

**MIRABEGRON AND URINARY URGENCY INCONTINENCE:  
THE CLINICAL RESPONSE AND THE FEMALE URINARY MICROBIOME**

**P.I. Alan Wolfe PhD  
Clinical P.I. Elizabeth Mueller M.D.**

**Version 2  
09/08/2015**

## 1. Background

Overactive bladder syndrome (OAB) is defined by the International Continence Society (ICS) as “urinary urgency, usually accompanied by frequency and nocturia, with or without urinary urge incontinence, in the absence of urinary tract infection (UTI) or other obvious pathology (Haylen et al., 2010a, b). OAB affects at least 15% of adult women, with higher incidence with aging (Hartmann et al., 2009). By 2018, the prevalence of OAB worldwide is estimated to rise to over 20% (Irwin et al., 2011). Rates of OAB in urogynecologic patients with pelvic organ prolapse (POP) or urinary incontinence (UI) are as high as 88% (de Boer et al., 2010; Sajadi and Vasavada, 2010).

OAB symptoms can be caused by multiple etiologies, including bladder infection, malignancy, or neurological disease, e.g. multiple sclerosis or spinal cord injury (Mostwin, 2002). For most patients with OAB, however, the exact cause is unknown. One current theory is that OAB results from dysregulation in the neural pathways controlling micturition. Thus, the current medications for OAB are anticholinergic medications that target the muscarinic receptors in the detrusor muscle of the bladder (Michel and Chapple, 2009).

Mirabegron is an exciting new oral medication marketed by Astellas for OAB. It is a  $\beta$ 3-adrenergic receptor agonist that relaxes the detrusor smooth muscle during the urine storage phase, increasing bladder capacity. At usual clinical doses, mirabegron is believed to display selectivity for the  $\beta$ 3-adrenergic receptor subtype compared to its affinity for the  $\beta$ 1- and  $\beta$ 2-adrenoceptor subtypes. Data support that  $\beta$ -adrenoceptors, predominately the  $\beta$ 3 subtype, mediate detrusor smooth muscle tone and promote the storage function of the human bladder. Efficacy is seen within 8 weeks; steady state achieved within 7 days. Mirabegron can be effective for some patients, providing good symptom relief. Most studies, however, have documented that many patients (~50%) do not experience these preferred results (Chapple et al., 2014a; Chapple et al., 2014b).

Any attempt to understand mirabegron's influence on clinical symptoms should take into account our recent discovery of the female urinary microbiome (FUM) (Brubaker et al., 2014; Hilt et al., 2014; Pearce et al., 2014; Wolfe et al., 2012). The following observations support our hypothesis that the FUM exists and that it contributes to OAB and patient response to treatment. First, the bladders of women with and without lower urinary tract symptoms contain a FUM (Brubaker et al., 2014; Fouts et al., 2012; Hilt et al., 2014; Khasriya et al., 2013; Pearce et al., 2014; Siddiqui et al., 2011; Wolfe et al., 2012). Second, the bacteria that comprise the FUM are clearly distinct from those that cause overt clinical urinary tract infection (UTI) (Hilt et al., 2014; Pearce et al., 2014; Wolfe et al., 2012). Third, the FUM is associated with pre-treatment OAB symptoms and protection against UTI (Brubaker et al., 2014). Fourth, several bacterial species are more common in OAB patients than in asymptomatic controls (Pearce et al., 2014). Finally, response to an Astellas OAB anti-cholinergic treatment (solifenacin) varies according to FUM status (see *Preliminary Data*). These exciting findings open previously unappreciated opportunities for scientific inquiry concerning prevention, etiology and treatment of OAB.

These exciting findings with solifenacin should be replicated in clinically relevant populations treated with mirabegron, as it would be advantageous to identify affected individuals who are likely to respond prior to prescription. Currently, physicians have limited ability to meaningfully personalize UUI pharmacologic treatment and thus broadly prescribe too many affected individuals, including those who are likely to have minimal symptom relief. Since the FUM can be assessed prior to treatment, we propose to determine if baseline FUM assessment can provide insight into future symptom relief

with mirabegron treatment.

