PROTOCOL TITLE:
Eating Disorder Individualized Therapeutics-Naltrexone Neuroimaging

SHORT TITLE*: Naltrexone neuroimaging*

CLINICALTRIALS.GOV: *NCT04935931*

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PROTOCOL DATE: 2/2/22

1.0 Study Summary

Study Title	Eating Disorder Individualized Therapeutics-Naltrexone Neuroimaging
Study Design	Open label, prospective trial
Primary Objective	Modulation of reward system measured by fMRI
Research Intervention(s)/ Investigational Agent(s)	Naltrexone 50 mg oral tablet x 1
Study Population	Adolescents aged 13-21 years
Sample Size	Pre-screening up to 1000 individuals, Up to n=50
Study Duration for Individual Participants	1 study visit (~10 hours)
Study Specific Abbreviations/ Definitions	FMRI – functional magnetic brain imaging BOLD – blood oxygenation level dependent AN – anorexia nervosa BN – bulimia nervosa BED – binge eating disorder ED – eating disorder ROI – region of interest MID – monetary incentive delay PFV – passive food view EPSI – eating pathology symptom inventory AKR – aldoketoreductase OPRM – opioid receptor mu NTX - naltrexone

2.0 Objectives

The overall goal of this project is to generate pilot data to support the development of fMRI as a pharmacodynamic biomarker of opioid antagonism in adolescents with ED, which will be accomplished through the following specific aims (SA):

SA1. Define the extent of within individual reward system modulation and identify the brain region most responsive to opioid antagonism in adolescents with binge/purge ED. We will use fMRI to detect percent blood oxygenation level dependent (%BOLD) changes pre- and post-opioid antagonist treatment (i.e., naltrexone) within individuals during a food reward and general reward-related task using regions of interest (ROI) analysis. We hypothesize that the anterior cingulate cortex (ACC) will be most responsive to naltrexone in adolescents with ED during food reward.

SA2. Determine the fMRI reward paradigm most sensitive to opioid antagonism in adolescents with binge/purge ED. Using the method described in SA1, we anticipate that the food paradigm will be more sensitive (e.g., higher t-score) in reward ROI to opioid antagonism in our target population.

SA3. Describe the naltrexone exposure-brain response relationship using fMRI in adolescents with binge/purge ED. We will link pharmacokinetic (PK) parameters of exposure with %BOLD change in subjects during the reward paradigms using ROI analysis. Based on our preliminary data suggesting

widely variable maximum plasma concentrations (C_{max}) of naltrexone in adolescents with ED (17-fold), we hypothesize that reduced C_{max} will be associated with reduced activation in reward-related ROIs.

3.0 Background

Naltrexone shows promise in treatment of binge eating and purging. Previous studies have demonstrated that naltrexone, a drug that interrupts the opioid reward circuit, reduces binge eating and purging in adults (1-3). Our recent retrospective case series revealed that naltrexone reduced binge/purge behaviors in approximately 60% of adolescents with no serious side effects (4). However, the patient-specific factors associated with response vs. non-response remain to be elucidated.
Naltrexone systemic exposure is highly variable. Preliminary data from our current naltrexone pharmacokinetic study demonstrate significant interindividual variability in the rate and extent to which naltrexone is absorbed in adolescents with ED. With systemic exposure varying by 16-fold, pharmacokinetic differences may contribute to variability in drug response.
Biomarkers of brain response are lacking. Opioid receptor binding studies done in adults using positron emission tomography (PET) show nearly 100% mu opioid receptor (OPRM) blockade with naltrexone 50 mg (5); however, 1 in 3 adolescents with ED fail to respond at this dose (4) and higher doses may be necessary to reach therapeutic effect in certain individuals (6, 7). Thus, biomarkers of brain response are critically needed to understand the impact of the opioid reward system, and opioid antagonism in adolescents with eating disorders.
Next Steps. Pharmacodynamic biomarkers of brain response are lacking yet are critically needed to untangle factors associated with response vs. non-response and advance precision therapeutics. This study will initiate the development of a biomarker (i.e., neuroimaging) of opioid antagonism in adolescents with eating disorders that will aid in drug development and repurposing.

4.0 Study Endpoints

Outcomes	***Exploratory Outcomes***
Primary: • ***RESPONSE*** *(SA1) - defined by Δ%BOLD pre/post-ntx in ROI* ***Secondary:*** ▪ ***ROI*** *(SA1) - defined by coordinates with largest response* ▪ ***OPTIMAL PARADIGM*** *(SA2) – paradigm (PFV or MID) resulting in larger response* ▪ ***EXPOSURE*** *(SA3) – defined by ntx C_{max}*	▪ *RESPONSE x OPRM1 genetic variation* ▪ *RESPONSE x metabolomic profile* ▪ *RESPONSE x impulsivity* ▪ *RESPONSE x negative urgency* ▪ *RESPONSE x delayed discounting* ▪ *EXPOSURE x AKR1C4 genetic variation* ▪ *EXPOSURE x metabolomic profile*

5.0 Study Design

This is an open-label, interventional trial to evaluate reward system modulation (detected by neuroimaging) in response to opioid antagonism (i.e., naltrexone) in adolescents aged 13-21 years with an eating disorder characterized by the target behaviors of binge eating and/or purging (e.g., AN-

BP, BN, BED). A pre/post design completed on the same day will be employed to quantify *within-individual change* while reducing potential confounding due to known neuroimaging variables (e.g., menstrual phase, treatment changes) that may occur with time elapsed between study visits.

Up to 50 individuals may be enrolled to meet our objectives.

