Evaluating the Efficacy of Dextromethorphan/Quinidine in Treating Irritability in Huntington's Disease

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STUDY PROTOCOL

Protocol Title:	Evaluating the efficacy of dextromethorphan/quinidine in treating Irritability in Huntington's disease
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Co-Investigators:	Natalia Pessoa Rocha, PhD; Shivika Chandra, MD; Joohi Jimenez-Shahed, MD (Baylor College of Medicine); and William G. Ondo, MD (Houston Methodist)
Study Coordinator:	Brittany Duncan; Jamie Sims
Population:	Include sample size, gender, age, general health status, geographic location
Number of Sites:	Single site (Baylor College of Medicine and Houston Methodist will refer patients to UTHealth as the primary study site. All study procedures will be conducted at UTHealth)
Study Duration:	One year
Subject Duration:	13 weeks

General Information

Huntington's disease (HD) is a devastating inherited neurologic disease that encompasses motor, cognitive and psychiatric symptoms, the latter often being the most troublesome leading to frequent hospitalizations and premature nursing home placement. Common neuropsychiatric symptoms include depression, irritability, impulsivity, and apathy and often precede the onset of motor symptoms. Irritability in HD frequently leads to aggressive behavior and emotional outbursts that can be harmful to both the patient and their caregiver. There are currently no medications approved specifically to treat irritability in HD. The current available treatments are off–label and imperfect.

We are proposing a clinical trial using dextromethorphan/quinidine (DM/Q), Nuedexta, a medication approved by the FDA in 2010 to treat pseudobulbar affect or exaggerated emotional expression incongruent to mood due to an underlying brain disorder. DM/Q has recently been studied in patients with Alzheimer's disease who had clinically meaningful agitation and was found to significantly improve agitation. Additional evidence suggesting a potential effect of DM/Q for agitation comes from controlled clinical trial data in nondemented patients with pseudobulbar affect, case descriptions, and anecdotal reports of improvement in patients with dementia and symptoms suggestive of agitation.

We plan to enroll 20 adults with HD and irritability. We are proposing a crossover trial design which means that half the patients (10 individuals) will be given the study drug (DM/Q) and half will be give placebo for 4 weeks, after which the reverse will occur. This study design will optimize our study results with a relatively small number of patients.

Background Information

Huntington's disease (HD) is a devastating inherited neurologic disease that encompasses motor, cognitive and psychiatric symptoms, the latter often being the most troublesome leading to frequent hospitalizations and premature nursing home placement. Common neuropsychiatric symptoms include depression, irritability, impulsivity, and apathy and often precede the onset of motor symptoms. Irritability in HD frequently leads to aggressive behavior and emotional outbursts that can be harmful to both the patient and their caregiver.

There are currently no medications approved specifically to treat irritability in HD. The current available treatments are off–label and imperfect. Multiple classes of medications have been studied to treat the neuropsychiatric symptoms of HD with varying levels of efficacy and evidence.

We are proposing a clinical trial using dextromethorphan/quinidine (DM/Q), Nuedexta, a medication approved by the FDA in 2010 to treat pseudobulbar affect or exaggerated emotional expression incongruent to mood due to an underlying brain disorder. DM/Q has recently been studied in patients with Alzheimer's disease who had clinically meaningful agitation and was found to significantly improve agitation. Additional evidence suggesting a potential effect of DM/Q for agitation comes from controlled clinical trial data in nondemented patients with pseudobulbar affect, published case descriptions, and anecdotal reports of improvement in patients with dementia and symptoms suggestive of agitation.

We plan to enroll 20 adults with HD and irritability. We are proposing a crossover trial design which means that half the patients (10 individuals) will be given the study drug (DM/Q) and half will be give placebo for 4 weeks, after which the reverse will occur. This study design will allow us to optimize our study results with a relatively small number of patients.