We propose the following hypothesis:

***In UUI-affected women treated with mirabegron, changes in urinary urgency incontinence are associated with changes to the FUM.***

## **2. Objectives:**

- A. In UUI-affected women treated with mirabegron, correlate patterns of urinary urgency relief with FUM characteristics.
- B. To develop clinically useful predictors for treatment response.

## **3. Materials and Methods:**

Following IRB approval, we will enroll 120 women with OAB. Human-research certified researchers will approach potentially eligible Loyola patients seeking care at the women's health or urogynecology clinics.

### ***Inclusion criteria:***

- Botherome idiopathic (non-neurologic) UUI who recall  $\geq 5$  urgency predominant urinary incontinence episodes in the prior week (urgency urinary incontinence or mixed urinary incontinence-urgency predominant) (Kenton et al., 2006); and
- No contraindications to taking mirabegron.
- Drug-naïve patients will account for at least 50% of enrolled participants. Patients on current OAB therapy will undergo a two-week drug washout period prior to baseline assessment in this study.

### ***Exclusion criteria:***

- Neurologic disease known to affect the lower urinary tract,
- Systemic immunologic deficiency,
- Current UTI (based on dipstick assessment) or recurrent culture-proven UTIs,
- History or current pelvic malignancy or radiation,
- Untreated symptomatic POP > POP-Q Stage II, or
- A contraindication to receiving mirabegron.

We also will exclude women of childbearing potential who are pregnant or nursing, or intend to become pregnant during the study, or who are not practicing a reliable method of contraception. Finally, patients must have not taken any antibiotics, for any reason, in the 4 weeks prior to enrollment (Smith et al., 1997).

### **Rescreening Opportunities:**

- Patients who had POP/UI surgery during the prior 12 weeks are ineligible, but may be rescreened at a later time.
- Patients on current OAB therapy can participate after undergoing a two-week drug washout period.

**Procedures:** Eligible woman will undergo an informed research consent process, which will be documented in their medication record. Participants who provide consent and sign the IRB-approved research consent form will complete a series of questionnaires that will be used to quantify symptoms. Symptom quantification will permit patient stratification based on phenotype. Stratification will be used to assess symptom-based correlates of response status. To quantify symptoms, we will use the following validated questionnaires: Urgency Severity and Life Impact Questionnaire (USIQ) (Lowenstein et al., 2012), Overactive Bladder Questionnaire (OAB-q) (Coyne et al., 2002), Urinary Distress Inventory (UDI-6) Pelvic Floor Distress Inventory (PFDI) (Barber et al., 2011), and Patient Global Impression of Severity (PGI-S) (Tincello et al., 2013).

From each patient-participant, a urine sample will be obtained by transurethral catheter and cultured (by standard clinical microbiology protocol) as part of their normal clinical evaluation. A portion of this urine will be saved for purposes of this study, but will be discarded if the patient declines study participation.

Once the research team confirms that the clinical culture is negative and the patient accepts the clinical recommendation for OAB oral medication, the patient-participant will be supplied with 25 mg daily of free mirabegron. Per the study protocol, the patient will be provided the free medication for the 12-week duration of the study.

Consistent with clinical follow-up for OAB treatment, the OAB patient-participants on mirabegron will return at 4, 8 and 12 weeks. In addition to their care, at each visit, each patient-participant will have her symptoms assessed by the questionnaires listed above and undergo catheterization for collection of urine specimen. To determine medication response, we will use the validated Patient Perception of Bladder Control (PPBC) (Coyne et al., 2006). If a subject's symptoms are adequately controlled with mirabegron 25 mg daily (based on a PPBC score of 4 or 5), she will continue at that study medication dose for the entirety of the study (an additional 8 weeks for a total of 12 weeks) and she will be considered a member of the 25-mg responder cohort. If a subject does not feel that they have adequate symptom control at 4 weeks (based on a PPBC score of 1, 2 or 3), she will be offered a dosage increase to 50 mg. At 12 weeks, if she feels that her symptoms are adequately controlled (based on a PPBC score of 4 or 5), then she will be considered to be a member of the 50-mg responder cohort. If, at 12 weeks, she feels that she does not have adequate symptom control, she will be considered a member of the non-responder cohort. The primary outcome, medication response, will be obtained at the end of the study (i.e., 12 weeks).

