**National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)**

# Summit on Urinary Incontinence Clinical Research in Women

**Natcher Conference Center, Building 45**
**National Institutes of Health (NIH)**
**Bethesda, MD**

**March 20, 2014**

**Meeting Summary**

## WELCOME

*Robert Star, M.D., NIDDK, NIH, Bethesda, MD*
*Tamara Bavendam, M.D., M.S., NIDDK, NIH, Bethesda, MD*

Dr. Bavendam welcomed participants to the meeting and introduced Dr. Star, Director of the NIDDK Division of Kidney, Urologic, and Hematologic Diseases, to provide welcoming comments.

Dr. Star noted that the Summit on Urinary Incontinence Clinical Research in Women has been a long time coming: Conversations began approximately 7 years ago to develop a women's urologic health communication and education project. One challenge that precluded the accomplishment of the project was determining the optimal messages to convey. Urinary incontinence (UI) is important, consequential, and costly, yet the studies needed to inform key messages and to determine the best way to move forward for treating women were not available at that time.

The focus of the Summit is a series of clinical trials sponsored by the NIDDK and the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) that were designed to evaluate UI treatment practices. Although these early clinical trials studied symptomatic patients seeking care, a current paradigm shift will foster the examination of early symptomatic patients as well, to move toward the prevention of UI. The time is right to move forward with this ambitious project, which has the support of the NIDDK Director, Dr. Griffin Rodgers. A request for applications (RFA) will be released soon to expand the frontier of the science in this area.

Dr. Star noted that the Summit was intended to be the third of three related meetings, but because of weather-related events, the second meeting, Path to Prevention of Lower Urinary Tract Symptoms (LUTS) in Women: Bladder Health has been rescheduled for May 3–4, 2014. The purpose of today's Summit is to pause to ascertain the status of the field, what is known, and what can be communicated to patients and the public about UI in simple, digestible messages informed by research results that were unavailable 7 years ago. The meeting also will address gaps in understanding of UI and how those gaps can be translated into future studies supported by NIDDK.

## INTRODUCTION: DRIVING CHANGE IN SUFFERER AND CLINICIAN BEHAVIOR TO INCREASE DIAGNOSIS AND SUCCESSFUL TREATMENT OF UI IN WOMEN

*Tamara Bavendam, M.D., M.S., NIDDK, NIH, Bethesda, MD*

Dr. Bavendam indicated that the Summit participants bring a diverse and deep wealth of expertise to contribute to the meeting discussions. She referred attendees to the biographies in the meeting folder. Dr. Bavendam explained that she had gathered individuals from multiple backgrounds and perspectives to reflect on the UI research completed by NIH-supported investigators. She noted that the participants care deeply about issues of UI and come from the fields of nursing, medicine, surgery, physical therapy, and other related disciplines. Dr. Bavendam expressed her appreciation to Summit participants. The panel members then introduced themselves.

Dr. Bavendam explained that two NIH-funded research networks have conducted clinical trials to investigate the efficacy of treatment options for UI. NIDDK has supported the Urinary Incontinence Treatment Network (UITN),[1] and NICHD has supported the Pelvic Floor Disorders Network (PFDN).[2] Five clinical trials from these networks, as well as an independent R01 study, will be discussed during the Summit. The UITN clinical trials include: Behavior Enhances Drug Reduction of Incontinence (BE-DRI); Stress Incontinence Surgical Treatment Efficacy Trial (SISTEr); and Trial of Midurethral Slings (TOMUS). The PFDN clinical trials include: Ambulatory Treatments for Leakage Associated With Stress Incontinence (ATLAS); and Anticholinergic Versus Botox® Comparison (ABC). The Program to Reduce Incontinence by Diet and Exercise (PRIDE) is an investigator-initiated clinical trial that was funded by NIDDK and the NIH Office of Research on Women's Health (ORWH).

Dr. Bavendam presented the meeting agenda. She explained that Dr. Sharon Tennstedt would begin with an overview of UI epidemiology, impact, and other background. The speakers will then describe each clinical trial, followed by a period for discussion and questions. The participants will be divided into two breakout groups in the afternoon to consider questions from a surgical and a nonsurgical perspective, respectively. Each breakout group will report back on the key messages and research priorities identified during the discussion.

With the overarching goal of identifying ways to get more women with UI diagnosed and successfully treated, the meeting will first reflect back on what NIH, researchers, and the clinical care community have learned from completed studies, and then look forward to research that could have the biggest impact on getting more women successfully treated. After hearing about completed research, participants will consider main points to take away from each study, including meaningful messages for clinicians and for women with UI; i.e., these clinical studies have been completed and published—what information is the most beneficial to communicate? NIDDK maintains Information Clearinghouses where patients and the public can find a wealth of information about a variety of health conditions, including UI, and it is important to ensure that the most helpful messages about UI are captured there. Additionally, there is a need to know more about how best to move information "beyond the Clearinghouse" and into practice. Dr. Bavendam acknowledged that although the participants are not expected to solve all of these challenges during the Summit, this meeting provides an opportunity to begin to address the most pressing

[1] Over its lifetime, the UITN has also received co-funding from the NICHD and from the NIH Office of Research on Women's Health (ORWH).

[2] Over its lifetime, the PFDN has also received co-funding from NIDDK and the ORWH.

needs. She encouraged participants to consider which trial results will inspire their colleagues to be more engaged in diagnosis and treatment of UI women.

During the second part of the meeting, participants will consider research needs and opportunities to reach the goal of increasing the diagnosis and successful treatment of women with UI. Dr. Bavendam thanked the panel members and speakers for responding to the pre-meeting question, "What would have the most impact on getting more women with urinary incontinence successfully treated?" The de-identified responses were included in the meeting folder. Dr. Bavendam explained that the responses fell into several categories: public education, prevention and intervention, screening, clinician education, treatment, and science. Most responses were related to public education and improved screening in the primary care setting.

