Title of Study: Open label placebo for children with functional abdominal pain and irritable bowel syndrome: A randomized crossover trial

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A. Specific Aims and Objectives

This study is aimed at investigating the efficacy of open label placebo for symptom relief in children with abdominal pain related functional gastrointestinal disorders.

B. Background and Significance

Some of the most commonly used drugs for the treatment of FGIDs have potential severe adverse effects including cardiac, psychiatric, urinary and gastroenterological problems. Moreover, studies have shown an increase in suicidal ideation in adolescents using some of the most commonly prescribed drugs for the treatment of FAP.[1,2] As a result the FDA has mandated discussing the possible increased risk of suicide among this group of patients. Parents often refuse treatment due to the potential life threatening risks.

A recent adult study has shown that non deceptive placebo use is beneficial in the treatment of IBS.[3] In this study, patients who were made aware that they would receive placebo had greater improvement of symptoms than those in the control group. This study opens the door to the possible use of non-deceptive placebo for the treatment of FGIDs in other populations including children. The use of placebo could potentially reduce health risks, decrease costs and increase parental acceptance. There have been no studies investigating the possible acceptance and efficacy of using non deceptive placebos for the treatment of FGIDs in children.

There are several hurdles to conducting non deceptive placebo studies including ethical issues. Although adult studies have used non-treatment as control to assess the efficacy of non-deceptive placebo, not treating children who are suffering of pain is not ethically acceptable. A possible mean of overcoming these ethical issues it to use placebo as an addition to conventional treatment. This design would allow assessing the superiority of the addition of placebo to the conventional treatment and still provide standard treatment for the child's symptoms. Standard of care of FAP includes use of as needed anticholinergic drugs at times of pain episodes. We propose a preliminary study aimed at investigating parental acceptance to the use of non-deceptive placebo and the possible additional effect of non-deceptive placebo to conventional therapy in children with FAP.

C. Preliminary Studies

A meta analysis has shown that 40% of adult patients with IBS improve with the exclusive use of placebo.[4] Studies on children with FGIDs have confirmed these findings by showing a consistent high placebo effect in randomized trials.[5,6]The largest randomized clinical trial investigating the

efficacy of the use of drugs to treat children with FAP (functional abdominal pain) has shown that placebo was as effective as the study drug in the treatment of these conditions.[6]

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D. Design and Methods

a. Study Design and Timeline

This is a prospective multicenter crossover study of the efficacy of administering placebo without deception.Eligible patients will complete a 1 week of observation prior to randomization to one of two arms: a) *Group 1*: Control period (CP) for 3 weeks, followed by open placebo (OP) for 3 weeks and b) *Group 2* : OP for 3 weeks, followed by a CP of 3 weeks, Our aim is to recruit at least 30 subjects in total across all sites (see below). Enrollment at Children's Hospital Boston will occur on Fegan 5, where Dr. Nurko and his colleagues see patients regularly. Prior to enrollment the physician will brief potential subjects on what a placebo is and how it works. The placebo will be described as an inert or inactive liquid, without any medication in it (see below). Additionally, subjects will be told that ''liquid placebo has been shown in rigorous clinical testing to lead to improvement of pain symptoms possibly by an effect on the interaction between the body and the mind.'' Following a description of placebos

and the study process, patients who give informed consent and fulfill the inclusion and exclusion criteria will be randomized into two phases: A 1.5 ml of placebo suspension twice daily, and a third dose if the pain has not resolved or B) no placebo. In both phases, subjects will be prescribed a rescue medication. The rescue medication prescribed will be hyoscyamine (an anticholinergic), which subjects may use to control pain on an as needed basis in both phases. Hyoscyamine is considered a standard of care medication for the treatment of functional gastrointestinal disorders.

Standard of Care - While there are no guidelines for the treatment of Functional Abdominal Pain, physicians most commonly prescribe an anticholinergic as the first line in treatment. For that reason, hyoscyamine, will be used as the rescue medication for subjects in this study. Subjects enrolled in this study will have a clinical indication to be prescribed hyoscyamine, per their primary gastroenterologist.

