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Study Title: Escitalopram Effects on CSF Amyloid Beta Total Concentrations

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Escitalopram Effects on CSF Amyloid Beta Total Concentrations
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Protocol

Abstract

Alzheimer's disease (AD) is a devastating illness, estimated to affect 5 million patients in the United States alone and projected to increase dramatically over the next decades as the population ages unless preventive measures can be developed. We have preliminary evidence that selective serotonin reuptake inhibitor (SSRI) antidepressants lower the amount of amyloid plaques in the human brain.

We now propose to study the effects of an SSRI (escitalopram) on levels of amyloid beta peptide (the major constituent of the plaques) in the cerebrospinal fluid (CSF) of cognitively-normal older adults. We will measure CSF Amyloid Beta levels before and after treatment with escitalopram. We will use a double blind, placebo-controlled study design with approximately 120 cognitively-normal participants across two sites. Participants will be age 60-85, with a Montreal Cognitive Assessment (MOCA) of 26 or higher. They will be recruited from the community. Participants will be randomized (approximately 30 per drug group and 30 in the placebo group).

Objectives

Overall objectives

To assess the effect of exposure to escitalopram on levels of amyloid beta peptide in the cerebrospinal fluid (CSF) of cognitively-normal older adults and to determine the ideal dose of escitalopram for reducing levels of amyloid beta. To assess whether there is a differential response to: escitalopram 20 mg for 2 weeks, escitalopram 20 mg for 8 weeks, or escitalopram 30 mg for 8 weeks.

Primary outcome variable(s)

Change in the level of Amyloid Beta peptides (Amyloid Beta 42 and Amyloid Beta 40) in the CSF between the measurement at baseline and the measurement after 2 weeks or 8 weeks of exposure with escitalopram 20 vs. 30 mg/day.

Secondary outcome variable(s)

CSF and blood will be stored for subsequent analysis of additional yet to be discovered biomarkers.

Background

Results from our R21 proposal "PET Amyloid Plaque Imaging in Late-life Depression" showed that those participants who had received any antidepressant medication for 12 months or more had significantly lower Amyloid Plaque mean Mean Cortical Binding Potential by PET imaging with the amyloid tracer Pittsburgh Compound B (PiB) than those who had received medication for less than 12 months. Following up on these results, a subsequent study was conducted using an APP transgenic mouse model of AD. Compared to vehicle-treated mice, both citalopram and fluoxetine reduced levels of A in brain interstitial fluid (ISF) almost immediately following drug administration with a significant decrease observed after 10-14 hours of treatment. We conducted a study of Amyloid Beta synthesis in healthy young adults. In this study, participants had an indwelling lumbar catheter placed so that CSF could be collected hourly. We now have data indicating a significant difference in total concentrations between participants who had received placebo vs. those who received citalopram. In the current protocol, we will extend these studies to healthy older adults who will be treated with escitalopram for two weeks or 8 weeks at 20 or 30mg. This study will measure steady state CSF

Amyloid Beta levels rather than Amyloid Beta synthesis as the primary endpoint. It is important to understand the effects of escitalopram/fluoxetine on Amyloid Beta levels after a short duration of treatment before proceeding to more long-term dosing studies as a prevention strategy. We chose escitalopram for this study because, among available SSRIs, it is among the most selective for serotonin, has excellent bioavailability, and excellent safety, tolerability and efficacy, with the fewest side effects (DeVane, 1999; DeVane and Boulton, 2002; Cipriani et al., 2009). We chose the dose of 20 mg, because it is commonly used as the upper end of usual doses in antidepressant treatment trials (DeVane, 1999; DeVane and Boulton, 2002). We have added the additional 30 mg dose because our initial study data was not showing quite the effect we hoped for based on trials in mice and younger humans (Sheline et al., 2014). Though the antidepressant effect has not been shown to increase after 20 mg/day, we are investigating a different mechanism, the effect on CSF levels of amyloid beta. Previous concerns about the QTc interval increase in escitalopram have been revised (Keller, 2013). Consequently this enables a dosing strategy that would achieve similar doses to those used in our rodent studies (Cirrito et al., 2011) which is equivalent to a human dose of 66mg/day. We have added a 3rd arm of the study with 30 mg of escitalopram because our preliminary data from our LP study show approximately a 10% decrease in Aβ on 20 mg, whereas in our animal studies there was a 25% decrease. Further, the human equivalent of the doses we used in the animal studies is approximately 25-30 mg and so we feel it is important to achieve the same equivalent doses for a greater effect size. We conducted a study of Amyloid Beta synthesis in healthy young adults. In this study, participants had an indwelling lumbar catheter placed so that CSF could be collected hourly.