Dr. Bavendam made a few additional points about the Summit: The purpose of the meeting is to learn from completed research. She cautioned the participants against commenting on the design of the trials; if the trials were conducted today, the designs would be different because much has been learned. The presentations will include a synthesis of high-level information; she encouraged attendees to ask additional questions that might be helpful in considering the Summit goals. Dr. Bavendam noted that the meeting summary will be posted on the NIDDK website. She explained that she would also like to identify individuals interested in working in a writing group that would leverage unique perspectives in organizing the Summit information and discussions into a peer-reviewed publication. Sharing proceedings from the Summit could help scientists think differently about research that needs to be pursued in this area. Dr. Bavendam encouraged all of the participants to think as broadly as possible to deliver on the meeting goals.

Dr. Bavendam commented on the spectrum of government agency representatives present in person and by teleconference. She noted that ideas generated during the meeting might lead to research opportunities and collaborations for NIDDK, as well as other agencies and NIH institutes. Together, the organizations will try to reach the goal of increasing the number of women with UI who are diagnosed and successfully treated.

The meeting participants from the various organizations introduced themselves, and Dr. Bavendam welcomed them all. She reminded the group that the focus of the Summit's discussion is on the treatment of UI, not prevention. Dr. Bavendam invited the Summit participants to attend the upcoming Path to Prevention of LUTS in Women: Bladder Health meeting on May 3-4, 2014. Dr. Bavendam also encouraged Summit participants to complete the attendee worksheet as they listen to the day's clinical trial presentations.

## OVERVIEW: EPIDEMIOLOGY/IMPACT/UNMET NEED

*Sharon Tennstedt, Ph.D., R.N., New England Research Institutes, Watertown, MA*

Dr. Tennstedt discussed the NIDDK-supported Boston Area Community Health (BACH) Survey to provide context for what is known about UI. In addition to being an investigator of the BACH study, Dr. Tennstedt is the Principal Investigator of the UITN Data Coordinating Center.

The BACH study is a population-based community health study that collected health data from participants at baseline and at a 5-year follow-up point. The study was conducted to assess the rates of and risk factors for urologic symptoms in more than 3,200 women and similar number of men, ages 30 to 79 years; the sample population included an equal number of Blacks, Whites, and Hispanics. In-home interviews and questionnaires were administered to collect self-reported data on all urological symptoms,

comorbidities, pregnancy history, and health care-seeking behaviors. A full medication audit was performed, and measurements of height, weight, and waist circumference were collected.

For the epidemiology study, BACH interviewers queried UI by asking: "Many people complain that they leak urine (wet themselves) or have accidents. In the last 12 months, have you leaked even a small amount of urine?" Responses were binned into weekly or monthly frequencies. The type of UI, either stress UI (SUI)[3] or urgency UI (UUI)[4], was also queried; individuals who reported both types were classified as mixed UI (MUI). The BACH study revealed that 10.4 percent of women experience weekly UI, and 14 percent experience monthly UI. MUI was the predominant type. Regarding duration, 41 percent of women reported at baseline that they had experienced UI for more than 5 years. Race/ethnic differences were identified. White women experienced higher rates of UI, predominantly SUI. Black and Hispanic women were more likely to experience MUI.

The researchers followed the change in symptoms over time. Surprisingly, they found evidence of improvement. After 5 years, 42 percent of women who reported weekly UI at baseline still experienced weekly UI (persistence), 14 percent improved to monthly UI, and 44 percent were no longer leaking any urine. This would be an interesting population to study further to determine contributing factors to symptom remission.

The BACH study confirmed several previously identified risk factors for UI. In the BACH population, likelihood of UI increased with age and central obesity (measured by waist circumference); UI was also associated with asthma, arthritis, vaginal delivery, and depression. Interestingly, although many believe UI to be an issue affecting older women, the rates of UI were high even in women younger than 50 years. Dr. Tennstedt commented that the younger population of women with UI deserves attention.

The BACH medication audit revealed that the risk of UI is elevated in women who take antihistamines, beta receptor agonists, angiotensin receptor blockers, anticonvulsants, and estrogen. Gabapentin is often prescribed to women to control hot flashes, but UI has been associated with initiating gabapentin; this is an instance of unintended consequences that must be considered in a women's overall quality of life (QOL). In addition to the medication audit, the research team collected nutritional data from the sample population. In women, higher risk of UI was associated with higher total caloric intake, higher ratio of saturated to polyunsaturated fat intake, and high vitamin C and calcium doses, as well as lower levels of physical activity. The fat ratio and doses of vitamin C and calcium could be potential points of intervention.

Known comorbidities with UI include diabetes, heart disease, and depression. As such, UI could be a sentinel symptom for major illnesses. The BACH study's 5-year data indicate that UI presents before the comorbid condition; this finding warrants further investigation, as the other possibility is that the comorbid conditions might be responsible for UI. The BACH findings suggest the need to revise current evaluation and treatment approaches for comorbid conditions.

The BACH study examined the effect of UI on the physical and mental health components of QOL, and found that QOL is worse in women who are younger and have more severe UI. Older women did not

[3] Stress urinary incontinence is the involuntary loss of urine with physical activity that increases the intra-abdominal pressure such as coughing, sneezing, lifting, etc.
[4] Urgency urinary incontinence is the involuntary loss of urine associated with a strong urge to urinate.

report the same impact, indicating a possible role for symptom accommodation. The effect of UI on mental health is similar to the effects of other comorbid conditions, such as vascular disease and asthma.