Specific methods

Patients will complete 1 week of observation and will then return to clinic. Eligible patients will then be randomized to one of two arms: a) *Group 1*: Control period (CP) for 3 weeks, followed by open label placebo (OLP) for 3 weeks and b) *Group 2* : OP for 3 weeks, followed by a CP of 3 weeks There will be no washout period between both treatments phases as there should be no carryover effect of an inactive compound.

<u>Visit 1: First encounter (Day 0/Week 1)</u>: Prior to the first encounter, the medical record of children seen in clinic will be reviewed to assess study eligibility. Eligible patients may also be sent a recruitment letter. The first encounter will occur in gastroenterology clinic.

1- A member of the research team will approach subjects in one of the gastroenterology clinics to introduce the study and to obtain consent.
    a. Families do not have to decide on the day approached if they would like to participate in the study. They can take the consent home and consider their participation at their leisure. They will be informed, however, that if they decide to participate in the study after the fact, that they will not be able to start the hyoscyamine until the completion of the 7-day baseline phase.
2- Daily diary sheets will be provided for the baseline week 1. . This diary will be used to gather baseline data (1st week of study)
3- The daily diary will include the visual analogue scale, and the Word-Graphic Rating Scale, which will help children to rate the severity of their abdominal pain. The subject will be instructed to rate the abdominal pain on a rating scale every day at bedtime.

<u>Visit 2: Second Encounter (start of week 2)</u>

1- Subject will be randomized into one of the 2 arms of the study
2- If randomized to Phase A, a three week supply of hyoscyamine and placebo will be provided to the family
3- If randomized to Phase B, only a three week supply of hyoscyamine will be provided.
4- Subjects will be asked a standardized set of questions regarding diagnosis, history and characteristics of pain.
5- Subjects will complete the Pediatric Quality of Life Questionnaire.

6- Subjects will be given a three week daily diary to complete which will be two pages each day inquiring about symptoms and the Diary will also be used by subjects to indicate whether hyoscyamine was used that day.

7- Collection of saliva for COMT testing

Visit 3: Third encounter (start of week 5): Will occur in gastroenterology clinic.

1- Family returns completed diary forms from 1 week of baseline and 3 weeks of study (the 3 weeks will either be for Phase A or Phase B).

2- Clinical evaluation.

3- Subjects will complete the Pediatric Quality of Life Questionnaire.

4- Physician addresses any study concerns and questions.

5- Patients will then be crossovered to the opposite treatment, either placebo with rescue medication, or rescue medication alone

Visit 4: Fourth encounter (End of week 7): Will occur in gastroenterology clinic.

1- Family returns completed diary forms for alternate phase of study and unused medication and placebo.

2- Clinical evaluation.

3- Subjects will complete the Pediatric Quality of Life Questionnaire

4- Family and subject are thanked for participating in the study.

At the conclusion of the study at visit 4 we will schedule four follow up appointments at 3-week, 3 months, 6 months, and 12 months after the completion of the study to follow up clinically with the patient.

If the patient has demonstrated significant improvement during the placebo treatment phase of the study, at the 3-week follow up appointment after completing the study, the family will be given the option to restart the open label placebo for a maintenance period of 6 months. Patients who elect to take part in the additional 6 month maintenance phase will be seen back in the gastroenterology clinic after 1 month, 2 months, 4 months, and 6 months to assess progress during this extended open label treatment phase. This 6-month open label placebo extension is entirely optional and will be offered primarily at the request of the patient and/or family in an effort to offer an effective therapy with limited potential for side effects.

All subjects will have the option to discontinue their participation in this study at any point. Should a subject begin in the placebo arm, see significant benefits from the study and as a result choose not to cross-over to the non-placebo arm, they will have the option to do so. If they do choose to do so, they will be provided with the placebo from the study. Our recruitment goal was adjusted to account for subject attrition.

b. Patient Selection and Inclusion/Exclusion Criteria

The informed consent process will occur in the gastroenterology clinic during the patient's scheduled doctor visit. Prior to each clinic, a member of the research team will review the schedule of patients and review the medical chart for each patient to screen for eligible subjects. Those children with a diagnosis of FAP or IBS will be considered for this study.