6.0 Inclusion and Exclusion Criteria

Inclusion Criteria

- *Adolescents aged 13-21 years*
- *Eating disorder diagnosis per DSM-V criteria that is characterized by binge eating (defined as loss of control of eating resulting in large amount of food consumed in a short period of time) and/or purging (e.g., vomiting, excessive exercising, laxative use)*
- *Stable medication regimen (no dose or drug changes in the past 4 weeks)*
- *Participant and parent/legal guardian (if under 18 years) are willing and able to provide informed permission/assent/consent for the study*

Exclusion Criteria

- *Pregnant (via UCG)*
- *Prior hypersensitivity reaction to naltrexone (e.g., anaphylaxis)*
- *Non-removable metal in the body*
- *Current naltrexone use*
- *Self-reported opioid use in the past 7 days*
- *A language barrier (e.g., non-English speaking) for the participant that precludes communication and/or ability to complete all study-related requirements.*

English speaking participants whose parent/guardian are non-English speaking may be consented using a translated PAC form. Participants will have suitable English proficiency to complete study questionnaires and logs. Determination of proficiency will be at the discretion of the PI. Non-English speaking participants are excluded because the validated questionnaires used in this study to measure eating disorder symptomatology (EPSI) is not yet available in languages other than English. This assessment was chosen because of the ability to discriminate eating disorder behaviors and validation in the target age range. It is also the main assessment used in the CM Eating Disorder Center and thus parallels clinical practice.

Non-English Speaking Subjects:

- Parent/guardians only
- language(s) other than English understood by prospective parent/guardians: Spanish
- ORI Translation Program to translate the PAC form

7.0 Prescreening

Prescreening will occur through discussion with treating clinicians and review of medical records (through automated EHR report for those with eating disorder diagnoses). We anticipate that ~5% of those pre-screening will enroll, thus we estimate pre-screening up to 1000 individuals.

8.0 Recruitment

Recruitment will occur throughout the region using various means of IRB approved media to achieve target enrollment, including the following:

- Social media
    - Potential participants may learn about this study from information posted on the internal Children's Mercy Hospital website and on the Children's Mercy Research Institute (CMRI) public facing website. Social media platforms, such as Twitter and Facebook, may be used to disseminate study information. The social media platforms will reference or link to study information available on the CMRI website. Use of social media to share study information will be compliant with any existing CMH policies. The use of social media to share study information will not begin until these policies have been developed. Presentation of study information and content posted on the CMRI website will be at the discretion of the Digital Team, Research Administration, and the research team. Modification of images may be applied by the Digital Team and Research Administration to in be consistent with the aesthetic of the CMRI webpage. All study information will be approved by the IRB.
- Flyers
- Email blasts (e.g., Daily E-news)
- Direct communication from study staff to potential participants (identified by pre-screening) via available contact information.
- Self-referral: Individuals who express interest may contact study staff or click the link provided on recruitment materials. If the potential participant would like to receive more information regarding the study, they can also complete a contact form so a team member may contact the individual.
- Provider referral: Potential participants may be referred to the study team by their health care provider. The provider may share the potential participant's contact information if they obtain permission to do so.

A member of the research team may call or email potential participant up to three times using CHM email, Microsoft Teams or CMH phones. When contacted, individuals will undergo a brief screen to determine potential eligibility. Interested individuals will then schedule a time (virtually or in person) to fully explain the study, answer questions and obtain informed consent. This may occur at initial contact based on participant preference.

9.0 Study Procedures

The study will involve a screening encounter and one study day.

Study Visit Element	Main Procedures/Data Collected	Approximate Clock Time
Screening and Consent	Inclusion/exclusion criteria, Consent	In person, telephone or e-consent prior to study visit
I/E confirmation and medical History	Inclusion/exclusion criteria review and confirmation, medical history, anthropometrics, pregnancy test (if applicable)	7 am
Meal #1 (1 hour before scan #1)	Standardized CHO:PRO:FAT content	8 am
Baseline/pre-dose measures	Impulsiveness (BIS-brief), negative urgency (UPPS-P subscale); delayed discounting, blood draw (targeted metabolomic panel, genetic analysis)	8:20 am
fMRI scan #1	Hunger rating, reward related tasks (PFV, MID)	9 am
Naltrexone (NTX) dosing	Naltrexone 50 mg PO 2 hours prior to scan #2	10:30 am
Meal #2 (1 hour before scan #2)	Standardized CHO:PRO:FAT content	11:30 pm

fMRI scan #2 (2 hours post-NTX)	Hunger rating, reward related tasks (PFV, MID)	12:30 pm
Pharmacokinetic analysis	3 mL blood samples - pre-dose, 0.5, 1, 1.5, 2, 3, 4, 6, 7 hours post-naltrexone dose.	5:30 pm (last PK draw & study end)

Screening and consent. The study will be reviewed in depth with the participant and his/her parents/legal guardian when applicable. They will be provided sufficient time to review the PAC form, have all questions answered, and concerns addressed. If they agree to participate, they will sign the PAC form. This may occur in person, over the phone (using telephone script) or via e-consent. In the event the parent/guardian is non-English speaking, interpreter will be offered along with provision of translated PAC form. The participant must have English proficiency to complete study procedures (see inclusion criteria).

Screening failures (i.e., participants meeting any exclusion criteria) may be screened again at a future time point at the discretion of the Principal Investigator.

Pre-visit Planning. Scheduled participants may be contacted ahead of study with a reminder of their study appointment. Once PAC has been obtained, participants will be reminded to avoid food for 4 hours prior to study day.