Of the women in the study with UI, 45 percent sought care. Of those, 60 percent received care, half of whom continued to have daily UI and were moderately or very frustrated by the continuing symptoms. The data indicate that more than half of the women with symptoms of UI did not seek health care.

In addition to the large epidemiological study, a qualitative study was embedded within BACH that included a random sample of men and women across the three racial/ethnic groups. The objective of the qualitative study was to explore perceptions concerning urological symptoms, health-care seeking, and symptom self-management. The qualitative study included 61 women and was conducted through in-home interviews. As determined through qualitative study, the factors related to care-seeking behavior varied. Women typically presented to a primary care physician during a routine visit or a visit related to another health problem. They sought care when the symptoms intensified or interfered with daily life, when they thought there might be health consequences, and when they had a good relationship with their primary care physician. These data indicate that doctors need to ask about UI during annual exam visits, as women tend not to bring up the topic themselves. The reasons women did not seek care varied by race/ethnicity. White women ascribed UI to aging and did not think UI was amenable to treatment. Black women attributed UI to personal behaviors over which they had control (e.g., fluid intake, weight control) and thus they did not think they needed physician oversight. Although Hispanic women were concerned about the health consequences of UI, they reported that they did not mention the topic to health care providers because they deemed it a private matter.

Women in the BACH study used many self-care strategies, often prior to seeking medical care. Approaches included fluid manipulation, complementary and alternative medicine (CAM; e.g., herbs, vitamins, minerals), and incontinent aid products.

The BACH study demonstrated that UI is common and increasing: projections indicate that 12 million women will experience UI by 2025. Central obesity is a major—and modifiable—risk factor, and the expanding obesity epidemic will contribute to more cases of UI. The risk factors identified in BACH and other studies suggest potential targets for intervention and prevention. Dr. Tennstedt closed by noting that a key take home message from the BACH study is that the majority of women with UI are not receiving effective treatment, for reasons ranging from a lack of care-seeking to health care providers not providing effective treatment, and that this represents a tremendous unmet need for women with UI.

***Discussion***

The BACH data sparked discussion of a number of issues and questions.

*Conditions comorbid with UI:* The association of depression and pain is very complicated, and it is unclear which condition arises first. Similarly, it is difficult to ascertain the temporal relationship between depression and UI. UI might be an associated symptom of depression, as women with depression have lower levels of physical activity. Dr. Tennstedt noted that one message should be for health care professionals working with a woman on weight reduction (or another condition, such as cardiovascular disease or diabetes) to inquire into UI symptoms.

The BACH study investigated the relationship between sleep patterns and UI. Those data, along with the incidence rate, are published. A participant noted that many women who present with nocturia are referred to a specialist to evaluate sleep apnea. Incontinence might be a warning symptom of another problem.

*UI prevalence in BACH study--methodology*: A participant noted that although the BACH study was evenly divided between White, Black, and Hispanic participants, this is not the same distribution as in the U.S. population and the Asian population, for example, was not represented. Dr. Tennstedt clarified that the sample was weighted to the representation of racial/ethnic groups within the U.S. population using known epidemiological procedures when the prevalence rates were calculated. Thus, the calculated rates are representative of the U.S. population.

In response to another question, Dr. Tennstedt also clarified that the same questions were asked at baseline and during the 5-year follow-up appointment to determine whether a person had UI and the frequency of UI episodes. Responses were classified as more than once daily, one or more times weekly, one or more times a month or less than monthly.

*UI symptom bother and QOL:* The frequency of UI symptoms and the amount of bother should be differentiated. The BACH queried bother using questionnaires and found that older women were less bothered, even when they experienced weekly or daily symptoms. There was a disconnect between measures of severity and bother. Also, younger women in BACH were very bothered, regardless of severity, because they are more active and the symptoms interfere with their daily life. One consideration is whether health care providers should target bother or severity in addressing UI. Another participant cautioned against concluding that older women are not bothered by UI, as QOL assessments might not be optimized for all ages and bother might be defined differently for older women.

*Risk factors and associations:* The BACH study queried childhood sexual abuse during the baseline survey. There was a relationship between a history of childhood sexual abuse and UI in adults.

*Challenges in health care seeking*: Anecdotal evidence mentioned by one participant indicated that Hispanic women in particular sometimes are rebuffed by their doctors when they mention UI; in line with data from BACH, having that conversation can be challenging for these women.

## AMBULATORY TREATMENTS FOR LEAKAGE ASSOCIATED WITH STRESS INCONTINENCE (ATLAS) STUDY

*Holly E. Richter, M.D., Ph.D., FACOG, FACS, The University of Alabama at Birmingham, Birmingham, AL*

Dr. Richter presented the results from the first randomized controlled clinical trial comparing effectiveness of continence pessary, behavioral therapy, and combination therapy for the treatment of SUI: the ATLAS trial. Treatment of SUI can be expectant (a wait-and-see approach), conservative, or surgical. A woman may have symptoms but determine that they are not bothersome enough to obtain treatment. Conservative treatment approaches for SUI include use of a pessary (a silicone or latex ring or disc inserted into the vagina that can press against the vaginal wall to provide support to the nearby urethra), urethral plugs, and behavioral therapy, such as pelvic muscle exercises. Surgical management is also an option, although many women prefer to avoid or defer surgery. Moreover, recent guidelines from professional societies, such as the American Urological Association, strongly encourage clinicians to offer non-surgical options to patients.

Behavioral therapy requires individual motivation, adherence to treatment, and access to trained practitioners. Use of continence pessaries is an alternative, nonsurgical treatment approach. In the mid-2000s, no randomized trials existed comparing pessaries to other evidence-based alternatives. The goal of the ATLAS trial was to evaluate the effectiveness of a continence pessary compared to evidence-based behavioral therapy in women with stress incontinence. Another goal was to determine whether combined therapy was superior to single-modality therapy.