There is an urgent need to identify improved medications to treat irritability in HD. The current medications available to treat the neuropsychiatric symptoms in HD often have unwanted side effects. Irritability in HD can lead to aggressive behavior which can result in injury to the patient and/or caregiver and even incarceration. An effective medication to address this significant disruptive and destructive behavioral symptom that can destroy patient/caregiver relationships and negatively impact quality of life is imperative. We hypothesize that dextromethorphan/quinidine (Nuedexta) will decrease irritability in individuals with HD and minimize aggression and outbursts.

Objectives

To prove efficacy and safety of dextromethorphan/quinidine 20mg/10mg (DM/Q 20mg/10mg) in patients with irritability due to Huntington's disease

Specific Aim 1: To determine the effectiveness of DM/Q 20mg/10mg (one capsule BID for 4 weeks) in addressing irritability in individuals with HD.

Specific Aim 2: To assess the motor response to DM/Q 20mg/10mg (one capsule BID for 4 weeks after one week of QD dosing both before and after the 4 weeks of BID and one week of washout) using the motor portion of the UHDRS 99' total motor score (TMS) and the chorea subscale (TCS).

Specific Aim 3: To evaluate the impact that DM/Q 20mg/10mg (one capsule BID for 4 weeks) has on functional independence using the Total Functional Capacity (TFC) and the Independence scale.

Study Design

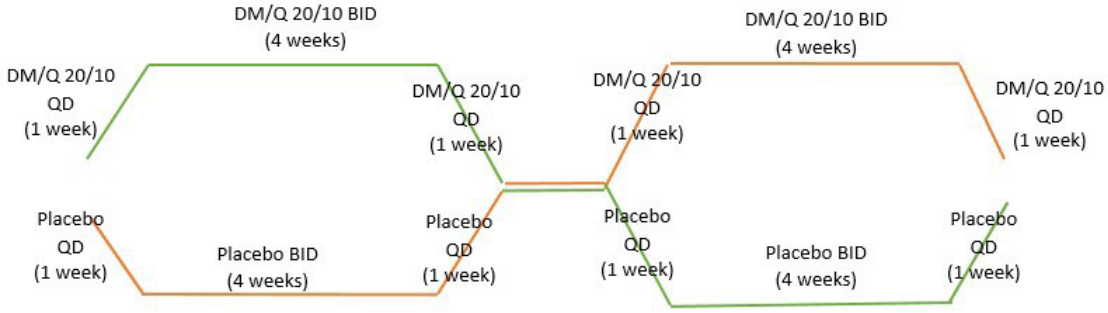
A randomized, double blind, placebo-controlled, crossover, proof of concept study. Investigator Initiated trial (IIT).

Expected duration of study: One year.

DURATION OF TREATMENT

- A total of 13 weeks:
- First treatment group: DM/Q 20mg/10mg one capsule once daily or placebo for 1 week, followed by DM/Q 20mg /10 mg or placebo twice daily for subsequent 4 weeks;
- First tapering and washout: DM/Q 20mg/10mg or placebo once daily for 7days followed by a washout phase of 1 week;
- Second treatment group (crossover): DM/Q 20mg/10mg or Placebo once daily for 1 week, followed by placebo or DM/Q 20mg/10mg twice daily for 4 weeks;
- Second tapering placebo or DM/Q 20mg/10mg once daily for 7 days.

The figure below illustrates how you will crossover from one treatment to another:



PRIMARY OUTCOME MEASURE(S):

To assess irritability in response to of DM/Q 20mg/10mg compared to placebo on irritability as quantified by the Irritability Scale, where the informant is a friend or family member familiar with the daily activities of the subject after four weeks of treatment with the study drug or placebo.

The primary efficacy parameter is the Irritability scale treatment adjusted for baseline. For this scale, we define the clinically significant improvement as 4 points change of the mean score from the baseline, i.e., we expect to see a reduction of 4 points with a standard deviation of 3 in the treatment group while no change in the placebo group. Considering a possible period effect in this crossover design due to the selfreported scale, to be conservative we use two-sample two-side t test for the sample size determination.

SECONDARY OUTCOME MEASURE(S):

- The following secondary variables will be analyzed:
- Irritability as quantified by the change the total score;
- Change of behavioral symptoms (UHDRS, HADS, NPI - Q),

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- Change in the motor symptoms (TCS within the TMS); Change in functional independence (TFC).

