-Menachem 2018), cannabidiol (CBD) doesn't have appreciable affinity with cannabinoid receptors and lacks psychoactive activity. It may also be associated with inhibition and induction of some CYP isoenzymes, such as CYP3A4, CYP2C9 and CYP2C19, which might in turn lead to pharmacokinetic interactions with anti-epileptic drugs (Devinsky, Cross et al. 2017, Brodie and Ben-Menachem 2018). CBD has been used in a variety of patient populations, has antipsychotic properties and actively reverses THC induced psychotic symptoms while lacking addictive properties (Devinsky, Cilio et al. 2014).

Like CBD, CBDV is also promising among the cannabinoids. Unlike  $\Delta^9$ -THC, CBDV does not activate the CB<sub>1</sub> or CB<sub>2</sub> receptors. Instead, it is a multi-target drug, interacting both with non-endocannabinoid systems and within the endocannabinoid system, including inhibition of the equilibrative nucleoside transporter (ENT) and the orphan G-protein-coupled receptor GPR55. CBDV is also an agonist of multiple transient receptor potential (TRP) channels, including TRPV1, TRPV2, TRPV4, and TRPA1 and is an antagonist of TRPM8 (Rock, Sticht et al. 2013). These channels possess diverse functions including the sensing of thermal and chemical signals, the reloading of intracellular stores of calcium, and pain processing (Iannotti, Hill et al. 2014). Moreover, CBDV is an analgesic and has anti-inflammatory effects (De Petrocellis, Ligresti et al. 2011, Deiana, Watanabe et al. 2012, Olah, Markovics et al. 2016). Multiple studies have demonstrated the anticonvulsant effects of CBDV in a broad range of seizure models (McHugh, Tanner et al. 2008, Hill, Mercier et al. 2012, Hill, Cascio et al. 2013, Devinsky, Cilio et al. 2014). CBDV may exert its effects through the modulation of intracellular calcium flux via G-coupled protein receptor protein 55 (GPR55); voltage dependent anion selective channel protein 1 (VDAC1); or act similarly to its propyl analog, CBD, by reducing neuronal excitability and neuronal transmission, and engaging inflammatory pathways by inhibiting adenosine reuptake or modulating the release of pro-inflammatory cytokine tumor necrosis factor alpha (TNF $\alpha$ ) (Carrier, Auchampach et al. 2006, Martin-Moreno, Reigada et al. 2011).

The therapeutic mechanisms of CBDV in humans with ASD can be deduced from their effects, and their homolog CBD's effects, on other neuropsychiatric conditions such as epilepsy, addiction, anxiety, depression and schizophrenia, as well as repetitive behaviors that are analogous to those observed in children with ASD. (Campos, Moreira et al. 2012). The anticonvulsant effects may result from activation and desensitization of transient receptor potential vanilloid (TRPV1) channels (Iannotti, Hill et al. 2014). Rats prenatally exposed to VPA exhibit ASD-like behavioral changes including reduced sociability and increased anxiety-related behavior, as well as alterations to cannabinoid targets. In particular, they have reduced expression of mRNA for PPAR $\alpha$  and GPR55 (a primary CBD target) at endocannabinoid receptor targets in hippocampus and frontal cortex (Kerr, Downey et al. 2013). Humans prenatally exposed to VPA have higher rates of ASD (Christensen, Gronborg et al. 2013, Meador and Loring 2013). CBDV has the potential to be a valuable therapeutic agent for individuals with ASD by virtue of its anti-inflammatory (Burstein 2015), antioxidative, neuroprotective, anti-anxiety and anticonvulsant properties.

### *Current Research and Clinical Trials*

The potential therapeutic mechanisms of both CBD and CBDV in ASD are currently being investigated in both rodent and human models. Media and parent communities have recently demonstrated heightened interest in artisanal marijuana strains with high ratios of CBD:THC. There is also an increased awareness of their ability to control seizures in children with treatment-resistant epilepsy (TRE), such as Dravet Syndrome. For example, the Charlotte's Web preparation of CBD oil was named after a patient, Charlotte Figi, with refractory SCNIA-confirmed DS (Brodie and Ben-Menachem 2018), and is a commonly used brand in this population. As a result of this heightened interest and the noted benefits of CBD and its variants in the treatment of certain medical and neurodevelopmental conditions, there has also been an increase in pre-clinical and clinical research in this area. For example, after the administration of CBD in a mouse model, there was an alleviation of marble-burying behavior, which is analogous to repetitive and compulsive behaviors observed in ASD. There is also preclinical