Women with stress-predominant UI were recruited across 10 sites in the United States. They were stratified by type of incontinence (stress or mixed UI) and symptom severity, and then randomized to one of three treatment arms: (1) pessary, (2) behavioral therapy, or (3) combined behavioral therapy and pessary. Interventionists were centrally trained; a standardized behavioral therapy was implemented in four visits at 2-week intervals. Outcomes were assessed at 3 and 12 months after randomization. Primary outcomes included participants' global impression of improvement and the stress incontinence subscale of the Pelvic Floor Distress Inventory. Secondary outcomes included participant satisfaction and the proportion of participants that had 75 percent reduction in UI episodes.

From May 2005 to October 2007, 740 women were assessed for participation in the trial; 446 were randomized. As calculated, 150 participants per arm at the start of the study would provide 80 percent power to detect a 15 percent difference in success rates under an intention to treat analysis. All three treatment groups had attrition; approximately 100 participants per group completed the trial. The mean age of the study population was 50 years and the majority of the participants were Caucasian. Twenty percent of the women had tried nonsurgical treatments; less than 10 percent had had prior surgery for incontinence. Fifty percent exhibited stress-only incontinence episodes, and approximately 50 percent experienced more than two UI episodes per day.

At 3 months, the pessary-only group had a higher attrition rate (26 percent) than either the behavioral therapy (15 percent) or combined therapy (12 percent) group. Reasons for attrition included an unwillingness to continue to participate, inadequate pessary fit, completion of alternate treatment after the assigned therapy, a desire for another treatment arm, and lack of efficacy. Under the primary analysis (intention to treat), there was no difference between behavioral therapy and pessary at 3 months for the Patient Global Impression of Improvement (PGI-I) outcome. However, a significantly larger proportion of women in the combined group reached success according to the PGI-I as compared to the pessary-only group. At 3 months, more women in the behavioral therapy group reported that they had no bothersome SUI symptoms than women in the pessary only group. Women in the behavioral therapy group also reported greater satisfaction than women in the pessary group. Combined therapy also yielded better results on these two outcomes than pessary only, but it was not significantly better than behavioral therapy. There was no significant difference between the three groups in the percentage that achieved at least a 75 percent reduction in weekly UI episodes. Moreover, at 12 months, there was no significant difference in any ATLAS outcome measure. Vaginal discharge was the most common adverse event that was reported, and 7 percent of women complained of yeast infection. Urologic events other than UI (e.g., UTIs) were infrequent.

Dr. Richter noted in closing that the key findings from ATLAS were that at 3 months, behavioral therapy resulted in fewer bothersome SUI symptoms and greater satisfaction than pessary, but none of the observed differences in outcomes persisted to 12 months. Finally, combination therapy was not found to be superior to single-modality therapy.

***Discussion***

Participants responded to the ATLAS findings with a number of comments and questions.

*Understanding success/failure with conservative treatments*: One participant commented that pessaries are underused—when they work for a person, they tend to work for a long time and are a good long-term solution. Dr. Richter responded that, with respect to pessaries and other nonsurgical treatment approaches, it would be interesting to know which women are successful with these approaches. An analysis of ATLAS data revealed that women who were menopausal, women with higher education,

women who hadn't had previous UI surgery, and women who had a lower severity of incontinence tended to have more success and satisfaction with the interventions, and these predictors were the same for all three treatment groups. This provides some interesting insights; it will also be important to study women who were not successful to understand why.

Body mass index (BMI, a measure of weight relative to height; it is the tool most commonly used to estimate overweight and obesity) and race/ethnicity characteristics were also evaluated as risk factors in success/failure of treatment, but the trial did not have a lot of diversity.

A participant commented on the interesting finding that the benefit of behavioral therapy at 3 months did not persist over time, and asked whether women in the two groups that received behavioral therapy had more intervention provider visits in the first 3 months than the pessary group, possibly explaining both the difference at 3 months and the "washout" afterwards. Dr. Richter noted that ATLAS tried to match participant/interventionist visits between the arms to minimize such an effect: The women receiving behavioral therapy had four visits with their intervention provider, 2 weeks apart. The women receiving a pessary were encouraged to come back to discuss the pessary and were allowed three appointments to adjust the pessary for optimal fit. However, it is clearly important to determine the causes of attrition that occurred between 3 and 12 months, as those factors could contribute to lack of success.

*Effect of conservative therapies on sexual function*: Women in the behavioral therapy group had improvement with respect to incontinence in the context of sexual function and sexual activity.

*Messaging*: A participant asked what is the bottom line message from ATLAS for women with UI, as any educational program on UI developed by NIDDK must be based on robust evidence and clear messages are needed. Dr. Richter noted that the bottom line is that every woman needs individualized treatment—there is no single message on UI treatment that applies to every woman, but non-surgical approaches should be offered first line as for some women they are of benefit.