ANALYSIS CONSIDERATIONS:

The primary outcome is the irritability scale and the secondary outcomes in this primary objective include PBA-s, CGI-S, CGI-I, NPI focusing on the agitation/aggression domain. For the irritability scale, we define the clinically significant improvement as 4 points change of the mean score from the baseline, i.e., we expect to see a reduction of 4 points with a standard deviation of 3 in the treatment group while no change in the placebo group.

Study Population

This study will include 20 individuals with verified HD mutation. Considering a possible period effect in this crossover design due to the self-reported scale, to be conservative we use two-sample two-side t test for the sample size determination. To detect the above difference, we need 20 subjects in total to achieve 80% power at an alpha level of 0.05. Considering a 10% dropout rate, we will enroll 22 subjects. With such a sample size, we will be able to detect a minimum effect size of 1.3 in other behavioral symptoms and outcomes in the secondary objectives (i.e., chorea, patient's global functioning).

Recruitment strategy:

At the clinical appointment, HD gene carriers (genetically confirmed by CAG repeat prolongation >36) presenting with clinically significant irritability as described per the patient and/or the caregiver/family member will be invited to participate in this study. Dr. Joohi Jimenez-Shahed (Baylor College of Medicine) and Dr. William G. Ondo (Houston Methodist) will refer potential patients to UTHealth as the primary study site. All study procedures will be conducted at UTHealth.

Inclusion Criteria:

- Verified HD mutation carriers aged 18 to 75 years;
- Irritable as diagnosed by the Irritability Scale with a score > 14;
- Stable concomitant medication (no change of medication during last 30 days prior to inclusion);
- Written informed consent by prospective study participant before conduct of any trial-related procedure. Participant must be able to make an informed decision of whether or not to participate in the study.

Exclusion criteria:

- Hypersensitivity to dextromethorphan (e.g., rash, hives), quinine, mefloquine, quinidine, or dextromethorphan/quinidine with a history of thrombocytopenia, hepatitis, bone marrow depression or lupus-like syndrome induced by these drugs;
- Pregnant or nursing women;
- Active suicidality based on the answer "yes" in questions 4 and 5 of the Columbia-Suicide Severity Rating Scale (baseline version);
- Woman of childbearing potential, not using highly effective methods of contraception such as oral, topical or injected contraception, IUD, contraceptive vaginal ring, or double barrier method such as diaphragm and condom with spermicide) or not surgically sterile (via hysterectomy, ovarectomy or bilateral tubal ligation) or not at least one year post-menopausal;

- Male not using an acceptable barrier method for contraception;
- Presence of any medically not controllable disease (e.g. uncontrolled arterial hypertension or diabetes mellitus);
- Clinically significant renal (calculated creatinine clearance < 30 ml/min) or hepatic dysfunction; Patients with pre-existing hepatic disease;
- Individuals with a history or complete heart block, QTc prolongation or tornadoes de pointes, or at high risk of complete AV block;
- Family history of congenital QT prolongation;
- History of unexplained syncope within the past year;
- Use of drugs containing quinidine, quinine, or mefloquine;
- Individuals currently taking strong CYP3A4 inhibitors or tetrabenazine;
- Use of certain antidepressants known as monoamine oxidase inhibitors (MAOis) or tricyclic antidepressants (TCAs);
- Use of certain heart rhythm medications--amiodarone, flecainide, procainamide, propafenone;
- Use of first-generation antipsychotics;
- Use of tamoxifen;
- Presence or history of seizures or diagnosed epilepsy;
- Severe cognitive disorders defined as a score < 18 on the MOCA;
- Clinically relevant abnormal findings in the ECG, the vitals, in the physical examination or laboratory values at screening that could interfere with the objectives of the study or the safety of the subject as judged by the investigator;
- Participation in another investigative drug trial within 2 months;
- Subjects who are unlikely to be compliant and attend scheduled clinic visits as required as determined by the Investigator.