Potential subjects will be approached in the exam room following the physician's visit. A member of the research team will approach subjects to introduce the study and to obtain consent. The study will be introduced as an open label trial of placebo and the potential risks and benefits of placebo will be outlined. The families recruited will be given adequate time to read the form and ask questions prior to obtaining a signature. If the family consents to entry into the study, written consent will be obtained from the parent/guardian of every subject and written assent will be obtained for all subjects between the ages of 8 and 18. A copy of the signed consent form will be given to the signers. The subject's parent(s) or guardian(s) may request that the subject be removed from the study at any time. In addition, the investigator may withdraw a subject from the study if he/she determines that it is in the subject's best interests. Medical care will not be altered whether or not consent is obtained.

In addition to approaching potential subjects in the gastroenterology clinic, patients may also be recruited through an informational flyer or online posting. Both briefly outline the purpose of the study and provide contact information for the study team.

Inclusion criteria:

1. Age 8 to 18 years.
2. Diagnosis of functional abdominal pain, or irritable bowel syndrome made by a pediatric gastroenterologist according to Rome III Criteria.
3. Mean daily intensity of pain of 25 mm in the week prior to the initiation of the study, based on the Word-Graphic Rating Scale score.

4. Children will not be excluded if they are adhering to any specific diet. Children will be asked to report any specific established diet prior to the study or dietary modifications that could have been made during the course of the study.
5. Normal laboratory tests including complete blood count, erythrocyte sedimentation rate, albumin, serum amylase, lipase, liver enzymes, urine analysis, stool examination for occult blood and ova and parasites one month prior the initiation of the study. Urinary culture will be obtained if the symptoms or urinalysis suggest the possibility of a urinary infection.
6. Normal lactose breath test or history of lack of resolution of symptoms on a lactose-free diet (2 weeks).
7. Patients receiving psychological treatment, hypnosis, biofeedback or guided imagery will not be excluded of the study if those were started at least one month prior to the initiation of the study and are not planned to be discontinued during the length of the trial. Patients will need to be prescribed hyoscyamine (clinically indicated) to be considered for this study, as the placebo will be in addition to their prescribed medication.

<u>Exclusion criteria</u>:

1. Inclusion criteria not met.
2. Evidence of organic gastrointestinal disease, hepatic disorders, urinary or cardiac disease.
3. Children below the 5th percentile for weight or height.

4. Hemoccult positive stools.
5. Patients with diagnosis of Inflammatory Bowel Disease, hyperthyroidism, CHF, cardiac arrhythmias, prostatic hypertrophy, autonomic neuropathy, biliary tract disease, children with spastic paralysis or chronic lung disease (we will consult a pulmonologist concerning the inclusion of children with chronic lung disease).
6. Patients who are taking any of the following drugs: AbobotulinumtoxinA, Acetylcholinesterase Inhibitors (Central), Cannabinoids, OnabotulinumtoxinA, Potassium Chloride, Pramlintide, RimabotulinumtoxinB, Secretin. Patients receiving antidepressant or anticholinergic drugs will be excluded from the study. PPIs will be allowed as long as the patient had been on a stable dose for at least 12 weeks.
7. Patients planning to change their diet during the time of the study will be excluded. Children will be asked to report any specific established diet prior to the study or dietary modifications that could have been made during the course of the study.
8. Patients planning to start psychological treatment, hypnosis, biofeedback, or guided imagery during the course of the study or have started any of these within the month prior to consent.
9. The participant is pregnant or is planning to become pregnant throughout the course of the research study

c. Description of Study Treatments or Exposures/Predictors

Description of Placebo: The Placebo will be in liquid form. It will be a Humco Brand simple syrup. Patients will take 1.5 ml of the Placebo in the morning and 1.5 ml at night using a plastic

3 ml syringe. The placebo will be stored and dispensed by the Children's Hospital Boston Pharmacy,

Description of Rescue Medication: Hyoscyamine will serve as the rescue medication for this study. Hyoscyamine works by decreasing the motion of the stomach and intestines and the secretion of stomach fluids, including acid. Subjects will be provided with a prescription for Hyoscyamine pills to use on an as needed basis. Families will be responsible for the cost of this medication. Children ages 8 through 21 may not exceed 4 pills per day.