evidence that supports the use of CBD for improvement of autism-like social behavior in mice with Dravet syndrome (Kaplan, Stella et al. 2017). Additionally, in a phase II randomized double-blind placebo-controlled study of 120 children and young adults with Dravet syndrome, the use of cannabidiol led to a greater reduction in convulsive-seizure frequency than placebo (Devinsky, Cross et al. 2017). CBD might also be a well-tolerated treatment option for patients with refractory seizures in TSC. In a study of CBD in Pediatric Drug Resistant Epilepsy/Refractory Epilepsy in Tuberous Sclerosis Complex (TSC), subjects with behavioral problems showed improvements suggestive of an improvement in irritability, and all 3 patients with cognitive impairment experienced cognitive gains, including improved alertness, comprehension, maintained eye contact, engagement and responsiveness (Geffrey AL 2014), but more studies assessing long term efficacy and safety are warranted (Hess, Moody et al. 2016). CBD may also be efficacious and well-tolerated for the treatment of drop seizures in Lennox-Gastaut syndrome, and is currently being studied (Thiele, Marsh et al. 2018). Current large clinical trials using cannabinoids for treatment of seizures and other disorders are summarized in *Table 2*. Studies are being conducted for the use of CBD in infantile spasms and Sturge-Weber syndrome, but as of now the patient sample size is very limited (5 patients included) and more studies are needed (Kaplan, Offermann et al. 2017). There is also a phase II double blind, randomized, placebo-controlled trial with crossover that aims to assess safety, tolerability and efficacy of cannabinoids mix [cannabidiol (CBD),  $\Delta$ 9-tetrahydrocannabinol (THC) in a 20:1 ratio] for behavioral problems in children and adolescents with ASD recruiting in Israel (Dr. A. Aran, NCT02956226). CBD and CBDV may also have anti-inflammatory effects, and similar treatments given to the Maternal Immune Activation (MIA) ASD rodent model have resulted in a reduction of repetitive behaviors analogous to those in ASD (Coiro, Padmashri et al. 2015). CBDV also reverses the short-term and long-term cognitive deficits observed in *Mecp2* KO mice, the animal model of Rett Syndrome, demonstrating a potential impact on the cognitive deficits of those with ASD (Geffrey AL 2014). This suggests that CBDV may have the potential to alleviate repetitive behaviors in ASD (Casarotto, Gomes et al. 2010). Our research center at Montefiore Medical Center, Albert Einstein College of Medicine is conducting a Phase 2 double-blind, randomized, placebo-controlled trial of CBDV, discussed further below, in children and adolescents with ASD (NCT03202303) but, as with the other disorders mentioned, more research is needed.

**Table 2** Key large clinical trials using cannabinoids for treatment of seizures and ASD

| Study              | Compound and dosage                               | NCT#        | Key features   | Publication                   |
|--------------------|---|-------------|--|-------------------------------|
| GW Pharmaceuticals | 10 mg/kg/day and 20 mg/kg/day of CBD for 14 weeks | NCT02224560 | 225 patients with Lennox-Gastaut syndrome (aged 2-55 years). Outcomes studied among others: change in seizures frequency (primary outcome measure), quality of life and caregiver global impression of change. Reduction in drop seizure frequency was significantly greater for CBD 20mg/kg (42%) and CBD 10mg/kg (37%) versus placebo (17%). Adverse events occurred in 94% of | (Devinsky, Patel et al. 2018) |

|                                    |   |             |  |                               |
|------------------------------------|---|-------------|--|-------------------------------|
|                                    |   |             | <p>CBD 20mg/kg, 84% of CBD 10mg/kg, and 72% of placebo patients, and most were mild or moderate. 5 (7%) CBD 20 mg/kg, 3 (4%) CBD 10 mg/kg, and 1 (1%) placebo patient achieved drop seizure freedom during the maintenance period.</p>   |                               |
| Thiele et al./GW Pharmaceuticals   | 20mg/kg/day of CBD for 14 weeks as adjunctive treatment | NCT02224690 | <p>171 patients with Lennox-Gastaut syndrome (aged 2 to 55 years). Outcomes studied among others: change in seizures frequency (primary outcome measure) and caregiver impression of overall improvement. 44% of patients on CBD had decrease in seizures versus 20% on placebo. 58% of patients on CBD achieved improvement in overall condition versus 34% on placebo. 5 patients on CBD were seizure free during maintenance phase.</p> | (Thiele, Marsh et al. 2018)   |
| Devinsky et al./GW pharmaceuticals | 20mg/kg/day of CBD for 14 weeks                         | NCT02091375 | <p>120 children and adolescents with Dravet syndrome (aged 2 to 18 years). Outcomes studied among others: change in seizure frequency (primary outcome measure), caregiver global impression of change, incidence of</p>   | (Devinsky, Cross et al. 2017) |

|                  |  |             |  |    |
|------------------|--|-------------|--|----|
|                  |  |             | adverse events as a measure of subject safety. 43% patients on CBD had >50% reduction in seizures versus 27% taking placebo. 62% caregivers noted that CBD receiving patients' condition has improved.   |    |
| Hollander et al. | 10mg/kg/day (up to 400mg BID) of CBDV for 12 weeks | NCT03202303 | 100 children and adolescents (aged 5-18 years) with diagnosis of ASD confirmed by the ADOS-2 and DSM-5 criteria, who meet among others following inclusion criterias:<br>Aberrant Behavior Checklist (ABC) - Irritability Subscale score of 18 or greater at screening visit;<br>Social Responsiveness Scale (SRS) score of 66T or higher at screening visit;<br>Clinical Global Impression Scale - Severity (CGI-S) score of 4 or higher at screening.<br>Outcomes measure would include:<br>change in ABC-I from baseline to endpoint (primary outcome measure);<br>change in RBS-R from baseline to endpoint;<br>change in ABC-SW from baseline to endpoint;<br>change in PedsQL from baseline to endpoint; | NA |



