Study Protocol
Cholinesterase Inhibitor Discontinuation (5/2/2019)
NCT002248636

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Cholinesterase Inhibitor (CI) Discontinuation
5/2/2019
PI: Stephen Thielke

Participant Identification

Potential participants will be identified from automated pharmacy data. A list will be produced of Veterans at the study sites who have received a prescription for either donepezil or galantamine for a period of 12 months.

Review of CPRS records will establish whether each potential participant meets initial inclusion and exclusion criteria:

Inclusion Criteria for All Participants:

- Males and females ages 60 and older.
- Taking stable dose of donepezil 5mg or greater per day, or galantamine 8mg or greater per day, for at least 1 year.

Exclusion Criteria for All Participants:

- Terminal medical condition for which life expectancy would be less than 6 months.
- Unstable or uncontrolled medical condition that would jeopardize safety or interfere with participation in the study.
- Receiving services from hospice.
- Current prescription with more than one CI.
- Receiving a medication in an investigational drug study.
- Parkinson's Disease or Lewy Body Dementia

Participating Sites

VA Puget Sound, VA Boise, VA Bedford, and VA Little Rock will participate in recruitment. The Puget Sound site is the coordinating cent

Approach Letter / Brochures

Potential participants will be mailed a letter and brochures describing the study, as well as a pre-stamped postcard. One of the brochures is geared at caregivers and patients, and the other at providers. The information in both is very similar, and can be understood by anyone with basic health literacy.

Potential participants who could not be contacted during the initial recruitment (prior to March 2018) will be sent one more letter that includes the pre-stamped postcard allowing them to request information or to opt out. Study staff may try once more to reach them by phone if the postcard is not received two weeks after sending the letter. Potential participants who express interest on the postcard will be mailed a blank copy of the consent form, and contacted at their convenience.

Case Review

Based on the information from the chart review and interview, the study coordinator and PI will ascertain if the participant meets inclusion criteria.

Phone Contact and Screening

Study staff will wait two weeks for potential participants to return the postcard.

The study coordinators or principal investigators will call potential participants who did not opt out and describe the purpose and process of the study with the Veteran and/or their caregiver.

For those participants who remain interested, the study coordinators or principal investigators will gather further information from the caregiver:

- Ensure presence of a primary caregiver who can assume responsibility for medication compliance, and can rate the patient's condition; OR residence in a VA nursing home with staffing capacity to address these issues
- The caregiver and Veteran are willing to have the CI medication discontinued for up to 6 weeks (although it can be restarted at any time).

Consent

Once patients are identified who are willing to join the study, or if the returned postcard expresses interest, the study coordinator will send a consent form and a information statement to them in the mail. If requested the study coordinator will arrange a time to go over the consent form with them over the phone. A letter will be sent along with the consent asking the Veteran and their caregiver to call (206) 764-2815 if they have any questions. The study coordinator will thoroughly explain all the details of the consent with the Veteran and their caregiver, including reading it to them if necessary.

After any and all the Veteran and Caregiver's questions have been answered, either the Veteran or their Caregiver will sign the consent form and send it back in a postage paid, self-addressed envelope. If the Veteran is unable to sign for himself, consent will be obtained through the Veteran's Durable Power Of Attorney and a copy of the DPOA paperwork will be kept on file with the consent. The Caregiver and the DPOA do not have to be the same person, but the DPOA will always be kept abreast of the study procedures. Once the study coordinator receives the signed consent back in the mail, they will mail a copy back to the Veteran. The original signed consent will go in the study file.

Boise will use their own site-specific consent form and information statement. Bedford will use their own site-specific consent form for each the Veteran and Caregiver.

Baseline Data Gathering

After the consent has been obtained, the study coordinator will call the participant and caregiver. This telephone visit will take about 30-45 minutes. The following scales will be applied.

Patient and disease variables
- -Age, sex, race
- -Duration of dementia symptoms / diagnosis (if relevant)
- -Duration of treatment with CI
- -Use of memantine (present / historical)
- -Use of neuroleptic (present)
- -Use of other psychotropic medication (present)

Outcome measures
- -Cognition: TICS (Veteran)
- -Functioning: ADCS-ADL (caregiver)
- -Behaviors: NPI-Q (caregiver)
- -Caregiver burden: ZBI (caregiver)

During this interview, the study coordinator will explain the process for medication administration during the study. The caregiver will be asked to repeat back the process of taking the study pill instead of the previous CI medication, and that the participant and caregiver may, at any time and for any reason, return back to the previous dose of medication and stop the study medication. At that point the participant is considered withdrawn from the study.

Randomization

Participants will be randomized to either Real Taper or Sham Taper, based on a randomization scheme generated by the study biostatistician.

Documentation for Provider

The participant's primary care provider will be sent a letter informing them of the study, and requesting a call if there are any questions. The participation will also be noted in CPRS.

Medication Distribution

Participants will receive the study medication by mail. The pill bottle and instructions will specify that the study medication is to be taken instead of (not in addition to) the pre-study CI. The instructions will repeat that the participant can return back to the pre-study dose of medication, and stop the study medication, at any time and for any reason. Emergency contact information will be provided.

The medication will take the form of two sets of pills: those for the first three weeks, and those for the second three weeks. The first three-week regimen involves either a half-dose of the pre-study medication (real taper) or the full dose of the pre-study medication (sham taper). The pharmacist may substitute formulations as needed. The second three-week regimen involves either placebo (real taper) or the full dose of the pre-study medication (sham taper).

