Understanding the Response to Fesoterodine Through Genetic Evaluation in the Elderly (URGE)

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URGE Study Protocol

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Study Population

Inclusion Criteria:

- Women ≥ 50 years
- ≥ 3 UUI episodes on a 3-day voiding diary
- Urge-predominant incontinence, >50% of total incontinence episodes
- No history of failure to fesoterodine
- 2-week washout period if currently on an anticholinergic for UUI

Exclusion Criteria:

- Contraindications to fesoterodine (e.g. bladder outlet obstruction, narrow angle glaucoma [open angle is OK if pt. knows], myasthenia gravis, severe hepatic or renal impairment)
- Urinary retention requiring catheterization
- Bladder outlet obstruction
- Symptomatic, untreated UTI not resolved prior to starting fesoterodine
- Recurrent UTI's (≥3 in one year), current UTI needs to be treated before pt. is enrolled
- Botulinum toxin injection for UUI in the last year
- Current therapy with PTNS or Interstim
- Neurologic conditions that may affect urinary function (any history of stroke, multiple sclerosis, spinal cord injury, Parkinson's disease)
- Women taking potent CYP3A4 inhibitors
- Pelvic Organ Prolapse, pessary use OK

Recruitment

Phone Screening

1. Complete a telephone screen for interested patients that contact research staff from CDWH mailings or flyers
2. If pt. is eligible, enter pt. into enrollment log on Interested tab with appropriate notes and add to CRMS as Interested
3. Go over study with pt. and answer any questions
4. Mail a consent and an URGE BD to pt. and instruct her to call to go over BD when completed to confirm eligibility (≥3 leaks in 3 days, >50% of leaks UUI related)
    - If pt. is taking an anticholinergic and willing to do 2 week washout have her begin BD after 1 week and then schedule for BL/week 0 visit after the 2 week washout ends
    - Pt. can skip a day on BD if needed due to plans/convenience
5. If pt. is eligible after BD is completed, schedule to come in for baseline/week 0 visit per steps below and have her bring completed BD to visit
6. If pt. is ineligible per phone screen or BD, add pt. to Ineligible tab in the enrollment log and add/change in CRMS as Ineligible then screen for ACE study if eligible

Recruiting in Clinic

1. Pre-screen all scheduled patients in EPIC before appointments according to inclusion and exclusion criteria
2. If pt. is eligible, note on your copy of printed clinic schedule and let MD know which pts. may be eligible, include any new patients who are presenting for UI symptoms as well

3. If pt. is interested, briefly describe the study and administer the in-clinic screen, give pt. an Urge consent to take home and look over
4. If pt. does not have a recent UDS BD, give pt. an URGE BD and voiding hat, ask her to call when BD completed to go over on the phone to confirm eligibility
    - If pt. is taking an anticholinergic and willing to do 2 week washout have her begin BD after 1 week and then schedule for BL/week 0 visit after the 2 week washout ends
    - Pt. can skip a day on BD if needed due to plans/convenience
5. If pt. has UTI based on urine dip, have pt. wait until antibiotics are done before starting BD
    - Note: If pt. calls in about possible UTI while not in clinic RNs can perform a 'Test to Cure', message RN to call pt. to come in for urine dip and if positive can get a Rx for antibiotics
6. Enter subject into enrollment log on the Interested tab and add to CRMS as Interested
7. Once BD is complete, go over to insure eligibility and schedule all study visits
    - Ask pt. to bring completed BD to study visit
    - Make a copy of BD and add pt. labels, place in medical records bin to be scanned
    - Update on the enrollment log and in CRMS as enrolled (pt. has to be active to be linked to study timeline)
8. If pt. ineligible add to Ineligible tab in enrollment log and change to Ineligible in CRMS, then refer to ACE if eligible

<u>Study Visits</u>

Before the study visit:

1. Give pt. a reminder call with date/time of appt. and remind her to bring completed BD to appt.
2. Have previously completed pt. screen to confirm eligibility and to complete page 2 at visit (de-identify and keep in study folder)
3. Obtain 4mg dose of study drug from Rex/HBO IDS supply

Baseline/Week 0 Visit

1. Read through consent/HIPAA with pt. and have pt. sign and date, research staff person to sign and date as witness
    a) Make a copy for the patient and a copy to scan to medical records keep the original and file at Rex
    b) Complete Documentation of Informed Consent and make a copy for medical records, staple the original to the original consent/HIPAA to be filed at Rex
    c) Place stapled and patient labeled copies in medical records bin to be scanned and give other copy to pt.
2. Print out patient medication list from EPIC (filter with View Active and Unverified Meds) and confirm with patient, have patient note any other meds not on the list or mark through meds pt. is no longer taking
3. Administer the following measures:
    a) Functional Comorbidity Index
4. Have pt. complete the following:
    a) Demographics form
    b) OABq-SF
5. Complete the following:
    a) P450 Drug Interactions form (exclude if patient is taking a strong/potent CYPD34A inhibitor)
    b) Physical Exam Form (with data from medical records)
    c) Bladder Diary Evaluation (based on BD pt. filled out for inclusion in study)
6. Complete the Medication Dispensing form
    a) Dispense 4mg dosage: 4mg = light blue, 8mg = dark blue
    b) Instruct pt. to take medication whole and with a liquid, can be taken with or without food
    c) Tell pt. she can take it at same time every day w/other daily meds to help her remember to take it and to bring back unused pill at next visit
7. Go over Medication/AE Diary with pt. and instruct her to bring back to go over at every study visit