Assessments (including categories of data collected). Self-report data will be captured via electronic surveys (e.g., Research Electronic Data Capture -REDCap), structured interview, study records. Anthropometrics. Height, blind weight will be obtained; body mass index (BMI), BMI z-score, % ideal body weight will be calculated. Structured interview. Study staff will obtain participant demographics, ED, medical, family & menstrual history. Confidential social history will be obtained via self-report electronic survey. Laboratory. Urine drug panel will objectively assess illicit substance use (e.g., nicotine, THC) at baseline along with urine pH and specific gravity and used as covariates in analysis. Eating Disorder Symptom Burden. The EPSI will evaluate symptom burden at baseline. The EPSI has excellent validity and reliability derived from a diverse population, has published normative data(8, 9) and includes various sub-scales (e.g., body dissatisfaction, cognitive restraint) that will allow characterization of our sample. Hunger. Before each scan, hunger will be assessed. Safety. Baseline heart rate and blood pressure will be recorded. Physical symptoms that may occur after naltrexone administration will be assessed.

Reward System Modulation by fMRI. Each participant will undergo two fMRI scans on the same day. Scan #1 (pre) will be in the fed state *before* naltrexone administration. Scan #2 (post) will be in the fed state 2 hours *after* naltrexone. Each scan will last approximately 1 hour and involve two reward activation paradigms(10-12): passive food view (PFV) and monetary incentive delay (MID). These two reward activation paradigms provide distinct insight and will generate pilot data to support the choice of the optimal paradigm for further testing of reward system modulation in adolescents with eating disorders. PFV provides a paradigm that is relevant to the target behaviors (i.e., binge eating, purging), has been evaluated in ED patients, in response to naltrexone in adults, and is expected to activate food cue-reactivity regions (e.g., prefrontal cortex). MID is a widely used paradigm in adolescents to detect reward anticipation and receipt particularly in the striatum and is currently being used to study the developmental trajectory of reward processing in the longitudinal Adolescent Brain Cognitive Development (ABCD) trial. To the greatest extent possible, we will harmonize our fMRI parameters with those published for ABCD.

Opioid Antagonism. A single oral dose of naltrexone hydrochloride 50 mg tablet will be administered by licensed study staff 2 hr (±1 hr) before scan #2. Complete opioid receptor blockade is evident at 1-hour post-dose, which overlaps with time at maximum concentration in plasma (T_{max}) and persists for at least 24 hours post-dose in adults(13, 14). In our PK study in adolescents with ED, preliminary analysis shows T_{max} at 2 hour. Thus, optimal timing of 2 hours was conservatively chosen while providing a feasibility window supported by evidence. Naltrexone is well-tolerated and difficult to distinguish from placebo in blinded trials(15-17). CM IDS pharmacy will dispense study medication. Naltrexone hydrochloride 50 mg tablet is FDA approved for opioid and alcohol use disorder and used off-label for the treatment of compulsive and impulsive behaviors in children, adolescents and adults. Examples of compulsive and impulsive pertinent to this study include binge eating and purging (e.g., vomiting). Evidence for safe and efficacious use of naltrexone for these behaviors is available (4). This study does not significantly increase the risk associated with naltrexone as the commercially available dose, formulation and route chosen is consistent with current clinical practice at doses ranging from 50 -200 mg/day. Additionally, a meta-analysis revealed that naltrexone,

when compared with placebo, is not associated with serious adverse events(17). It is not the intent of this study to generate data for submission to the FDA or to support a significant change in advertising of the drug. Storage, control and dispensation of the drug will occur through collaboration with IDS pharmacy. Use of naltrexone for this study meets criteria for IND exemption, category #1 (21 CFR 312.2(b)(1)).

Meals. Imaging will occur in the fed state using a standardized meal to avoid prolonged fasting that may compromise the health and recovery of the target population. This is not expected to meaningfully interfere with the detection of reward system modulation within individuals. Previous fMRI studies in adults suggest that individuals with disordered eating and/or obesity/overweight may exhibit stronger reward activation in the fed state compared with healthy controls(18, 19). Healthy weight individuals still exhibit strong reward activation, particularly in the ACC, in the fed versus fasted state, even though small reductions are seen(20).

Systemic Drug Exposure-Response Linkage. Plasma and urine will be obtained to measure systemic exposure to naltrexone and it primary, active metabolite, 6-beta-naltrexol, using a validated UPLC-MS/MS assay. Blood samples (3 mL) will be obtained from a peripheral intravenous catheter (PIV) to minimize discomfort associated with repeated blood draws (**Table 1**). *Genomic Variation.* To understand the impact of genetic variation on the naltrexone exposure-response relationship**,** DNA will be extracted from whole blood and genotyped for variants of interest.

Exploratory Assessments. [redacted].

Total blood sampling. No more than 8 teaspoons (40 ml) of blood will be obtained during the study visit (9 PK time points, 1 genomic sample, 2 metabolomic samples, each 3 ml).

Compensation. Participants will be given $400 via greenphire or CM preferred mechanism for completion of Study Day 1.

Biosafety Information. This study will involve handling, processing and transporting human biosamples from Hoglund to CMRI Clinical Pharmacology labs. Biosafety regulations will be followed.

10.0 Risks to Subjects and Mitigation Strategies

- Small risk of loss of confidentiality, but every effort will be made to prevent this and keep participant information confidential. If the participant/LAR wish provides an email address and/or phone number, the study team may communicate with them and they will be informed that this is not a secure method and could be accessed by someone else in the event of a security breach. The hospital is not liable for security breaches.
- Minimal discomfort or bruising may occur with drawing blood and IV placement. The participant may be given the option of a numbing agent to help ease the pain of needle sticks.
- When answering the brief questionnaires, the questions asked may be uncomfortable or embarrassing. These risks are minimum and unlikely to occur. The participant does not have to give any information they do not want to give. Confidentiality will be protected to the greatest extent possible and answers will not be released to the care team.