Consistent with clinical care, any patient with an active UTI will undergo catheterization for collection of a urine specimen with subsequent appropriate antibiotics, as indicated and consistent with the patient's allergy profile. For patient-participants who have a UTI at the time of a study visit, we will defer the completion of questionnaires and repeat catheterized urine specimen to the subsequent week in order to ensure appropriate clinical care of the UTI.

#### **Urine specimens handling:**

All urine samples obtained will be split into two aliquots. One aliquot will be sent to the clinical microbiology laboratory to undergo the normal clinical urine culture. The other aliquot, without any patient identifiers, will be sent to the laboratory of Alan Wolfe, PhD to undergo processing for expanded quantitative urine culture (EQUC) and 16S rRNA gene sequencing. These complementary assays will allow us to identify the bacterial species present in the urines of these women.

## **HUMAN SUBJECTS**

### **Protection of Human Subjects**

*Recruitment & Informed Consent.* Participants will be counseled by study personnel (Drs. Brubaker or our experienced study coordinator, Mary Tulke, RN) prior to their signing of the Loyola-IRB approved informed consent for study participation.

*Participant Safety.* Urinary catheterization for baseline assessment is part of normal clinical care. Participants will have two catheterizations that are not part of their normal clinical care. There is a possibility of an increase in UTI that would be readily identified and treated with conventional antibiotic therapy. We do not anticipate any other increased risks to participants as a result of their participation in this study as there are no research interventions & the participant's normal clinical care will proceed at the discretion of her individual physician. This protocol will comply with all prevailing regulations that govern human subject research. Dr. Brubaker will oversee the safety and confidentiality of study participants. Any adverse events, including unintentional breaches of confidentiality, will be documented & reported to the Loyola IRB.

*Protection Against Risk.* In compliance with regulations that govern human subject research, we will safeguard protected health information by using an assigned study ID number for participants. Documents linking patient identifiers & study ID will be kept in an appropriately secured location.

Potential benefits of research to subjects and importance of knowledge gained by participation in this study will have no direct benefit to individual subjects, as clinical care will be performed independently of study findings. However, the data obtained has the potential to improve the clinical ability to prevent and treat OAB, to advance our understanding of the urinary microbiota in the subset of women with OAB, and to generate important hypothesis regarding changes in the urinary microbiota in women who have bothersome OAB symptoms.

#### **4. Adverse Event Reporting:**

As with all clinical protocols, a variety of adverse events could occur. The risk of serious adverse event from study participation in this protocol is low. Reportable adverse events would include allergic reactions, heart palpitations and changes in EKG's...

There is also an unlikely risk of privacy violation despite diligent adherence to protection of all identified human data, using the Loyola secure server and in compliance with our institutional policies.

#### **5. Data Collection:**

We will collect demographic data (age, race, BMI, medical co-morbidities, tobacco use, medical history including estrogen status, and surgical history) on all participants. We will also collect the responses of the USIQ, PFDI, OABq and UDI-6, PGI-S, and PPBC. The urine specimens will be split into two specimens, one will be sent to the clinical microbiology laboratory for routine culture while the other de-identified specimen will be sent to the Wolfe laboratory for EQUIC and sequencing.

#### **6. Plan to protect the identifiers from improper use and disclosure:**

In compliance with regulations that govern human subject research, we will safeguard protected health information by using an assigned study ID number for

participants. Documents linking patient identifiers and study ID will be kept in an appropriately secured location. Data will be maintained on the secure Loyola Research server.