Emergency Procedures

The consent form and the instructions sent with the medications both include contact information, including after-hours numbers, to address any study-related health issues.

Withdrawal from study

Participants may withdraw from the study at any time and for any reason, and return to their pre-study dose of medication.

Assessment Contacts

Every two weeks, the study coordinator will contact the caregiver by phone. Any questions will be answered. The following will be reviewed:

1. Reiterate ability of the participant to return to the pre-study medication at any time, or for any reason.
2. Document adverse events in prior 2 weeks (death, hospitalization, urgent medical visit, fall causing injury).
3. Ascertain if study medication was stopped.
4. Ascertain current CI medication (if non-study drug).

Follow-Up Data Gathering

At six weeks (at which point the medications will have been consumed), the study coordinator will contact the caregiver to complete the exit interview. This interview will establish:

Adverse events in prior 2 weeks (death, hospitalization, urgent medical visit, fall causing injury).
Continuation or discontinuation of study medication.
Current CI medication (if not taking study medication).

Outcome measures
-Cognition: Six-Item Screener (Veteran)
-Functioning: ADCS-ADL (caregiver)
-Behaviors: NPI-Q (caregiver)
-Caregiver burden: ZBI (caregiver)

Unblinding

During or shortly after the exit interview the PI will call the subject and unblind the treatment arm (using information provided by the pharmacist). The caregiver will be asked, based on this information, if they intend to return to the pre-study medication.

Outcome measure
-Decision to continue pre-study medication

Follow-up

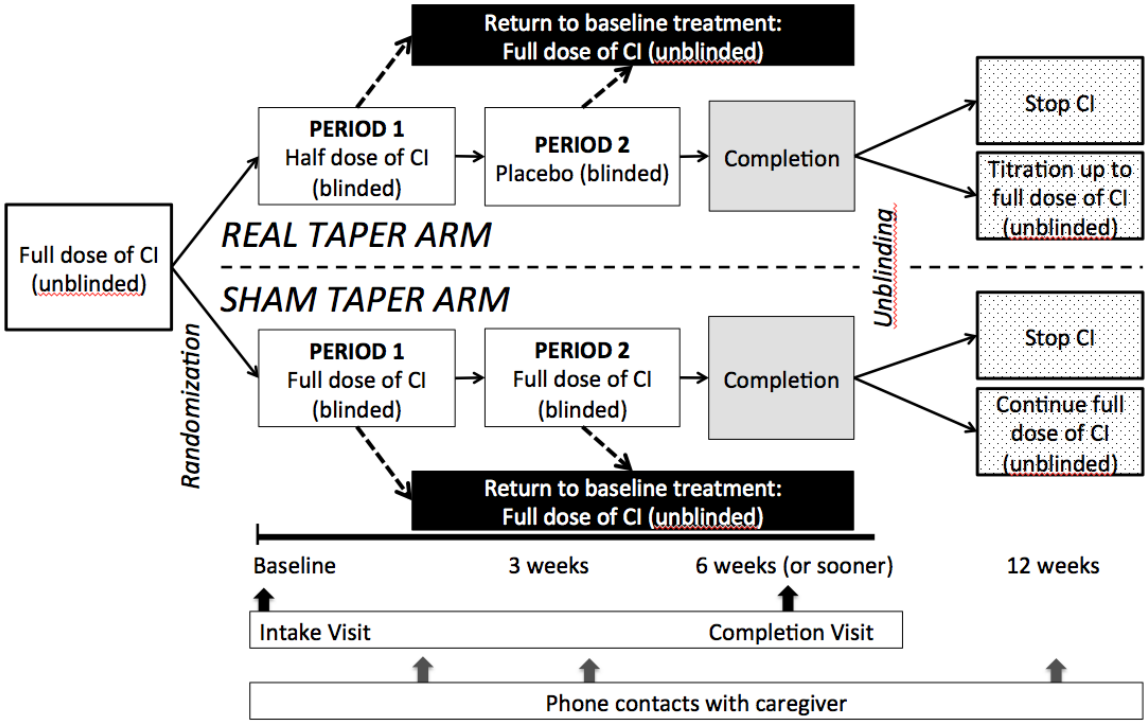
At 12 weeks and 24 weeks from the start of the study, the study coordinator will contact the participant to ask what medication is being used (pre-study CI, no treatment, or other). Any remaining questions will be answered.

Data Transfer

Data will be transferred between Seattle and Boise and Seattle and Bedford via placement in a secure research folder housed on the secure research drive through the Seattle VA. Only study staff members have access to this folder.

Re-randomization

In order to give participants more useful information about the effects of the medications, those who were initially in the "sham taper" arm will be offered the option of being re-randomized to either real taper or sham taper. They will be offered the re-randomization option after they have been unblinded. If they choose to be re-randomized, the same data will be captured. At the end of this period, the caregiver and Veteran will (as just above) be told which medication they had received. The Veteran and Caregiver may, but are not required to re-enroll as many times as it takes to be randomized into the "Real Taper" arm in order to assess the effects of actual discontinuation.
Study Flow Chart



Background rates:

In order to interpret the rates of discontinuation observed in different groups during the study, national pharmacy data from the study period will be analyzed in order to ascertain the following in the underlying population:

1. The prevalence of different diagnoses among those who were prescribed cholinesterase inhibitors.
2. The mean duration of cholinesterase inhibitor treatment among different groups, based on diagnoses, age, and number of medications.
3. Discontinuation-free survival rates among different groups, based on diagnoses, age, and number of medications.