- Side effects to naltrexone occur in ~10% of patients, are typically mild and go away on their own (e.g., nausea) and do not differ from those receiving a placebo (e.g., sugar pill). Allergic reaction to naltrexone is rare and usually happens right away after taking the medicine. Symptoms include hives and difficulty breathing. Medications for immediate treatment of severe allergic reactions and trained personnel will be available in the clinic where the study drug is given.
- Genetic testing carries the possibility of discrimination. However, a Federal law called the Genetic Information Nondiscrimination Act (GINA) generally makes it illegal for health insurance companies, group health plans, and most employers to discriminate based on genetic information. Additionally, results will be kept in the study record and not released to your medical record.
- Incidental finding from the neuroimaging (e.g., fMRI) may occur. Whenever brain imaging is done, there is a chance of finding something unexpected and unrelated to the research study that may have some clinical implications. The neuroimaging used in this study is for research purposes only and is not the same as clinical neuroimaging.

11.0 Potential Benefits

Participants have the possibility of direct benefit should they experience eating disorder symptom reduction after taking naltrexone (e.g. reduced urge to binge and/or purge or lack of positive reinforcement from binge/purge). It is plausible to experience an effect after a one-time dose based on evidence of complete opioid antagonism as soon as 2 hours after a one-time dose(13, 14). Should individuals experience a benefit, they may choose to share this information with their treating clinician and consider initiating ongoing therapy with naltrexone. Sharing such information with the treating clinician is outside the scope of this study and would solely be at the discretion of the participant.

The knowledge gained from this study has the potential to further our understanding of alterations in the reward pathway and their contribution to eating disorder and benefit society through advancement of mental health knowledge and treatment.

12.0 Investigator Assessment of Risk/Benefits Ratio:

Select as applicable:	**Pediatric Risk Category:**	
☐	Category 1	Research not involving greater than minimal risk (45 CFR §46.404 and 21 CFR §50.51)
☒	**Category 2**	**Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects. (45 CFR §46.405 and 21 CFR §50.52)**
☐	Category 3	Research involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition. (45 CFR §46.406 and 21 CFR §50.53)
☐	Category 4	Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children. (45 CFR §46.407 and 21 CFR §50.54)
Select if applicable:	**Adult Risk Category:**	
☐	Not Greater than Minimal Risk	
☒	Greater than Minimal Risk	

13.0 Payment, Reimbursement and Tangible Property provided to subjects

Payment to Subjects: Greenphire or CM approved equivalent will be used to provide payment of $400 to each participant at the conclusion of the study day as renumeration for their time.

Tangible Property: *N/A*

14.0 Compensation for Research-Related Injury

No compensation for research-related injury will occur. Should a serious adverse event occur during the study day, the participant will be taken to the nearest emergency department or the emergency department of their choice (e.g., Children's Mercy or KUMED).

15.0 Economic Burden to Subjects

Participants will not be responsible for the cost of any study procedure.

16.0 Permission/Assent/Consent Process and HIPAA authorization

Full written permission and assent and HIPAA authorization will be obtained for pediatric participants and consent for adult/emancipated participants. The study will be explained, and participants/LAR will be given as much time as they need to review PAC, ask questions and come to a decision. This may occur over the phone, virtually (e.g, CM approved platform like Teams) or in person based on participant preference and available resources to the study team. PAC will be signed by hand or electronically.

The study is requesting the option of using a telephone/telemedicine consent process for initial consenting. CM telephone/telemedicine consent process research policy will be followed.

A waiver of written documentation of consent and alteration of HIPAA authorization (p/a/c form provided but signature will NOT be obtained, e.g. verbal consent) is requested for participants who will re-consent at age 18 per CMRI policy. Patients who were <18 at initial enrollment, but turn 18 after study procedure completion will have signed parental consent/participant assent (confirmed by study staff) and completed all study procedures, but may have PHI stored in the study DCF while the study remains open which represents no more than minimal risk to the participant (and involves no procedures for which written consent is normally required outside of the research context). PHI will not be reused or disclosed to anyone not involved in this research. The research cannot practicably be conducted without the Alteration of HIPAA authorization as many of the patients who turn 18 after study procedure completion may already be treated and discharged. Data from all these participants is needed to describe aims of the study. These participants will be identified by review of study participant DCFs. If verbal re-consent cannot be accomplished via telephone/telemedicine, de-identification of study samples and data will occur.

A partial waiver of HIPAA authorization is requested for pre-screening/recruitment. A report will be generated from HIM that includes PHI of potential participants (e.g., name, MR, diagnosis code). Use of PHI is no more than minimal risk to the privacy of the individuals because PHI will be kept on CM protected network, accessed by study team and destroyed with other study documents. This will allow for the description of recruitment efforts in aggregate form (e.g., number of patients enrolled/number of patients eligible). This PHI will not be reused or disclosed to anyone or entity outside of the study team. Without this waiver, recruitment would not be feasible as we would fail to identify potential study participants. Relying solely on provider or patient self-referral for study participation would compromise the ability to complete the study given the relatively small patient pool of which to recruit from. In addition, these individuals may be screened for inclusion/exclusion criteria to avoid unnecessary

contact if patient does not meet criteria. This approach has been successful in recruiting for an IRB-approved study in adolescents with eating disorders.