Using 4 pills is much lower than the highest recommended dose. In children <12 the maximum recommended dose is 0.75 mg, and in those > 12 years it is 1.5 mg The dose we are recommending here is 0.6 mg. Even if the patients take more it is unlikely they will overdose. Patients will be instructed not to take more than the recommended number of pills. If there is a nocebo effect, or more pain, they will be instructed to contact the investigative team. This medication has anticholinergic properties so the families will be instructed on those side effects. The first point of contact if there is increasing pain will be the research team. Patients/families will be instructed to go to the ED if the investigator thinks there are anticholinergic side effects, or judges that the pain merits consultation to rule out surgical problems. This has been added to the Risk section of the protocol.

Catecholamines play a key role in cognitive[7], behavioral[8], sensory[9], endocrine[10] and autonomic nervous system regulation[11]. Thus functional polymorphisms in catechol-O-methyltransferase (*COMT*), an enzyme that metabolizes catecholamines may be associated

with a variety of clinical conditions. The most extensively studied *COMT* single nucleotide polymorphism (SNP), rs4680 or val158met, is a G to A transition that encodes a valine (val) to methionine (met) substitution at amino acid 158 in the membrane form of the enzyme and amino acid 108 in the secreted form[12]. The G or val variant is 3-4 times more enzymatically active than the A or met variant[13]. The differences in enzymatic activity are inversely correlated to endogenous levels of dopamine[14] and other COMT substrates including epinephrine, norepinephrine and catechol estrogens[15,16], both at rest and with stress induced by exercise[17] or cardiac surgery[18]. In turn, variation in the levels of these signaling molecules have been related to functional pain syndromes[9], as well as in irritable bowel syndrome in adults[19].

Based on a study conducted in adults with IBS[19], in which IBS patients homozygous for the COMT val158met methionine allele (met/met) were the most responsive to placebo treatment, we hypothesize that the COMT functional val158met polymorphism will be a predictor of placebo effects.

Specific aspects of the encounters:

Design of a script and validation of the script to introduce the placebo phase

A defined script to approach each family/individual was designed. Different scripts were designed specifically for each group and visit type including enrollment, randomization to either group and crossover. The script for the placebo group included the following concepts:

a) the placebo effect is very powerful in randomized clinical trials;

b) although we have much more to learn about how it works, we do know that it takes advantage of the mind-body connection;

c) one reason for its effect may be that the body automatically responds to taking the placebo suspension and activates responses that help reduce pain and swelling;

d) the placebo jump-starts this beneficial response;

e) another good thing about a placebo is that you do not need to believe in it for it to work – a positive attitude helps, but is not necessary;

f) however, for the placebo to work, it is important that you to take the suspension on a regular basis, and finally

g) the great thing about placebos is that there are no side effects.

The script were practiced to be sure they were delivered in the same way to all individuals, and given the multicenter nature of the trial a video was created and distributed to the centers. One of the members of the BCH team then witnessed and validated to scripts at the other sites to ensure uniformity.

d. Definition of Primary and Secondary Outcomes/Endpoints

Primary Outcome Measures**:**

Primary outcome

The primary outcome that will be used will the mean daily pain (0-100 VAS scale). It will be assessed at the end of the 3-week and 6-week treatment periods (at the end of each treatment arm prior to switching to the next arm of treatment) (see statistical section below)

Secondary outcomes

The study will assess two global outcome measures of patient's symptomatic response: *satisfactory relief of symptoms and overall improvement*. Both patient reported outcome (PROs) measures have been widely studied [20] and used in adult and pediatric studies including a large randomized clinical trial conducted by our research group on a similar group of patients.[6] Landmark studies leading to the approval of medications for IBS have used adequate or satisfactory relief of symptoms and overall improvement as outcome measures.[21,22] Following the design of most high quality clinical trials in IBS both global assessment questions will be analyzed as binary outcomes.[23] Both binary improvement endpoints have shown excellent construct validity and were not impacted by baseline severity in adult studies [24,25] , and have demonstrated adequate psychometric properties in pediatric studies conducted by our group.[26] Clinical global improvement will be assessed by obtaining symptomatic improvement using the following questions:

1- Satisfactory relief: "Overall how do you feel your problem is?" Patients will select an answer from a list of 3 possible answers (better, same, or worse). In order to establish a binary assessment of outcome patients answering: "better" will be compared to "worse" and "same"
2- Satisfaction with treatment: "How did the medication relieve your pain?" Patients will select an answer from a list of 5 possible answers (excellent, good, fair, poor, or failed). In order to establish a binary assessment of outcome patients answering: "excellent" and "good" will be compared with those answering: "fail", "poor" and "failed".

Other secondary outcomes were the use of rescue medication (assessed by pill count) , change in disability, anxiety and quality of life before and after the placebo or the control period.

Evaluation tools and questionnaires

1- Demographic Information (age, race, gender).

2- QPGS.- Questionnaire on Pediatric Gastrointestinal Symptoms: Rome III version (***QPGS-RIII***), Validated questioannire to establish Rome criteria ()

3- Word-Graphic Rating Scale is a simple, valid, sensitive and developmentally appropriate self-report test to assess pain intensity in children. It consists of a 10 cm horizontal scale anchored by the words “no pain”, “little pain”, “medium pain”, “large pain” and the “worst possible pain” at regular intervals from left to right end of the line respectively.

4- Functional Disability Inventory consists of 15 self-report items assessing the perceived degree of physical and psychosocial difficulty in functioning due to the patient’s health status. This inventory has high levels of internal consistency, construct validity and high levels of test–retest reliability for patients with recurrent abdominal pain. The FDI is sensitive to changes in patient status subsequent to medical treatment making it an appropriate instrument for outcome measure.

5- Pediatric quality of life.- Validated age appropriate questionnaire to assess quality of life in children

- Pediatric Quality of Life GI Questionnaire- the GIPedsQoL is a validated age appropriate questionnaire that was used in multiple studies of GI pain in children {Kovacic, 2017 #861;Krasaelap, 2020 #1128}
- RCADS.- The Revised Child Anxiety and Depression Scale (RCADS) is a 47-item, youth **self**-report questionnaire with subscales including: separation anxiety disorder, social phobia, generalized anxiety disorder, panic disorder, obsessive compulsive disorder, and low mood (major depressive disorders
- CDI. Children's Depression Inventory 2™ (CDI 2) is a brief self-report test that helps assess cognitive, affective and behavioral signs of depression in children and adolescents
- Children's Somatization Inventory assesses the extent of children's somatic complaints on the previous two weeks. The CSI had good concurrent validity with another self-report measure of somatic symptoms and a low but significant correlation with parents' reports of their children's somatic symptoms on the parent version of the CSI. A total score is obtained by summing the ratings of its 35 questions and can range from 0 to 140.5-
- To assess expectations of success the question: "How well do you think the treatment will work in a scale 1-10" will be asked at the beginning of each arm of the study

Informational Pamphlet

A 1-page informational pamphlet will be given to subjects and their families. This short pamphlet provides additional information about the placebo effect and the ability of placebo treatments to provide symptom relief for patients with certain conditions. The aim of this

pamphlet it to provide subjects and their families with standardized and consistent background information on the placebo effect.

E. Adverse Event Criteria and Reporting Procedures

Adverse events will be considered as significant deviations from normal health, especially any gastrointestinal symptoms which require hospitalization. If health issues arise in any subjects we will refer them to their primary care physician. Treatment will be made available to the subject at Children's Hospital Boston should they choose to see us. Cost of treatment will be the responsibility of the patient. The investigator may choose to remove these subjects from the study.