|             |   |             |   |    |
|-------------|---|-------------|---|----|
|             |   |             | change in VABS-II from baseline to endpoint;<br>change in CGI-I from baseline to endpoint.  |    |
| Aran et al. | cannabidiol (CBD), Δ9 tetrahydrocannabinol (THC) in a 20:1 ratio for 3 months | NCT02956226 | <p>150 children and adolescents (aged 5 to 21 years) with ASD and moderate or greater behavioral problems as measured by a rating of moderate or higher (<math>\geq 4</math>) on the Clinical Global Impression-Severity (CGI-S).</p> <p>Outcomes measures would include:<br/>change from baseline home situations questionnaire-Autism Spectrum Disorder (HSQ-ASD) score at three months (primary outcome measure);<br/>change in Clinical Global Impression scores (CGI, improvement and efficacy index items) at three months from baseline; change in Social Responsiveness Scale scores-2 (SRS-2, parent and teacher rated) at three months from baseline; change in Autism Parenting Stress Index (APSI) score at three months from baseline; change in Modified Liverpool Adverse Events Profile (LAEP).</p> | NA |

|                 |  |             |  |  |
|-----------------|--|-------------|--|--|
| McAlohan et al. | single acute dose of 600mg of CBD or 600mg of CBDV | NCT03537950 | <p>This study investigates brain response to single acute dose of cannabidiol, cannabidivarin, and placebo in healthy men (n=38, aged 18 to 50 years) with and without autism spectrum disorder.</p> <p>Outcome measures would include:<br/> brain biochemistry response to pharmacological stimulation (primary outcome measure);<br/> measurement of low frequency brain activity using resting state fMRI;<br/> measurement of brain functional connectivity using resting state fMRI</p> |  |
|-----------------|--|-------------|--|--|

### Conclusion:

This review highlights novel therapeutic agents for the ASD population. Current treatments are limited in efficacy and are associated with debilitating side effects. ASD is a common comorbidity in treatment resistant epilepsy (TRE). CBD is effective in several treatment-resistant childhood onset epilepsies (i.e., Lennox-Gastaut and Dravet Syndromes), but has not been studied in a large randomized double-blind clinical trial in ASD. Like CBD, CBDV could also be a promising treatment for ASD, linking both epileptiform and immune dysfunction hypotheses without adding the psychoactive effects of THC. The effect of CBDV on multiple mechanisms dysfunctional in ASD and its apparent low toxicity makes it attractive therapeutic agent, worthy of additional research.

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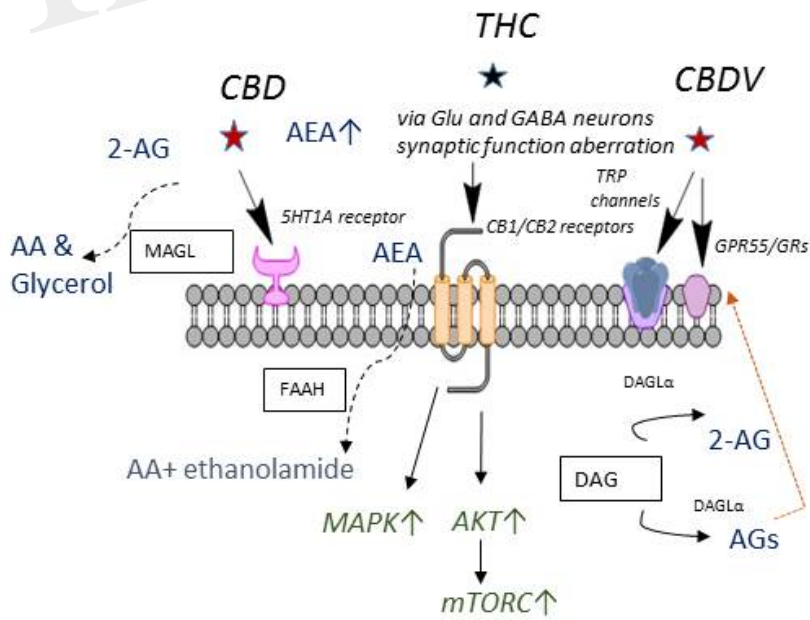
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Figure 1.JPEG

In review



- 2-AG 2-arachidonoylglycerol
- AG arachidonoylglycerol
- AA arachidonic acid
- DAGL DAG lipase; DAG diacylglycerole
- AEA anandamide
- mTORC mammalian target of rapamycin
- MAPK mitogen activated protein kinase
- FAAH fatty acid amide hydrolase 1
- MAGL monoacylglycerol lipase
- GPRs orphan G-protein coupled receptors