## BE-DRI STUDY

*Kathy Burgio, Ph.D., The University of Alabama at Birmingham, Birmingham, AL*

Dr. Burgio described the BE-DRI trial, which was conducted at nine UITN clinical sites around the country. Behavioral therapy is recommended as the first line of treatment. It is safe and effective, but most patients do not achieve complete continence. Similarly, another conservative (non-surgical) approach to treating UUI is drug therapy, but the available drugs[5] are not always fully effective for achieving complete continence and people may discontinue these medications due to side effects. However, it might be possible to increase overall efficacy of conservative therapy for UUI by combining treatments that may work synergistically by targeting different mechanisms important to achieving continence. The specific aim of the BE-DRI trial was to determine whether adding behavioral therapy to antimuscarinic drug therapy improved short-term outcomes of active drug therapy at 10 weeks, and whether reduction of incontinence was sustained after discontinuing drug therapy. The clinical trial had two stages. In stage 1, women were randomized either to 10 weeks of drug therapy alone or to drug therapy combined with behavioral training. In stage 2, active treatments were stopped; participants in the

[5] The most common medications for treating UUI come from a class of drugs called anticholinergics; of those, the most common types are antimuscarinics. These drugs target portions of the nervous system governing contraction of involuntary muscle groups; they help in UUI by preventing inappropriate bladder contractions that lead to uncontrolled release of urine.

combination arm were instructed to continue with the behavioral therapy program on their own, to maintain its effects; and all participants were followed for 6 months. The primary outcome was a between group comparison of the percentage who were able to discontinue drug and sustain at least a 70 percent reduction in incontinence episodes at 8 months, which was 6 months after cessation of drug therapy. Secondary outcomes included the percent reduction in reduced incontinence; symptom distress and bother; patient satisfaction and perceived improvement; and QOL.

The BE-DRI study participants were 307 women with urge-predominant UI; their mean age was 57 years. Drug therapy consisted of Detrol LA (4 mg/day) administered in four visits across 10 weeks. Behavioral training consisted of four visits across 10 weeks and included teaching pelvic floor muscle control and exercise; urge suppression; delayed voiding to increase voiding intervals (for those who voided more than 8 times per day); fluid management for those with excessive urine output, >70 oz. per day)and instructions for daily home practice between clinical visits. At the end of active treatment at 10 weeks, 69 percent of participants receiving the combined treatment and 58 percent in the drug only group had a 70 percent reduction in episodes of incontinence. Patient satisfaction and perceived improvement were statistically greater in the combined treatment group than in the group receiving drug alone both at 10 weeks (end of active treatment) and at 8 months (6 months off of drug treatment). However, there was no difference between the two groups in the percentage of subjects who were able to stay off drug and maintain a 70 percent reduction in UI episodes—41 percent in each group met this primary endpoint, indicating that combined therapy was not effective for enhancing the ability to discontinue drug and sustain improvement. The urogenital symptom distress score as assessed by the Urogenital Distress Inventory (UDI) survey improved substantially between baseline and 10 weeks for both treatment groups, but the group receiving combined therapy improved more through 10 weeks of treatment and worsened less over the following 6 months than the group receiving drug alone.

A separate analysis of BE-DRI data showed that the only variable that predicted successful outcome (70 percent reduction in incontinence) at 10 weeks was younger age; at 8 months, only greater anterior vaginal wall prolapse was associated with the ability to discontinue drug and sustain 70 percent reduction in incontinence episodes. A variety of characteristics—including demographics, UI severity or duration, and prior treatment—were not associated with successful outcomes. These findings are not strong enough to provide justification for withholding conservative therapies from any woman needing treatment for UUI (i.e., these treatments are safe, and there is not enough evidence to enable targeting conservative therapy to specific subgroups of women), but could be used to guide expectations from treatment.

Currently, behavioral therapy is recommended as first line of treatment in clinical practice guidelines. Obstacles to adoption of behavioral treatments include reimbursement, availability of providers, and time and effort. Dr. Burgio closed by noting that, while the primary outcomes were not met, BE-DRI results suggest that there are added benefits in active combined therapy; further, there is a need to understand the best ways to combine conservative therapies.

***Discussion***

*Challenges of messaging from BE-DRI:* The BE-DRI trial provides a cautionary tale, because the trial has been interpreted in the evidence-based medicine arena as a negative trial because it did not meet primary outcome. The fact that adding behavioral therapy improved both short-and long-term outcomes of drug therapy has been totally lost. In addition, the finding that 41 percent of participants in the drug only arm had a 70 percent reduction in UI episodes 6 months after drug was discontinued provides an explanation for the general low persistence on antimuscarinics. The choice of the primary outcome, although interesting scientifically, had a negative effect on disseminating a message about behavioral

therapy. Another key point from an ancillary study to this trial was that many of the participants had unrealistic expectations regarding the trial interventions, believing that they were going to be cured for life—underscoring how important it is to craft accurate messages and set reasonable expectations for people with UI symptoms.

*New medications for UUI:* A participant commented that drugs are effective, but are discontinued at a high rate—often because of the cost in the case of newer, non-generic drugs,. There is a strong need for more drug therapies that are cost-effective and available.

*Longer term outcomes*: A participant noted that it would be helpful to follow up on the study to evaluate longer-term (3 or 5 year) results; Dr. Burgio noted that they do not have long-term follow up data on BE-DRI participants.

*Adherence to behavioral therapy*: A participant noted that this well-done study is disappointing because it seems to show that patients must remain on drugs indefinitely to treat UUI. However, that may be related to the construct of the combined therapy arm of the study—i.e., was adherence to the behavior program controlled in the 6 months following cessation of drug treatment in this group? Perhaps an excessive number of patients stopped the behavioral therapy, and that affected the outcome--better adherence to behavioral therapy might show sustained improvement after the drug treatment is terminated. Dr. Burgio noted that an analysis of adherence was performed, and that adherence to the behavioral therapy was very good during the active stage, and, though there was some tapering off, remained very good in at the end of 8 months.