Study Design

Phase*

Phase IV

Design

This is a double-blind, placebo-controlled, parallel-assigned design. Participants will be randomly assigned to one of four arms:

- Arm 1 – Escitalopram 20mg 2 weeks
- Arm 2 – Escitalopram 20 mg 8 weeks
- Arm 3 – Escitalopram 30 mg 8 weeks
- Arm 4 – Placebo 2 or 8 weeks

Participants and investigators will be blinded to drug status. Participants will undergo lumbar puncture (LP) for CSF analysis and determination of amyloid status pre- and post- treatment. Blood will be used for genetic testing for APOE and also to determine drug levels in plasma.

Characteristics of the Study Population

Target population

Approximately 120 cognitively-normal research participants aged 60-85 who have a MOCA score ≥ 26 will be recruited from the community.

Key inclusion criteria

- 1) Age 60-85 (inclusive), male and female, any race.
- 2) Capacity to give informed consent and follow study procedures.
- 3) English speaking.

4) Montreal Cognitive Assessment (MOCA) of 26 or higher.

Key exclusion criteria

- 1) Known history of relevant severe drug allergy or hypersensitivity (e.g. to Citalopram, Escitalopram, or Fluoxetine)
- 2) Does not speak English
- 3) Cannot give informed consent
- 4) Diagnosis of Major Depression
- 5) Previous history of neurological disorders, such as Parkinson's disease, Alzheimer's disease or traumatic brain injury, cognitive impairment or dementia.
- 6) Diagnosis of a chronic psychiatric illness
- 7) Significant hearing or visual impairment
- 8) Bleeding diathesis
- 9) Clinically significant hepatic, renal, pulmonary, metabolic or endocrine disturbances as indicated by history, which in the opinion of the investigator might pose a potential safety risk to the subject.
- 10) Current clinically significant cardiovascular disease. Clinically significant cardiovascular disease usually includes one or more of the following: cardiac surgery or myocardial infarction within the last 4 weeks; unstable angina; acute decompensated congestive heart failure or class IV heart failure; current significant cardiac arrhythmia or conduction disturbance, particularly those resulting in ventricular fibrillation, or causing syncope or near syncope; uncontrolled high blood pressure; QTc greater than 450msec (by history for subjects with cardiac disease); documented prior stroke.
- 11) Clinically significant abnormalities on EKG. Primary AV block or Right bundle branch block are not necessarily exclusionary.
- 12) History of drug or alcohol abuse within the last year or prior prolonged history of abuse
- 13) Use of an Investigational medicine within the past 30 days
- 14) Use of Coumadin, Warfarin or other blood thinners within the past 6 months (not including short-acting anti-coagulants that are okay for surgery after 24 hours off medication)
- 15) Use of antipsychotic medication or antidepressant medication (e.g. MAOIs, SSRIs, SNRIs).
- 16) Use of the following drug/drug classes: Pimozide, Triptans, Tricyclics, Lithium, Tramadol
- 17) Use of over-the-counter supplements such as tryptophan or St. Johns Wort
- 18) Any other factor that in the investigator's judgment may affect patient safety or compliance (e.g. distance greater than 100 miles from this facility)

Study Procedures

Procedures

- *Participant Selection and Recruitment:* This study will be made known to the community through flyers, brochures, online, print, and radio advertisements. Interested participants will contact study personnel. Personnel will explain the study, including the time commitment required for participation, the basic procedures to be done, and will review the inclusion and exclusion criteria. This initial screening will be pre study consent and will take place as a phone interview, as a self-report measure on RedCap, or as a combination of these 2 methods. Following the initial screening, the study coordinator will contact interested participants and will schedule an in- person visit (Visit 1).
- *Consent:* All interested participants, meeting the basic eligibility criteria and willing to consider participating, will have the opportunity to review the Informed Consent Form (ICF) in detail with a member of the study team. Participants will be given the opportunity to read the consent in full, ask any questions they have, and have their questions answered before being asked to sign the ICF.

Individuals may choose not to sign the ICF at the time of the consent conversation and may take it home with them to review further and may share with their physician to assist them in making an informed decision about participation. No study procedures will be conducted until the ICF has been signed by the participant. The participant will receive a copy of their signed ICF.