17.0 Identifiable Information

1. Name/Initials	☐ Accessed only	☒ Recorded
2. All elements of date (except year) directly related to an individual (e.g. date of birth, admission date, discharge date, date of death)	☐ Accessed only	☒ Recorded
3. Medical record number	☐ Accessed only	☒ Recorded
4. Account number	☐ Accessed only	☒ Recorded
5. Health plan identification number	☐ Accessed only	☐ Recorded
6. Social Security Number	☐ Accessed only	☒ Recorded (only if needed, see above)
7. Device identifiers and serial number	☐ Accessed only	☐ Recorded
8. Certificate/License number	☐ Accessed only	☐ Recorded
9. Telephone number	☐ Accessed only	☒ Recorded
10. Fax number	☐ Accessed only	☐ Recorded
11. Email addresses	☐ Accessed only	☒ Recorded
12. Web addresses (URLs); Internet IP addresses	☐ Accessed only	☐ Recorded
13. Street address, city, county, precinct, zip code or equivalent geographical codes	☐ Accessed only	☒ Recorded
14. Full face photographic images and any comparable images	☒ Accessed only	☐ Recorded
15. Biometric identifiers, including finger and voice print	☐ Accessed only	☐ Recorded
16. Vehicle identifiers and serial numbers, including license plate number	☐ Accessed only	☐ Recorded
17. Any other unique identifying number, characteristic or code that may help identify individual participants including their initials (e.g. student or employee ID number)	☐ Accessed only	☐ Recorded
18. Elements of date, including year, for persons 90 years or older	☐ Accessed only	☐ Recorded
19. Other:	☐ Accessed only	☐ Recorded

18.0 Genetic Analysis Information

Single nucleotide polymorphism (SNPs) analysis and genomic sequencing may occur as part of this study for research purposes only to explore the impact of genetic variation on pharmacokinetics, pharmacodynamics and/or disease. Genetic information may be stored in the Adolescent Medicine Pharmacogenomic Repository (AMP) (IRB#13020033).

19.0 Sharing of Results with Subjects

Results (including genetic analysis or any incidental findings on neuroimaging) will not be shared individually with participants. It is the intent of study to publish study results and thus participants may learn about study results in such publications.

20.0 Storage/Banking of Data and Specimens for Future Research

Data and leftover specimens will be stored in the existing Adolescent Medicine Pharmacogenomic Repository (AMP), IRB#13020033 which describes the potential for sharing of deidentified samples with other researchers per IRB protocol.

21.0 Withdrawal of Subjects

Participants may withdrawal at any time during the study. To withdrawal participants will notify the study team in writing that they wish to withdrawal. Study procedures will cease. Any data collected will be retained for potential analysis.

22.0 Data Analysis:

Outcome analyses. Outcomes are defined per Table 2. SA1*. Response*. fMRI data will be analyzed in AFNI in two ways: 1) region of interest (ROI) analysis in *a priori* reward ROIs including the ventromedial prefrontal cortex, ACC and striatum and 2) exploratory whole brain analysis to identify regions outside the reward network that may also respond to naltrexone (e.g., insula, dorsolateral prefrontal cortex, dorsal ACC). We have chosen to use a pre-defined ROI analysis which will be selected from a meta-analysis of passive viewing food tasks and MID studies using neurosynth.org or similar(29). Although ROI approaches do present challenges in fMRI analyses, this hypothesis-driven approach has been chosen to focus the primary analysis to test targeted reward related changes associated with treatment. Exploratory analysis described below will use advanced fMRI analysis approaches to take advantage of the richness of the whole-brain data. SA2*. Optimal paradigm.* The %BOLD changes will be compared between paradigms by LMM using paradigm (PFV, MID) and time (pre, post) as fixed-effects, and random individual and/or paradigm intercepts. SA3*.* The changes in %BOLD and changes in *Exposure* (log-scale) will be correlated by Pearson's correlation coefficient; the 95% CI will be estimated by non-parametric bootstrap using the bias-corrected and accelerated method.

PKPD analysis. Kinetica 5.0 or similar software will be used to model PK parameters (e.g., C_{max}, $AUC_{0\text{-}inf}$).

23.0 Adverse Events and Unanticipated Problems

Any adverse event that occurs during study participation will be recorded. The primary safety end point will be based on frequency of AEs during the Study Day.

Definition and Grading Intensity of Adverse Events

An adverse event is defined as any undesired change in the body structure (signs) or body function (symptoms), whether or not considered drug-related. For the purposes of this study, drug-related is independent from study-related, as described above. During the entire duration of the study, subjects will be instructed to report all adverse events. All adverse events, whether volunteered, elicited, or noted on physical examination, will be recorded throughout the study. Each adverse event will be described by 1) its duration 2) severity grade (see below for definition), 3) its relationship to the medication studied (none, possible, probable, definite) 4) the action(s) taken.

The <u>severity</u> of adverse events will be categorized as follows:

- MILD = Experience is minor and does not cause significant discomfort to subject or change in activities of daily living (ADL); subject is aware of symptoms but symptoms are easily tolerated.
- MODERATE = Experience is an inconvenience or concern to the subject and causes interference with ADL but the subject is able to continue with ADL.
- SEVERE = Experience significantly interferes with ADL and the subject is incapacitated and/or unable to continue with ADL.

Serious Adverse Event (SAE) Reporting

A serious adverse drug experience (by FDA definition) is any adverse test material event occurring at any dose that results in any of the following outcomes:

- Death
- Life-threatening adverse experience
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant disability/incapacity
- Congenital anomaly/birth defect

Any serious adverse event will be reported verbally to the primary investigator (see contact info below) and naltrexone prescriber within 24 hours of notification. Written notification will be sent to the IRB within 3 working days.

Stephani Stancil, PhD, APRN [redacted], slstancil@cmh.edu

NOTE: The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as a severe headache). This is not the same as "serious," which is based on participant/event outcome or action criteria usually associated with events that pose a threat to the participant's life or functioning. Seriousness (not intensity) serves as a guide for defining regulatory reporting obligations.

24.0 Provisions to Monitor the Data to Ensure the Safety of Subjects

A data safety/monitoring committee will be established to monitor the safety of the study and include the PI, senior mentor(s), and a medical provider not part of the study. Cumulative and new safety data will be reviewed at least every 6 months or sooner if serious adverse event occurs.

Data reviewed will include any adverse event occurring during the study day or reported by participant to have occurred after the study, but thought to be associated with the study (via participant initiated communication).