All adverse events will be evaluated and reported on case report forms by Dr. Samuel Nurko on a daily basis. He will record any adverse events , and Children's Hospital will be the coordinating center., The chair of the DSMB will receive the information from all centers on a monthly basis, unless serious in which case they will be reviewed by the DSMB within 72 hours. All adverse events will be reported to the committee on clinical investigation within 7 days. Severe adverse events will be reported within 24 hours. Once a report is issued, responses such as suspensions will be quickly verbally communicated to study investigators.

The DMSB will be responsible for monitoring the data, and will be involved in the interim analysis if necessary. We do not anticipate any interim analysis for early discontinuation for efficacy due to the small sample size and the descriptive and exploratory nature of the study. After half the patients are enrolled, an interim analysis will be performed primarily focused on

adverse events, data quality and completeness, and study accrual. For the interim analysis, a committee will be formed comprised of two physicians and one biostatistician, none of whom are involved in the study. The trial may be discontinued at any time at the recommendation of the investigator or Data Safety and Monitoring Board (DSBM) based on a significant number of severe adverse events of similar nature.

Stopping rules:

The stopping rules will be the following: a) Worsening of the pain to the point that the parent/child think is unbearable

b) Visit to the ED because of the pain

c) Admission to the hospital because of the abdominal pain.

d) Development of vomiting or weight loss

The DMSB may recommend stopping the trial before its planned end for any of the following reasons:

a) Placebo administration to patients suffering from FGIDs worsens the pain experienced

b) adherence to trial protocol may be below acceptable goals, such that the ability of the trial to achieve its goals would be severely compromised or

c) adverse events may be unacceptably high.

The investigators from the respective sites have a well-established relationship working collaboratively in the area of pediatric gastrointestinal research. If at any point an adverse event or new development arise at any of the sites, the principal investigator of that site will

verbally communicate the findings or data to the corresponding site within 24 hours. Any follow up information or recommendations of the IRB will be forwarded as it is received. All data communicated between sites will not have identifiers and PHI attached. Subjects will be referred to by their assigned study ID number only in all communications.

In the event of an injury resulting directly from a patient's participation in this research study, medical treatment will be provided if the injury is reported in a timely manner to the Principal Investigator, Dr. Samuel Nurko, and the research team. If any research-related injury occurs, you/your child should contact research staff using the phone numbers provided at the end of this form to report the incident. Provision of such medical care will not imply any negligence or other wrongdoing on the part of Boston Children's Hospital or any of the physicians or other personnel involved in the study (in Boston or a coordinating center). Where applicable, BCH reserves the right to seek payment from third-party payers for any medical care or services rendered. The Hospital has no program to provide the research participants with any additional compensation as a result of any such injuries.

UNFORESEEN INJURIES

The use of placebo's in children and adolescents with functional gastrointestinal disorders is not well studied and is not an approved treatment. It is possible that there may be some side effects or risks with the use of the placebo that are not yet known. Sometimes, during the course of a study, we may learn new information about the placebo that might change whether or not the participants want to continue in the study. If this happens, the Principal Investigator

(Dr. Samuel Nurko) will tell the participants about it in a timely manner, and they will be given an opportunity to withdraw from the study.

Additionally, there may be an additional unforeseeable risk to participants who are pregnant or become pregnant throughout the course of the study. The use of placebo in pregnant women has not been extensively studied and could carry a risk to the embryo or fetus, which is currently unforeseeable. If the participant is or becomes pregnant throughout the course of the study, they will be requested to inform Research Staff as soon as possible.

If significant new findings occur during the course of the research that may relate to the subject's

willingness to participate, such information will be disclosed to them in a timely manner and they will be given the opportunity to withdraw at that time and will be reminded it will be with no consequences (Just as if they were to withdraw at any other time)

This information is available in the ICF.

F. Data Management Methods

The diary forms and questionnaires will be identified by a study ID number and not include subject names. The Study ID number will be a 3 digit number including one random digit and will not in any way be derived from personal patient information. The data will be analyzed as a whole by the statistical department at Children's Hospital Boston; individual survey results will not be disclosed. All links to individual subjects will be deleted at the end of data collection. Data will be stored on a password-protected database that only the research staff will have

access to. The data from all institutions will be transferred to Children's Hospital Boston, and data transfer agreements will be in place.