## ANTICHOLINERGIC VERSUS BOTOX® COMPARISON (ABC) STUDY

*Anthony Visco, M.D., Duke University, Durham, NC*

Dr. Visco explained that UUI is highly prevalent and negatively impacts QOL. The first-line and likely most common therapy is treatment with anticholinergic medications, but the drugs do not work for everyone and can have bothersome side effects. (Botulinum toxin therapy is an alternative to anticholinergic therapy (as demonstrated in randomized trials of onabotulinumtoxinA versus placebo), but botulinum toxin and anticholinergics had not been compared directly prior to the ABC trial. The ABC trial compared the safety and efficacy of a standardized 6 month anticholinergic regimen *vs*. a single 100-unit onabotulinumtoxinA injection into the bladder for the treatment of UUI in women. Women in the anticholinergic group were started on solifenacin (5mg/day) and were dose escalated to (10mg/day) if they had inadequate symptoms control. They could later be changed to Trospium XR 60mg if they continued to experience inadequate symptom control.

Among inclusion criteria for the trial were having had at least five UUI episodes over a 3 day period and the ability to perform self-catheterization (in case of experiencing urinary retention); of note, study participants averaged five or more UUI episodes per day. The study cohort was randomized in a blinded, double-placebo fashion to either solifenacin 5mg initially and a placebo (saline) injection or a onabotulinumtoxinA injection and placebo pills. The participants were followed for 6 months, at which time the pills were stopped and the participants were followed for an additional 6 months.

Participants included those who were drug naïve to the study drugs, as well as some who had failed up to two previous treatments with other drugs for UUI. The primary outcome evaluated was change from baseline in the mean number of UUI episodes per day, as assessed by 3-day voiding diaries administered

monthly in the first 6 months. Secondary outcomes included the proportion with complete resolution of UUI, total UI, QOL, and adverse events (e.g., dry mouth, dry eyes, UTIs).

With respect to the primary outcome, both treatment groups experienced a significant reduction in the number of UUI episodes per day (an average reduction of 3.4 UUI episodes per day from an average of 5 UUI per day). Complete resolution of incontinence was achieved in 13 percent of participants treated with solifenacin and 27 percent of those treated with onabotulinumtoxinA. However, UTIs were significantly more prevalent in the onabotulinumtoxinA-treated volunteers (33 percent) versus those treated with solifenacin (13 percent). Subgroup analysis revealed that being drug naïve vs having had UUI drug treatment prior to the trial did not have a statistically significant effect on the primary outcome for either solifenacin or onabotulinumtoxinA intervention.

The solifenacin treatment ended at 6 months, and there was a slow degradation of symptom resolution for both treatment groups, both of which started with approximately 70 percent of participants with adequate symptom control at 6 months. For example, following a single injection of 100 units of onabotulinumtoxinA, 52 percent of study participants still experienced adequate symptom control at the 9-month mark. As expected, there was a more rapid decline in adequate symptoms control in the participants in the solifenacin arm after cessation of treatment: only 32 percent of volunteers in this group experienced adequate symptom control at 9 months.

The ABC study demonstrated that solifenacin pills and onabotulinumtoxinA (100 units) bladder injection both significantly improve UUI and QOL, and that there was no significant difference between the treatment groups. OnabotulinumtoxinA provided a two-fold higher likelihood of achieving resolution of UI symptoms, but increased the risk of transient urinary retention and UTIs. In terms of cost-effectiveness, a single injection of onabotulinumtoxinA is more expensive upfront, but solifenacin treatment incurs expenses regularly. Further analysis of ABC data showed that, in the first 6 months, the medications have similar cost-effectiveness. However, when considered through 9 months, onabotulinumtoxinA treatment provides a cost savings compared to regular solifenacin treatment while providing similar UUI symptom control. Future UUI research will evaluate the effectiveness and acceptance of multiple botulinum toxin injections, determine how to minimize botulinum toxin side effects, and consider how to maximize adherence to anticholinergic drugs.

***Discussion***

*Cost analysis*: In response to a participant question, Dr. Visco noted that direct (e.g., cost of onabotulinumtoxinA, UTI treatment) and indirect (e.g., cost due to lost work, dry cleaning) costs were measured. The cost-effectiveness model for quality-adjusted life years (QALY) addressed only direct costs.

Also related to costs, a participant asked how the Botox® injections were administered. Dr. Visco responded that all injections were performed in an office setting, using local anesthetic.

*Demographics*: The average BMI and waist circumference of patients were representative of a wide demographic.

Participants noted that older women (and those with high BMIs) tend to be more deterred by self-catheterization. Retention by age could be evaluated.

## STRESS INCONTINENCE SURGICAL TREATMENT EFFICACY TRIAL (SISTEr) STUDY

*Mike Albo, M.D., University of California, San Diego, San Diego, CA*

Dr. Albo explained that when the SISTEr trial was initiated as the first trial performed by the UITN, there were many surgical procedures for SUI. Each procedure was undergoing modifications in pursuit of greater efficacy. Nevertheless, there was a lack of evidence to discuss the merits of one procedure versus another with patients. This was due to a number of reasons: There were very few prospective, randomized clinical trials; none of the studies had adequate patient numbers; there were no standardized criteria either for patient entry or for measuring efficacy of treatment; and long-term follow up was inadequate. In 1998, standards to measure efficacy were established by the standardization committee for the International Continence Society. Under these standards, UI is regarded as a multidimensional phenomenon, and outcomes in studies of UI should be reported in at least five areas: patient observations (symptoms), quantification of symptoms, clinicians' observations, measures of QOL, and socioeconomic issues.

The UITN was established under RFAs NIDDK released in 1999 and 2000. The objectives for this multidisciplinary research network were to (1) design and perform clinical trials to determine the long-term efficacy and safety of the most commonly used surgical procedures for women with urinary incontinence; (2) develop standardized diagnostic and outcome measures, including QOL and satisfaction measures to be used in all trials evaluated by the network; and (3) determine the influence of demographic and clinical parameters on the efficacy and safety of incontinence treatments. When the UITN convened, it was decided that the first study should evaluate the most important and most common UI procedures.