Study Procedures

This study will request a total of 4 visits and 2 phone interviews, as described below:

VISITS	**Visit 1 Screening visit**	**Visit 2 Baseline visit**	**Phone Interview 1**	**Visit 3 (Crossover)**	**Phone Interview 2**	**Visit 4**
Week	**Week -1**	**Week 0**	**Week 3**	**Week 6**	**Week 10**	**Week 13**
Informed consent	X					
Inclusion and exclusion criteria	X	X				
Randomization		X				
Medical History	X					
Physical Examination	X			X		X
Concomitant medication	X	X	X	X	X	X
Vital signs, ECG	X			X		X
Labs	X			X		
Pregnancy test	X	X		X		X

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CAG-repeats	X					
Adverse Events			X	X	X	X
IS	X	X		X		X
C-SSRS	X	X		X		X
UHDRS 99’		X		X		X
UHDRS TFC		X		X		X
HADS		X		X		X
NPI -Q		X		X		X
PBA-S		X		X		X
MoCA	X	X		X		X
CGI		X		X		X

1. Laboratory examinations (haematology, clinical chemistry, and urinalysis) at screening visit, week 6 (at the end of the first arm of the study and just prior to crossover) and week 13 (at the end of the study).
2. Dispensing and collection of study drug at baseline visit, Day 0 first dosing; Dosing from day 1 to day 7: DM/Q 20/10 /placebo (1 capsule) once daily for one week, then BID for 4 weeks, then QD for one week. One week washout before crossing-over.
3. A phone interview will be conducted at weeks 3 and 10 at which time questions about any adverse effects will be asked.
4. A serum pregnancy test will be performed at the screening visit and a urine pregnancy test during the subsequent in person visits.
5. ECG and vital signs examination will be performed at Screening, Visit 3 and visit 4, and at any other time if judged necessary for medical reasons by the treating physician.

A comprehensive description of data collection at each visit or phone interview can be found at the CRF/Data Collection Form attached to this protocol.

Data and Safety Monitoring

Dextromethorphan/quinidine is an FDA-approved medication (NUEDEXTA).

Expected adverse reactions: The most common adverse reactions (incidence of ≥3% and two-fold greater than placebo) in patients taking NUEDEXTA are diarrhea, dizziness, cough, vomiting, asthenia, peripheral edema, urinary tract infection, influenza, increased gamma-glutamyltransferase, and flatulence.

Warnings and precautions:

***Thrombocytopenia and Other Hypersensitivity Reactions:** Quinidine can cause immune-mediated thrombocytopenia that can be severe or fatal. Non-specific symptoms, such as lightheadedness, chills, fever, nausea, and vomiting, can precede or occur with thrombocytopenia.

***Hepatotoxicity:** Hepatitis, including granulomatous hepatitis, has been reported in patients receiving quinidine, generally during the first few weeks of therapy.

***Cardiac Effects:** NUEDEXTA causes dose-dependent QTc prolongation. QT prolongation can cause torsades de pointes–type ventricular tachycardia, with the risk increasing as the degree of prolongation increases. Some risk factors include use with CYP3A4 inhibitors or drugs that prolong QT interval, electrolyte abnormalities, bradycardia, or left ventricular hypertrophy or dysfunction. If patients taking NUEDEXTA experience symptoms that could indicate the occurrence of cardiac arrhythmias (eg, syncope or palpitations), NUEDEXTA will be discontinued, and the patient further evaluated.

Concomitant Use of CYP2D6 Substrates: NUEDEXTA inhibits CYP2D6 and may interact with other drugs metabolized by CYP2D6.

Dizziness: NUEDEXTA may cause dizziness. Take precautions to reduce the risk of falls.

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Serotonin Syndrome: Use of NUEDEXTA with selective serotonin reuptake inhibitors (SSRIs) increases the risk of "serotonin syndrome."

*NUEDEXTA will be discontinued immediately if any of these occur.