G. Quality Control Methods

Possible Risks

Risks of PLACEBO:

Some research studies have shown that subjects may have a negative response to the use of placebo.[30] In studies where subjects are not told whether they will receive medication or a placebo some subjects in the placebo group will experience the side effects associated with medication given in that particular study. Other studies have shown that subjects who enter a study with negative expectations (or a pessimistic attitude) may also have a negative response to placebo.[31,32]

There is also a potential for the participant and family members to loose trust in the participant's gastroenterologist who is dispensing a placebo to treat their problem. There is limited knowledge to date regarding children's perception of placebos. The participant and family members will be reassured that they are being recruited into this study because their child's primary gastroenterologist believes there is a possibility of symptom improvement from their child's participation.

GENERAL RISKS:

The participant will receive a prescription for hyoscyamine at the beginning of this trial, but will be asked to hold off on taking the medication for the first 7 days (baseline phase). There is a risk here that the participant could experience symptoms during this period, and we are asking that they, if possible, delay taking the rescue medication until the first phase of the trial begins in

order to get an accurate baseline measurement. The participant and family will be asked to delay hyoscyamine usage, but will not be forced to delay treatment should the symptoms be unbearable.

Due to the possibility of a breach of confidentiality personal identifiers (other than date of birth and gender) will be removed from all documents before they are placed in the central research record to insure confidentiality. Subjects will be assigned an identification number, which will be used in place of personal identifiers. The study database will be password protected and all information will be handled confidentially. To minimize the risks associated with placebo, subjects will be provided with rescue medication to take on an as needed basis.

This study involves filling out questionnaires on quality of life and pain. It is possible that filling out questionnaires may not be comfortable for the patient so they will be informed verbally and through the ICF that this is voluntary and it is not absolutely mandatory that they fill out the questionnaires. They will just be asked to fill out as many as they feel comfortable with.

<u>Possible Benefits</u>

There is the possibility that subjects will feel better and have improved symptoms following participation in this study. Subjects may also benefit by participating in this study because the results will be used to benefit future patients and their medical treatment.

H. Data Analysis Plan, Statistical Power and Sample Considerations

I. **Power Analysis**

J. The within-subjects design of the study allowed each participant to serve as his or her own control, which tends to increase statistical power. We used G*Power 3 software to

conduct the power analysis. Using a two-tailed test with alpha set at 5%, we calculated that a repeated measures analysis of variance with a sample size of 30 would provide 99% power to detect large effects (e.g., η^2_p = .14), and 75% power to detect medium effects (e.g., η^2_p = .06).

K. **Statistical Analysis**

Values will be expressed as mean + SD when normally distributed, or as medians if applicable. For the categorical outcomes of interest, either a Fisher's Exact test of a chi-square test will be used. Each of the outcomes will be analyzed separately. Paired tests will be used when comparing baseline values to values after the different interventions . Statistical significance will be set at $p<0.05$.

As an assessment as to the necessary inclusion of potential covariates, the drug therapy and the drug + placebo groups will be compared on descriptive variables (e.g., age, etc.). If the groups are statistically different on any of these variables, then they will be included as covariates in subsequent analyses.

The order of the two conditions (open label placebo vs. no treatment control) will be counterbalanced to minimize order effects methodologically (we also controlled for order effects statistically, as detailed below). The primary outcome measure will mean daily pain (0-100 VAS scale). We will compare mean daily pain scores during the 3-week open label placebo condition with mean daily pain during the 3-week no treatment control condition using a repeated measures analysis of variance. In addition, we will control for treatment order and for mean daily pain during the 1-week baseline period by including those variables in the model as covariates. The model will also include the

interaction between order and treatment condition, as well as the interaction between baseline pain and treatment condition, thus controlling statistically for these interaction effects as well. Effect sizes will be computed using partial eta-squared (η^2_p), which can be interpreted as the percent of variance in the dependent variable that can be accounted for by the independent variable, after controlling for all other variables in the model. By convention, η^2_p = .01 is considered a small effect, η^2_p = .06 is considered medium and η^2_p = .14 is considered large

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