There are two "gold standard" operations for SUI treatment: abdominal colposuspension (Burch procedure) and autologous rectus fascia pubovaginal sling (PVS). The sling procedure differs from the Burch in that it adds support behind the urethra. The methods have sufficiently different mechanisms of action that a trial was conducted to determine overall and stress-specific UI treatment success at 24 months. The secondary aims were to compare the two procedures with respect to complications, QOL measures, sexual function and satisfaction. Success in resolving overall UI was defined as a negative pad test, no self-reported leakage by a 3-day voiding diary, no self-reported stress-type UI symptoms, a negative stress test, and no retreatment for SUI. SUI-specific success rates also were assessed. A total of 655 women with stress-predominant UI (88 percent of whom had some UUI symptoms) were randomized to one of the two surgeries. Eighty percent completed the 2-year visit. At 24 months, the SUI-specific success rates showed that the sling procedure (66 percent) was more effective than the Burch procedure (49 percent). Overall UI treatment success also was higher for the sling (47 percent) than the Burch procedure (38 percent). One important finding—demonstrating the importance of standardized definitions of success for UI treatment—was the low success rates for both procedures, as these treatments were previously thought to be 80 to 90 percent effective. When the outcome criteria were evaluated individually, success rates were much higher. For example, a negative pad test alone as the outcome would have resulted in an 85 percent success rate and the two procedures would have been considered equivalent. The high standard imposed by use of the composite outcome explains the low success rates.

The sling procedure yielded higher satisfaction rates (86 percent), but also higher rates of complications (63 percent) than the Burch (78 percent satisfaction and 47 percent complications). Postoperative complications included voiding dysfunction, incontinence (persistent or *de novo*), and UTIs, all of which occurred more frequently in the sling procedure group. Voiding dysfunction that required additional surgery occurred only in the sling group, whereas recurrent stress incontinence was more prevalent in the Burch group. QOL improved after both surgeries, and was maintained at 2 years after both procedures.

Factors that predicted SUI-specific treatment failure included greater severity of UUI (not SUI) symptoms at baseline and no use of hormone replacement therapy in post-menopausal women; these risk factors were similar between the two treatment groups. Factors such as BMI, diabetes, previous UI surgery, or previous hysterectomy did not have a significant impact on outcome success. Participant satisfaction at 2 years was associated with a greater reduction in SUI symptoms and overall symptom distress; SISTEr participants were less likely to be satisfied with outcomes if they had greater pre-operative UUI symptoms, detrusor overactivity at 2 years, or a positive stress test at 2 years..

The Extended SISTEr (E-SISTEr) 5-year follow up study was designed to compare the long-term effectiveness and durability of the sling and Burch procedures for the treatment of SUI. Overall success was defined differently in E-SISTEr than in SISTEr, as no self-reported symptoms by questionnaire or a 3-day voiding diary and no retreatment of SUI. Applying this definition to the SISTEr participants who enrolled in E-SISTEr, the success rate at 2 years post-surgery (i.e., the same time point as the SISTEr primary outcome) was 43 percent for the Burch procedure and 52 percent for the sling procedure. At 5 years, E-SISTEr showed that the success rates decreased to 24 percent for the Burch procedure and 35 percent for the sling. Interestingly, participant satisfaction rates remained high after 5 years, regardless of whether the procedure resulted in complete continence—thus, it will be important to continue to examine outcomes most important to women treated for UI. Conversely, there is a need to communicate better to women with UI what can reasonably be expected from surgical procedures, as many do not achieve complete resolution of UI symptoms. For example, many SISTEr participants believed that their UUI would be cured by the surgery they received, despite being informed that it was designed to treat SUI. Postoperative UUI was associated with lower success rates, less improvement in QOL, and lower satisfaction rates.

Overall, the sling was more effective than the Burch procedure at resolving UI symptoms and had higher rates of satisfaction at 2 and 5 years after surgery. However, the sling procedure caused more voiding problems and UTIs than the Burch procedure. QOL and sexual function improved after each successful surgery, and women remained highly satisfied with the outcomes of surgery. Dr. Albo concluded by noting that the SISTEr findings about the impact of UUI on outcomes are important and need to be addressed.

***Discussion***

*Applicability of SISTEr to current practice:* A participant noted that the new era in synthetic sling materials means that the surgical procedures studied in SISTEr are declining in popularity. Dr. Albo noted that conducting a trial takes a long time, and innovative surgical procedures are always being developed. The UITN, however, needed a standard by which to evaluate other procedures, and this goal was accomplished by SISTEr.

*Satisfaction with SUI surgery:* It is important to decide how to counsel women with SUI about the different surgery options. The SISTEr trial provided a direct comparison about the different possibilities. It was noted that patients who have elective surgery are happier than others, possibly because there is a bias of the patients in the study (they want to be successful).

## TRIAL OF MIDURETHRAL SLINGS (TOMUS) STUDY

*Mike Albo, M.D., University of California, San Diego, San Diego, CA*

Dr. Albo described the mid-urethral sling (MUS) procedure to treat SUI, which was first developed in 1995. It is a minimally invasive procedure, and the initial cure rates are 80 to 90 percent. Complications include postoperative voiding dysfunction. It is the procedure of choice that replaced the Burch procedure

in Great Britain, although no direct comparisons had been performed between the standard sling (i.e., PVS) and the MUS. However, because the procedures are vastly different, it was not considered feasible to randomize patients to the two procedures for a trial. For example, the standard sling requires an incision to harvest fascia and the MUS, which uses synthetic mesh sling material, does not. Instead, the UITN decided to address a different issue, the rapid adoption of different versions of the minimally invasive MUS procedure. TOMUS compared two MUS procedures, the retropubic MUS and the newer and possibly more benign transobturator MUS, which differ primarily in how the synthetic mesh sling is inserted. The primary aim was to compare the 12-month efficacy and safety of these two MUS procedures.