25.0 Data Management

Data will be collected and recorded during the study by members of the study team. Categories of data collected as listed in section 9.0 The investigator and members of the research team are bound to keep this information confidential and will do everything within their power to avoid loss of confidentiality. The documents will be stored on the hospital's secure system (e.g., OneDrive) with access restricted to members of the study team.

The investigator agrees to adhere to the document retention procedures and retain essential documents for 3 years after the completion or discontinuation of the trial. Essential documents include:

1. IRB approvals for the study protocol and all amendments
2. DCF
3. subjects' signed PAC forms
4. any other pertinent study documents

26.0 Multi-site Research

Study procedures and imaging data analysis will occur at Hoglund Biomedical Imaging Center, part of the CTSA located on the campus of University of Kansas Medical Center. Additional sample processing and data analysis will occur at Children's Mercy Kansas City.

CM will be the IRB of record with a request for KUMC to rely on CM.

27.0 Equitable Selection and Vulnerable Populations

Age range was chosen based on relevance to the population of interest (e.g., adolescents with eating disorders) and alignment with validated eating disorder symptom burden questionnaire (EPSI).

Vulnerable Populations:

☐ Children/Minors (under 7 years of age)
☒ Children/Minors (7-17 years of age)
☐ Neonates (infants less than 30 days old)
☐ Neonates of Uncertain Viability (infants less than 30 days old)
☐ Non-Viable Neonates (infants less than 30 days old)
☐ Wards of the State
☐ Fetuses
☐ Pregnant Women
☐ Adults with impaired decision-making capacity
☒ CM Employees
☒ CM Students/Residents/ Fellows (categorized as "trainees")
☐ Economically or Educationally Disadvantaged Persons
☐ Prisoners

For CM employees or trainees, the risk of coercion will be minimized by ensuring that they will not be recruited or enrolled by their direct supervisor and through reassurance that their decision regarding participation does not impact their employment or educational status at CM.

REFERENCES

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PERMISSION/ASSENT/CONSENT TO PARTICIPATE IN A RESEARCH STUDY AT CHILDREN'S MERCY HOSPITALS
VERSION 10.20.2020
Eating Disorder Individualized Therapeutics-Naltrexone Neuroimaging (EDIT-N^2)

SUMMARY

We are asking you or your child to be in this research study. Being in a research study is completely voluntary, and your choice will not affect you or your child's regular medical care at Children's Mercy. This research study is done to improve our understanding of the medical treatment of adolescents with eating disorders and help us understand why certain patients respond to a certain medication, naltrexone, and others don't. The following things are part of this study: fMRI (brain scan), blood draws, medical chart review, questionnaires, a brief computer game. Being in this study involves 1 study visit lasting approximately 10 hours. The biggest risks from being in this study are adverse reaction to naltrexone (rare), discomfort from blood draw and loss of confidentiality. There is the potential for direct benefit of being in this study if you or your child experience reduction in eating disorder symptoms (e.g., urge to binge or purge) after taking naltrexone. Instead of being in this study, you or your child can choose not to be in the study.

Study Visit	Main Procedures	Approx. Duration	Payment
Screening *(can occur on the phone or combined with study day, depending on scheduling)*	Consent, Inclusion/Exclusion Criteria	30 min	
Study Day	*Clear liquids only for 4 hours prior to scheduled start time.* Medical history, Pregnancy test (if applicable), Vital signs & measurements (BP, pulse, ht, blind wt), Peripheral IV for blood sampling, Urine Collection, Dose of naltrexone, Brain scan (fMRI) to measure reward response while playing a game (choosing money rewards) and viewing pictures of foods and non-foods, Questionnaires (~30 min)	10 hours	**$400**

WHO IS DOING THIS STUDY?

A study team led by Stephani Stancil, PhD, APRN is doing this study. Other health care professionals and researchers may help. The study team will not receive any direct personal financial benefits as a result of your decision.

We are asking you or your child to be a part of this research study. Please read the information below and ask questions about anything that you do not understand before you make a choice.

WHY IS THIS STUDY BEING DONE?

We are looking to improve the treatment of adolescents with eating disorders. Naltrexone is one medication used to treat eating disorders, but not everybody responds the same way. We do not know yet why certain people respond, but others don't. This study will look at brain activity and will also collect and store samples and information from adolescents and young adults. The samples and information we collect will be used for research now and in the future to improve the care of eating disorders.

Naltrexone has been approved by the FDA to treat substance use in adults, but is not yet approved in children and thus has not been fully tested in children. Nearly 80% of medications used in children are only approved in adults. Studies in adults and children have shown that naltrexone is not associated with serious adverse events at the dose used in this study.

WHO CAN BE IN THIS STUDY?

We are asking you or your child to be a part of this research study because you or your child have been diagnosed with an eating disorder that causes binge eating or purging (for example, vomiting or excessive exercise). About 50 patients aged 13 to 21 years old will be asked to be in this study.

WHAT WILL HAPPEN TO ME IN THIS STUDY?

If you decide to be in this study, the following things will happen:

- We will ask you/your child questions about your medical history, health, and the medicines you are taking. Your medical records may be reviewed, if available, to assess your health.
- You/your child can have only clear liquids (e.g., no food) for 4 hours prior to their scheduled start time. Standard meals will be provided (see table below).
- You or your child will have one brain scan called an fMRI (see picture) before taking naltrexone and one brain scan after to look at response to naltrexone. During the brain scan, you/your child will view pictures of food and play a game.

- We will be collecting blood and urine samples for 7 hours after you/your child takes naltrexone. To minimize the discomfort associated with repeated blood draws, blood will be collected through an IV (small tube in the arm) on the Study Day whenever possible (needle stick may be used if needed or you/your child prefers). We will take less than 1 teaspoon of blood at each collection. The total blood collected for the study will be no more than 8 teaspoons during the Study Day. All urine will be collected during the study day and a small amount stored.