Measures in place to minimize the risks listed above:

1. Participants will be asked to report any experienced adverse reactions to the study staff immediately;
2. Screening for adverse reactions will be performed periodically;
3. ECG and vital signs examination will be performed at the screening visit, visit 3 (at the end of the first arm of the study and just prior to crossover) and week 13 (at the end of the study).
4. Laboratory examinations (haematology, clinical chemistry, and urinalysis) will be performed on visit 1 (screening visit), visit 3 (at the end of the first arm of the study and just prior to crossover) and week 13 (at the end of the study).
5. A phone interview will be conducted at weeks 3 and 10 at which time questions about any adverse effects will be asked.

The study investigators will be responsible for safety monitoring, which will be performed by periodic data review. Any unanticipated problem, including adverse events and protocol deviations will be reported in the CRF.

Statistics

For the data analysis, descriptive statistics will be provided for measures at each visit. For the primary objective, we will apply linear mixed effects model for the repeatedly measured irritability scale and other outcomes to account for the within-subject correlation. The independent variables include the treatment group, sequence, period, and the baseline values. For the missing data, if missing is random, we will analyze the data as it is. Otherwise, we will follow Ibrahim and Molenberghs' book on longitudinal study for data analysis. The analysis for the secondary aims will be similar. For safety analysis, descriptive statistics will be provided for all adverse events. We will stop the study if there is evidence to support rate of one type of adverse events more than 30% in all participants. The stopping rules are based on exact lower 95% Blyth-Still-Casella confidence bounds. If the number of cases of one type of adverse event exceed the specified stopping rules: ≥ 7 in 10 patients or ≥ 11 in 20 patients, then patient accrual will be paused pending a review by the Safety Monitoring Committee. A significance level of 0.05 will be used.

Ethics

Approval to conduct this trial will be sought from the Institutional Review Board (IRB) for the University of Texas Health Science Center at Houston. Baylor College of Medicine and the Methodist Hospital IRB reciprocity will be requested.

The University of Texas-Houston has its own IRB and Committee for the Protection of Human Subjects (CPHS). There are two classifications of adverse events: adverse event (AE) or serious adverse event (SAE). AE information will be documented throughout the study. The study team will record all AEs on the Adverse Event case report form. AEs will be monitored until they are adequately resolved or explained as mentioned previously.

The trial will be performed in accordance with the protocol, International Conference on Harmonization Good Clinical Practice Guidelines, and applicable local regulatory requirements and laws.

The informed consent form will be in compliance with the International Conference on Harmonization GCP, local regulatory requirements, and legal requirements. Informed consent must be obtained prior to performance of any protocol specific procedures. Consent will be obtained by a qualified member of the study team, in a private room and in accordance with local and federal regulations. Participants will receive a detailed explanation about the study protocol and the associated risks and benefits. The written informed consent will be used in this trial, and any changes made during the course of the trial will be approved by our local IRB before use.

The investigator will ensure that each trial subject is fully informed about the nature and objectives of the trial and possible risks associated with participation.

Data handling and record keeping

- Case report forms will not contain identifiers.
- Key linking codes to identifiers will be stored securely and separately from study data.
- Source documents and other regulatory documents containing identifiers will be kept securely in locked cabinet with access control.

Publication Plan

- All data will be summarized and analyzed by the University of Texas Health Science Center at Houston by a PhD level statistician with NIH funding supported by the Neurology department. The Investigator will prepare a clinical narrative which will include at least a description of the study methods, results, implications, and safety profile. The Principal Investigator and collaborators will prepare an abstract submission to appropriate national and international scientific meetings and a manuscript for submission to a peer-reviewed journal. Authorship will be based on guidelines issued by the editors of medical scientific journals, and will require active input into protocol design or manuscript preparation. The order of authors will be determined by mutual agreement. Negative publication bias is a significant problem in modern medical research; the results of this trial will be published, after manuscript approval by all parties.
- We plan to publish/disseminate the results even if the results are negative as even a “negative” trial can be helpful in the management of individuals with HD and the evaluation for future therapeutic agents.
- We plan to implement the use of this medication as needed if we have favorable results as this drug is already FDA approved. We will consider moving forward with modifying the indication for the medication and future studies pending the study results.
- If needed, future funding will be sought through the NINDS/NIH and/or nonprofit organizations that fund HD related research.
- Clinically significant results will be returned to research subjects.