    a) Tell pt. to contact you if any moderate to severe AEs occur, this will be immediately reported to the PI/physician and serious AEs reported to the IRB
8. Give patient BD to complete 3 days before next visit (or as close to it as possible), record the dates on BD before handing to pt. and tell her to bring to next visit
9. Obtain two 10mL lavender top EDTA tubes of blood via intravenous phlebotomy (**Note**: blood draw can be done at any visit)
    a) Label each tube with BSP label, date, and time of blood draw
    b) Place tubes in sample refrigerator (samples need to be stored at 4 degrees Celsius)
10. Remind pt. of Week 2 and Week 4 visits, or schedule if needed
11. Dispense two $20 gift cards (for Baseline and Visit 0)
    a) Fill out the Gift Card Form and staple to inside of pt. study folder
    b) Track cards on the Gift Card Reconciliation Log
12. Update enrollment log
13. Make a copy of the BD with labels to be scanned in to medical records and create a telephone encounter for the pt. that states that a BD has been completed and scanned in to medical records
14. Transport blood to BSP in a biohazard cooler with ice packs *within 2 days*
15. **NOTE:** If pt withdraws from study via phone prior to the end of the study please complete:
    a) AE form for all AEs reported (start/stop dates and severity)
    b) Med Diary: how many days they took the medication (start/stop dates)

Before Week 2 Visit:

1. Before the study visit, obtain 8mg dose of study drug from IDS or from Rex/HBO supply following instructions above for the 4mg dose
2. Give pt. reminder call and remind her to bring unused pills, completed BD, and Med/AE diary

Week 2 Visit:

1. Ask if patient has had any med changes since last visit and notes changes on med printout
2. Have pt. complete the following:
    - OABq-SF
    - Treatment Benefit Scale
3. Complete the following:
    - Bladder Diary Evaluation
    - P450 Drug Interactions
    - Medication Dispensing Form
4. Go over Medication/AE diary with pt. and record any AEs on the Adverse Event form
    - Discuss with pt. whether AEs are mild, moderate, or severe using the AE definitions and criteria
    - Report to PI any AEs and to get rating for un/expectedness and causality
    - Report any serious AEs to the IRB as an unanticipated problem on IRB immediately
    - Study drug-related AEs: dizziness, somnolence/sedation, insomnia, confusion, cognitive impairment, dry mouth/throat, constipation, dyspepsia, nausea, dry eyes, blurry vision, and urinary retention
    - If pt. wants to discontinue study drug, have the patient follow-up with their provider to discuss other options for management of their UUI symptoms, log as drop-out in enrollment log and CRMS, then message PI
5. Give patient BD to complete 3 before Week 4 visit (or as close to it as possible), record the dates on BD before handing to pt. and tell her to bring to next visit
6. Dispense one $20 gift card
10. Dispense 8mg study medication and return any unused pills to IDS (write date pt. returned meds on bottle)
11. Make a copy of the BD with labels to be scanned in to medical records
12. **NOTE:** If pt withdraws from study via phone prior to the end of the study please complete:
    - AE form for all AEs reported (start/stop dates and severity)
    - Med Diary: how many days they took the medication (start/stop dates)

Before Week 4 Visit:

1. Give pt. reminder call and remind her to bring unused pills, completed BD, and Med/AE diary

Week 4 Visit:

1. Ask if patient has had any med changes since last visit and notes changes on med printout
2. Have pt. complete the following:
    - OABq-SF
    - Treatment Benefit Scale
3. Complete the following:
    - Bladder Diary Evaluation
    - P450 Drug Interactions
    - Medication Dispensing Form
4. Go over Medication/AE diary with pt. and record any AEs on the Adverse Event form
    - Discuss with pt. whether AEs are mild, moderate, or severe using the AE definitions and criteria
    - Report to PI any AEs and to get rating for un/expectedness and causality
    - Report any serious AEs to the IRB as an unanticipated problem on IRBis immediately
    - Study drug-related AEs: dizziness, somnolence/sedation, insomnia, confusion, cognitive impairment, dry mouth/throat, constipation, dyspepsia, nausea, dry eyes, blurry vision, and urinary retention
5. Dispense one $20 gift card
13. Ask pt. to let MD know whether she would like a Rx to study drug, and if so which dosage she felt she responded better to, or to let MD know if she wants to try another Tx option
14. Update enrollment log and change to completed in CRMS
15. Make a copy of the BD with labels to be scanned in to medical records
16. Return any unused pills to IDS (write date pt. returned meds on bottle)
17. File pt. study folder at Rex clinic

Statistical Analysis Plan

<u>Data-cleaning efforts and assessment of overall population and two cohorts</u>

Univariate statistics to check each variable, distribution, outliers

- Follow-up on any questionable data points, outliers

Compare sociodemographics of two cohorts

- Bivariate analysis with chi-square, Fisher's exact, Student's t-test, Mann-Whitney U as appropriate
- Variables include: age, race, education

Compare health, ADLs between cohorts using bivariate analysis

- Variables include: functional comorbidity index (FCI), current smoking status, Katz ADL, Lawton IADL scores

Evaluate urinary incontinence information between two cohorts using bivariate analysis

- OABq questionnaires (symptom bother and health-related QoL)

<u>Primary outcome analysis</u>

Primary outcome of effectiveness (Treatment benefit scale, dichotomized)

- Compare rate of effectiveness between two cohorts, Fisher Exact, Risk Ratio (95% CI)

<u>Secondary outcome analysis</u>

Secondary outcome of moderate to severe AEs (Dichotomous response – Yes/No to mod-severe AEs per CTCAE grading)

- Compare rate of moderate to severe AEs between two cohorts, Fisher exact, Risk Ratio (95% CI)