Study Visit Element	**Main Procedures/Data Collected**	**Approximate Clock Time**
Screening and Consent	*Review inclusion and exclusion criteria, Consent*	*In person, telephone or e-consent prior to study visit*
Vital signs and medical history	Inclusion/exclusion criteria review and confirmation, medical history, height, blind weight (not shared with participant), blood pressure, pulse pregnancy test (for participants of reproductive potential)	7 am
Meal #1 (1 hour before scan #1)	Standardized meal	8 am
fMRI scan #1	During the brain scan, you/your child will view pictures of food and play a game.	9 am
Naltrexone (NTX) dosing	Single dose of naltrexone by mouth 2 hours prior to scan #2	10:30 am
Meal #2 (1 hour before scan #2)	Standardized meal	11:30 pm
fMRI scan #2 (2 hours post-NTX)	During the brain scan, you/your child will view pictures of food and play a game.	12:30 pm
Pharmacokinetic analysis	Blood samples obtained from IV pre-dose, 0.5, 1, 1.5, 2, 3, 4, 6, 7 hours post-naltrexone dose.	5:30 pm (last PK draw & study end)

OPTIONAL EEG: Some participants may qualify to have an EEG done before taking naltrexone. An EEG involves wearing a special cap that measures brain signals.

For participants under 18: Information and samples will be stored past your child's 18th birthday. We will attempt to contact your child for verbal consent once they turn 18. If we cannot reach your child, all samples and information will be de-identified.

For all participants: Samples will be stored and used only for research and will not be sold. This research might include looking at you/your child's genetic code (e.g., genome sequencing or genetic analysis), at blood markers or medication levels. A human cell contains thousands of genes. Genes contain the information needed to build and operate a human body. The basic structure of genes is DNA, which stands for deoxyribonucleic acid. Everyone's genes are different. This explains differences in eye color, hair color, and blood type. Gene differences also partly explain why some people, but not others, get certain diseases. Information about gene differences among people can help researchers discover new tools to diagnose and treat inherited diseases. DNA testing will be done on your child's sample collected for this study. You or your child's de-identified information and samples could be used for future research without additional permission.

The fMRI and genetic results will not be shared with you/your child. Aggregate de-identified study findings will be available to participants in peer-reviewed scientific publication, a process which can take years. If you/your child want to be sent a copy of the publication(s), please indicate so at the end of this form.

You should know that research sometimes results in discoveries that may one day have commercial value. For example, discoveries could eventually lead to new tests, drugs, or other products. Development of new products relies on the study of samples from hundreds or thousands of people, not on any one person. If this happens, you or your child should not expect to share in any of the profits. You and your child will not receive money or other compensation for use of these samples.

Optional Future Research Contact: You will be asked whether we may contact you in the future about your child taking part in future research studies related to your child's disease or condition. Your decision will not affect your child's ability to be in this research study and will not affect your child's routine care. You will be able to mark your choice at the end of this form.

WHAT ARE THE RISKS OF THE STUDY?

- Small risk of loss of confidentiality because we are keeping your identified study records, but every effort will be made to prevent this and keep your information confidential. By providing your email or phone number, the study team may communicate with you regarding setting up appointments, sending copies of permission/assent forms and any other non-clinical, study related communication. If you are enrolled in the My Children's Mercy Portal, the study team may also communicate with you via the portal. Please be aware of the following:
    - Corresponding through electronic communication methods is not a secure method of sending information and others may be able to access the information sent.
    - The information may not be secure if storing or viewing the permission/assent document on a personal electronic device (PED), especially if that PED is shared with other users or is lost, hacked, or subject to a search warrant or subpoena.
    - Information that is sent electronically may be kept on the Hospital's or your service provider's (Google, Yahoo, MSN, etc) network servers. Unlike paper copies, e-copies delivered directly to your PED may not be able to be permanently removed.
    - Information shared through the portal may be saved as a part of your child's permanent medical record.
    - The Hospital is not liable for any security breaches of your information sent electronically.
    - Under Missouri law, a competent minor (less than 18 years old) may consent to his or her own diagnosis or treatment without parental permission for reproductive health care, drug or substance abuse. Negative test results cannot be released to a parent or guardian without the minor's permission. Positive test results can be discussed with the parent or guardian at the discretion of the provider. Because pregnancy testing is being done as part of this study, this privacy protection is not possible. If participants do not want these test results shared, they should not enroll in the study.
- Minimal discomfort or bruising may occur with drawing blood and IV placement. You/your child may be given the option of a numbing agent to help ease the pain of needle sticks.
- When answering the brief questionnaires, the questions asked may be uncomfortable or embarrassing. These risks are minimum and unlikely to occur. You or your child do not have to give any information you do not want to give. You or your child's confidentiality will be protected to the greatest extent possible and your answers will not be released to your care team.
- Side effects to naltrexone occur in ~10% of patients, are typically mild and go away on their own (e.g., nausea) and do not differ from those receiving a placebo (e.g., sugar pill). Allergic reaction to naltrexone is rare and

usually happens right away after taking the medicine. Symptoms include hives and difficulty breathing. Trained personnel will be available in the clinic where the study drug is given. Caution is advised with naltrexone use in pregnancy, although there is no expected risk of harm to an unborn baby based on available information. If you/your child is pregnant, you cannot be in this study.

- Genetic testing carries the possibility of discrimination. However, a Federal law called the Genetic Information Nondiscrimination Act (GINA) generally makes it illegal for health insurance companies, group health plans, and most employers to discriminate based on genetic information. Additionally, you/your child's results will be kept in the study record and not released to your medical record.
- Some patients may feel claustrophobic during the brain scan; however, only a small amount of the upper body will be in the scanner. Incidental finding from the neuroimaging (e.g., fMRI) may occur. Whenever brain imaging is done, there is a chance of finding something unexpected and unrelated to the research study that may have some clinical implications. The neuroimaging used in this study is for research purposes only and is not the same as clinical neuroimaging.