### **7. Access to protected health information:**

Clinical study investigators will have access to the information for data entry only. All identifiers will be removed from the samples submitted for laboratory analysis. Following completion of data entry, the data will be de-identified for analysis. HIPAA-compliant, anonymous data from this project will be available for sharing with interested researchers.

### **8. Use of data/Statistical Analysis Plan:**

There is no statistical analysis plan. The data are intended to add to available information on the understanding of the female urinary microbiome, mirabegron and OAB in order to better treat our patients.

### **9. Bibliography:**

Barber, M.D., Chen, Z., Lukacz, E., Markland, A., Wai, C., Brubaker, L., Nygaard, I., Weidner, A., Janz, N.K., and Spino, C. (2011). Further validation of the short form versions of the Pelvic Floor Distress Inventory (PFDI) and Pelvic Floor Impact Questionnaire (PFIQ). *Neurourol Urodyn* 30, 541-546.

Brubaker, L., Nager, C.W., Richter, H.E., Visco, A., Nygaard, I., Barber, M.D., Schaffer, J., Meikle, S., Wallace, D., Shibata, N., *et al.* (2014). Urinary bacteria in adult women with urgency urinary incontinence. *Int Urogynecol J*.

Chapple, C.R., Cardozo, L., Nitti, V.W., Siddiqui, E., and Michel, M.C. (2014a). Mirabegron in overactive bladder: a review of efficacy, safety, and tolerability. *Neurourol Urodyn* 33, 17-30.

Chapple, C.R., Nitti, V.W., Khullar, V., Wyndaele, J.J., Herschorn, S., van Kerrebroeck, P., Blauwet, M.B., and Siddiqui, E. (2014b). Onset of action of the beta3-adrenoceptor agonist, mirabegron, in Phase II and III clinical trials in patients with overactive bladder. *World J Urol*.

Coyne, K., Revicki, D., Hunt, T., Corey, R., Stewart, W., Bentkover, J., Kurth, H., and Abrams, P. (2002). Psychometric validation of an overactive bladder symptom and health-related quality of life questionnaire: the OAB-q. *Qual Life Res* 11, 563-574.

Coyne, K.S., Matza, L.S., Kopp, Z., and Abrams, P. (2006). The validation of the patient perception of bladder condition (PPBC): a single-item global measure for patients with overactive bladder. *Eur Urol* 49, 1079-1086.

de Boer, T.A., Salvatore, S., Cardozo, L., Chapple, C., Kelleher, C., van Kerrebroeck, P., Kirby, M.G., Koelbl, H., Espuna-Pons, M., Milsom, I., *et al.* (2010). Pelvic organ prolapse and overactive bladder. *Neurourol Urodyn* 29, 30-39.

Fouts, D.E., Pieper, R., Szpakowski, S., Pohl, H., Knobloch, S., Suh, M.J., Huang, S.T., Ljungberg, I., Sprague, B.M., Lucas, S.K., *et al.* (2012). Integrated next-generation sequencing of 16S rDNA and metaproteomics differentiate the healthy urine microbiome

from asymptomatic bacteriuria in neuropathic bladder associated with spinal cord injury. *J Transl Med* 10, 174.

Hartmann, K.E., McPheeters, M.L., Biller, D.H., Ward, R.M., McKoy, J.N., Jerome, R.N., Micucci, S.R., Meints, L., Fisher, J.A., Scott, T.A., *et al.* (2009). Treatment of overactive bladder in women. *Evid Rep Technol Assess (Full Rep)*, 1-120, v.

Haylen, B.T., de Ridder, D., Freeman, R.M., Swift, S.E., Berghmans, B., Lee, J., Monga, A., Petri, E., Rizk, D.E., Sand, P.K., *et al.* (2010a). An International Urogynecological Association (IUGA)/International Continence Society (ICS) joint report on the terminology for female pelvic floor dysfunction. *Int Urogynecol J* 21, 5-26.