- *Visit 1 - Screening:* After informed consent is obtained, eligibility criteria are reviewed. This will include a review of current and recent medications, medical and psychiatric history, and the administration of the Montreal Cognitive Assessment (MOCA). Participants meeting eligibility criteria will be scheduled for Visit 2 – Baseline Assessment.
- *Visit 2 – Baseline/Pre-treatment Assessment:* This visit will include a blood draw, lumbar puncture, and administration of study drug. Participants will be asked to fast overnight (no food after midnight) the evening before this visit. Participants may drink water and may take medications. Participants will arrive at the study site at in the morning. The following study procedures will take place:
 - *Blood Draw:* About 1 ½ tablespoons of blood will be tested for APoE 4 genotype as well as any other factors in the future that are determined to be related to the biology of Alzheimer's disease. Some blood will be retained and banked for future research.
 - *Lumbar puncture (LP):* LP will be performed by one of the study physicians; LP will be at the L3-4 interspace with a 22 g Sprotte (atraumatic) needle. The area around the site of the LP will be numbed with a small injection of Lidocaine prior to the start of the procedure. Once the area is numb, a small amount (~ 4 teaspoons) of cerebrospinal fluid (CSF), a fluid found in the brain and spinal column, will be drawn through a needle inserted into your back. An LP is the most common and safest method of obtaining CSF samples. The CSF will be stored for future research.
 - Participants will be randomized into one of the 4 study arms: escitalopram 20 mg 2 weeks, escitalopram 20 mg 8 weeks, escitalopram 30 mg 8 weeks or placebo (2 weeks or 8 weeks). Participants and study physicians will be blinded as to the treatment arm. Participants will be given the study drug in capsules and will be provided written and oral instruction on how to take the study drug, including details regarding the titration schedule. Titration Schedule:
 - escitalopram 20 mg 2 weeks: 10mg (1 cap) qd for 5 days; 20mg (2 caps) qd for 9 days.
 - escitalopram 20 mg 8 weeks: 10mg (1 cap) qd for 5 days; 20mg (2 caps) qd for remainder of 8 weeks
 - escitalopram 30 mg 8 weeks: 10mg (1 cap) qd for 5 days; 20mg (2 caps) qd for 5 days; 30mg (3 caps) qd for remainder of 8 weeks
 - Placebo (2 weeks or 8 weeks): 1 cap qd for 5 days; 2 caps qd for remainder of 2 or 8 weeks
- *Phone Call:* The study coordinator will call participants after their visit to check on their status following the procedures (e.g., side effects from the LP, study medication) and to make sure that participants are comfortable with the instructions. Participants will be contacted by research staff to inquire about their experience with the drug/placebo and to assess for tolerance and side effects (e.g., nausea) from the drug/placebo. These calls will occur approximately every 3 days until day 10 and then once per week after. If participants experience side effects from the higher dosage, they may be instructed to reduce the dose down to the last tolerable dose for the remainder of their participation.
- *Visit Three – Post-treatment Assessment:* This visit will include a lumbar puncture, drug accountability, self-report questionnaire, and administration of study drug for taper off. Participants will be asked to fast overnight (no food after midnight) the evening before this visit. Participants may drink water and

may take medications. Participants will arrive at the study site at in the morning. The following study procedures will take place:

- *Lumbar puncture (LP)*: LP will be performed by one of the study physicians; LP will be at the L3-4 interspace with a 22 g Sprotte (atraumatic) needle. The area around the site of the LP will be numbed with a small injection of Lidocaine prior to the start of the procedure. Once the area is numb, a small amount (~ 4 teaspoons) of cerebrospinal fluid (CSF), a fluid found in the brain and spinal column, will be drawn through a needle inserted into your back. An LP is the most common and safest method of obtaining CSF samples. The CSF will be stored for future research.
 - Participants will be provided the study drug in capsules and will be provided written and oral instruction on how to *taper off of the study drug*. Taper Down Schedule:
 - escitalopram 20 mg 2 weeks: 10mg (1 cap) qd for 3 days
 - escitalopram 20 mg 8 weeks: 10mg (1 cap) qd for 3 days
 - escitalopram 30 mg 8 weeks: 20mg (2 caps) qd for 3 days; 10mg (1 cap) qd for 3 days;
 - Placebo (2 weeks or 8 weeks): 1 cap qd for 3 days
 - To address *drug accountability*, participants will be asked to bring their pill bottles to Visit 3 so that the number of pills consumed and the number of pills remaining can be recorded.
 - Participants will be asked to complete a *self-report questionnaire* regarding their experience in study.
- *Phone Call*: The study coordinator will call participants the day after Visit 3 to inquire about side effects from the LP, study medication or other study procedures.

There will be no additional follow up with study participants. However, study participants are encouraged to contact the study personnel regarding any potential Adverse Events that may occur following in the days following the lumbar puncture procedure and in the days following the termination of the study drug.

Deception

Does your project use deception? No

Analysis Plan

We will conduct standard demographic comparisons to ensure that the groups are matched in age, gender and race. We will then conduct paired t-tests to compare CSF values for each participant before and after drug/placebo administration (within participant comparison) and will conduct an unpaired t- test to compare CSF values between groups (placebo and escitalopram) at baseline and at the end of the study. Based on our results in young people we expect that 30 subjects per drug arm and 45 in the placebo group (acquired across two sites) will provide sufficient power to detect a difference between placebo and treated groups and to detect a change between baseline and the end of participation for those treated with escitalopram. The effect size was estimated based on preliminary data collected over a 36 hour period in 24 young healthy cognitively-normal adults (15 treated with citalopram and 9 with placebo). The mean and SD for the groups was 30.0 (15.8) and 42.3 (11.0), respectively. This provides an effect size of 0.77, which is larger than the effect size (0.73) necessary to detect a significant difference with n of 30 per group at a power of 0.80 and an alpha of 0.05. The additional numbers of subjects will protect against potentially greater variability in an older age group and the smaller number of samples (2 versus 24).