If you have any of these problems or changes in the way you/your child feel, you/your child should tell the investigator or other study personnel as soon as possible.

WHAT ARE THE BENEFITS OF BEING IN THIS STUDY?

There may be a direct benefit to you/your child from being in this study. Possible benefits may include reduction in eating disorder symptoms, such as urge to binge eat or purge (e.g., vomit) after taking naltrexone. By being in this study, you/your child may help teens and young adults with eating disorders in the future.

WHAT ABOUT EXTRA COSTS AND INSTITUTIONAL RESPONSIBILITIES?

You will not have to pay anything extra if you or your child are in this study and nothing will be billed to your insurance. Naltrexone and meals will be provided to you at no charge. Basic expenses such as transportation and the personal time it will take to come to the study visit will be your responsibility

Research-related injury is not expected and no compensation for research-related injury is available. Should a serious adverse event occur during the study day, you/your child will be taken to the nearest emergency department or the emergency department of your choice. Care will be provided by that institution at the usual charge and you/your child will have the benefit of the coverage of any existing health insurance you own. You will be responsible for any treatment costs not covered by any existing health insurance/third-party payor.

WHAT ABOUT CONFIDENTIALITY?

The information we collect about you or your child during this study will be stored in the research record on a secure server at Children's Mercy and may also be recorded in you/your child's medical record. The research record is separate from the medical record. This record will have you or your child's name, contact info, medical record number, date of birth, medical history and research data. We will do our best to protect this information so that no one else can see it. You or your child's answers to the questionnaires will not be shared with the clinical team. We believe this will allow you or your child to provide honest answers without fear of negative consequence.

By signing this form, you are allowing the research team to keep this information. The law says we must keep this information secure and private. All research records will be maintained in a confidential manner.
By signing this form, you are also permitting the following people to have access to you/your child's medical record and PHI:

- The research team, which includes persons involved in this study at Children's Mercy Hospital and the University of Kansas Medical Center
- Hoglund Biomedical Imaging Center
- The Institutional Review Board at Children's Mercy Hospital and the University of Kansas Medical Center
- A group that oversees the data (study information) and safety of this research
- People from organizations that provide independent accreditation and oversight of hospitals and research
- Government/regulatory agencies such as the Office for Human Research Protections whose job it is to protect human subjects and oversee the conduct of research

Information (e.g., name, contact info, date of birth, SSN only if needed) will remain on the Greenphire secure server 7 years after study closure and then will be destroyed. This information is needed for tax purposes related to compensation only.

WHAT ARE THE ALTERNATIVES TO BEING IN THIS STUDY?

Participating in research is your choice. You/your child can choose not to participate.

WHAT WILL I RECEIVE FOR BEING IN THIS STUDY

You or your child will receive $400 for completing the Study Day. Standard meals will also be provided during the study day.

If you receive a total of over $600 in the calendar year from Children's Mercy for participating in research, the IRS requires the collection of your social security number (SSN) or individual tax identification number (ITIN) and you will receive a copy of this tax form. If collected, your SSN or ITIN will be kept securely. Accepting payment for taking part in the study may affect eligibility for Medicaid or other programs.

WHAT ARE MY RIGHTS AS A STUDY PARTICIPANT?

Being in a research study is voluntary. You do not have to be in this study to receive medical care at Children's Mercy. If you choose not to be in this study or withdraw from this study, there will be no penalty or loss of benefits to which you are otherwise entitled. If you are an employee of Children's Mercy, your decision will not impact your employment.

WHO SHOULD I CALL IF I HAVE QUESTIONS OR PROBLEMS?

Stephani Stancil, PhD, APRN is in charge of this research study. You may call her at 816-960-3040 with questions at any time during the study. You should call Dr. Stancil if you believe that you or your child has suffered injury of any kind as a result of being in this research study.

You may also call Children's Mercy Hospitals' Pediatric Institutional Review Board (IRB) at (816) 731-7474 with questions, compliments or complaints about this study. The IRB is a committee of physicians, statisticians, researchers, community advocates, and others that ensures that a research study is ethical and that the rights of study participants are protected.

PERMISSION/CONSENT OF PARTICIPANT

The purposes, procedures, and risks of this research study have been explained to me. I have had a chance to read and discuss this form and ask questions about the study. Any questions I had have been answered to my satisfaction. I understand that I/my child don't/doesn't have to be in the study and can quit at any time. A copy of this signed form will be given to me.

PERMISSION/CONSENT:
I give permission or provide consent for _____ to participate in this research study.

_____ _____
Signature of Adult Participant or Parent/LAR Date Relationship to Participant

ASSENT OF MINOR:
I agree to be in the study and with the paragraph above.

_____
Signature of minor Date

Optional Future Research Contact:

I agree for a member of the Children's Mercy study team to contact me in the future to ask about me /my child participating in future research studies.
_____Yes_____No_____Initials

I would like to be sent a copy of the scientific publication(s) that contain de-identified, aggregate findings from this study.
_____Yes_____No_____Initials

STUDY PERSONNEL

I have explained the purposes, procedures, and risks involved in this study in detail to:

_____
Print name(s) of Adult Participant/Parent/LAR

_____ _____ _____
Signature of Person Obtaining Permission/Assent/Consent Date Time

Print Name of Person Obtaining Permission/Assent/Consent _____

INTERPRETER

☐ Interpreter Used ☐ Qualified Bilingual Study Staff Used
I was present and provided interpretation services during the signing of this document.

_____ _____
Signature of Interpreter Date

Printed Name of Interpreter: _____
(Must also sign the translated document)

Relationship of Interpreter to Participant/Parent/LAR:_____