Haylen, B.T., de Ridder, D., Freeman, R.M., Swift, S.E., Berghmans, B., Lee, J., Monga, A., Petri, E., Rizk, D.E., Sand, P.K., *et al.* (2010b). An International Urogynecological Association (IUGA)/International Continence Society (ICS) joint report on the terminology for female pelvic floor dysfunction. *Neurourol Urodyn* 29, 4-20.

Hilt, E.E., McKinley, K., Pearce, M.M., Rosenfeld, A.B., Zilliox, M.J., Mueller, E.R., Brubaker, L., Gai, X., Wolfe, A.J., and Schreckenberger, P.C. (2014). Urine is not sterile: use of enhanced urine culture techniques to detect resident bacterial flora in the adult female bladder. *J Clin Microbiol* 52, 871-876.

Irwin, D.E., Kopp, Z.S., Agatep, B., Milsom, I., and Abrams, P. (2011). Worldwide prevalence estimates of lower urinary tract symptoms, overactive bladder, urinary incontinence and bladder outlet obstruction. *BJU Int* 108, 1132-1138.

Kenton, K., Fitzgerald, M.P., and Brubaker, L. (2006). What is a clinician to do-believe the patient or her urinary diary? *J Urol* 176, 633-635; discussion 635.

Khasriya, R., Sathiananthamoorthy, S., Ismail, S., Kelsey, M., Wilson, M., Rohn, J.L., and Malone-Lee, J. (2013). Spectrum of bacterial colonization associated with urothelial cells from patients with chronic lower urinary tract symptoms. *J Clin Microbiol* 51, 2054-2062.

Lowenstein, L., Rickey, L., Kenton, K., Fitzgerald, M.P., Brubaker, L., Tulke, M., Fordham, J., and Mueller, E.R. (2012). Reliability and responsiveness of the Urgency Severity and Life Impact Questionnaire (USIQ). *Int Urogynecol J* 23, 193-196.

Michel, M.C., and Chapple, C.R. (2009). Basic mechanisms of urgency: roles and benefits of pharmacotherapy. *World J Urol* 27, 705-709.

Mostwin, J.L. (2002). Pathophysiology: the varieties of bladder overactivity. *Urology* 60, 22-26; discussion 27.

Pearce, M.M., Hilt, E.E., Rosenfeld, A.B., Zilliox, M.J., Thomas-White, K., Fok, C., Kliethermes, S., Schreckenberger, P.C., Brubaker, L., Gai, X., *et al.* (2014). The female urinary microbiome: a comparison of women with and without urgency urinary incontinence. *MBio* 5, e01283-01214.

Sajadi, K.P., and Vasavada, S.P. (2010). Overactive bladder after sling surgery. *Curr Urol Rep* 11, 366-371.

Siddiqui, H., Nederbragt, A.J., Lagesen, K., Jeansson, S.L., and Jakobsen, K.S. (2011). Assessing diversity of the female urine microbiota by high throughput sequencing of 16S rDNA amplicons. *BMC Microbiol* 11, 244.

Smith, H.S., Hughes, J.P., Hooton, T.M., Roberts, P., Scholes, D., Stergachis, A., Stapleton, A., and Stamm, W.E. (1997). Antecedent antimicrobial use increases the risk of uncomplicated cystitis in young women. *Clin Infect Dis* 25, 63-68.

Tincello, D.G., Owen, R.K., Slack, M.C., and Abrams, K.R. (2013). Validation of the Patient Global Impression scales for use in detrusor overactivity: secondary analysis of the RELAX study. *BJOG* 120, 212-216.

Wolfe, A.J., Toh, E., Shibata, N., Rong, R., Kenton, K., Fitzgerald, M., Mueller, E.R., Schreckenberger, P., Dong, Q., Nelson, D.E., *et al.* (2012). Evidence of uncultivated bacteria in the adult female bladder. *J Clin Microbiol* 50, 1376-1383.