A total of 597 women with stress-predominant UI enrolled in TOMUS, which was designed as an equivalence trial[6]. The primary outcome was objective success at 1 year, as measured by a negative stress test, negative 24-hour pad test, and no retreatment for SUI. Subjective success was measured by no self-reported symptoms of SUI, no leakage on a 3-day voiding diary, and no retreatment for SUI. At 1 year, the objective success rates were sufficiently similar for the two procedures to be considered equivalent; however, the subjective success rates did not demonstrate equivalency. There were no differences in the secondary outcomes of postoperative urinary symptom bother or QOL between the two groups, and patient satisfaction was about the same. At 2 years, the TOMUS researchers could no longer say that the two procedures were equivalent by either objective or subjective outcome measures, but the differences were not sufficient to say with statistical certainty that one procedure is better than the other.

Complications assessed at the 2 year mark differed by procedure. Complications associated with the retropubic MUS included voiding difficulty and bladder perforations, whereas those associated with the transobturator MUS included neurologic symptoms of numbness or weakness. These differences may be sufficient reason for a patient or her physician to select one procedure over the other.

The goal of the Extended TOMUS (E-TOMUS) follow-up study is to assess treatment success, patient satisfaction, and safety of the retropubic and transobturator MUS 5 years after surgery. The E-TOMUS prospective observational trial enrolled 404 of the TOMUS participants.

In summary, the TOMUS study provided the highest level of evidence for equivalence between the retropubic and transobturator MUS in objective success rates 12 months after surgery. The evidence strongly suggests that for the typical patient seeking surgical treatment for SUI, the two MUS procedures are similar in regard to how well they cure incontinence. Participant satisfaction is similar between the two procedures, although the complications vary; also, TOMUS revealed that new complication events occur over time.

Importantly, the UITN SISTEr and TOMUS trials showed that women are willing to participate in randomized controlled surgical trials assessing the comparative outcomes of SUI procedures. The resulting data help women with SUI and their physicians make better-informed choices based on clear benefits, risks, and personal preferences. Dr. Albo closed noting that questions that remain to be addressed include determining the best measure of success for surgical treatments for SUI; understanding the long-term consequences of the minimally invasive slings; and understanding more complex phenotypes (e.g., SUI vs. MUI; neurologic patients; repeat-surgery patients).

[6] In an equivalence trial, statistical methods are employed to answer the question of whether two treatments under study can be considered clinically equivalent.

***Discussion***

*Challenges with understanding sling surgery failure in prospective studies*: When a surgery fails to cure UI, it is not possible to determine from simple follow-up physical exams whether the sling was doing what it was supposed to do or whether another factor could account for the continued or recurrent UI symptoms. E.g., the E-TOMUS included a vaginal exam, but the purpose is to rule out erosion of the sling mesh material into the vaginal wall (another complication), not to assess for urethral stability.

*Tailoring treatment for UI*: The issue of combination therapy was mentioned. It was noted that no single "magic bullet" exists to cure UI. Instead, there is a need to look at the big picture, which includes advances in technology and treatment approaches that are continuously emerging and being adopted in clinical practice. Dr. Albo acknowledged these points and noted that the UITN studies are valuable in that they show that researchers have the ability to set standards and conduct the right kind of studies to determine effectiveness of surgical treatment approaches; a current challenge occurs when many patients receive a new procedure before good data on safety and efficacy are collected. Another participant commented that several publications show a higher risk of failure among different subgroups in TOMUS, partly because SUI is not a single disease; it has multiple etiologies, so one surgery will not cure all patients. Every patient requires a unique approach to treatment; thus, NIH is encouraged to look at SUI as a group of conditions and support research that will help to determine what approach (e.g., which surgery) is appropriate for each unique individual. The emphasis should be that SUI is not ONE condition, but multiple conditions, with a range of treatments that address the multiple conditions.

*UITN performance data:* The differences in complications between UITN study centers, in terms of surgeon performance, were controlled for in the analysis. The Data Safety Monitoring Board (DSMB) had access to blinded results by UITN center so that an outlier with respect to efficacy or complications would have been identified. However, this is sensitive information that was not shared with UITN investigators at the surgical sites. Another participant commented on how having this type of data in some format would be helpful to the broader community because it would provide insight into how well (and where) procedures, especially newer procedures, are being done. Dr. Albo commented that the trial information wouldn't have enough statistical power to provide that kind of certainty in assessment; he also noted that an important aspect of the trials was to try to ensure standardization of procedures (e.g., with video instruction) across trial sites and surgeons.

*Other challenges:* A participant commented that late night advertisements about surgical mesh lawsuits have led to an increase in the number of practitioners not offering mesh slings for SUI treatment because of patients confusing total vaginal mesh (the subject of FDA concern) and the MUS. Further, patients do not always listen to potential adverse events prior to surgery, so it is unexpected when problems arise.

The TOMUS and E-TOMUS provide high quality evidence about the efficacy and safety of the MUS in the hands of experts; how this should be used by individual surgeons that are not as experienced is a concern.

## PROGRAM TO REDUCE INCONTINENCE BY DIET AND EXERCISE (PRIDE) STUDY

*Leslee Subak, M.D., University of California, San Francisco, San Francisco, CA*

Dr. Subak began by remarking that on the interrelationships between UI and obesity. Approximately 35 percent of U.S. women are obese, and approximately 60 percent are either obese or overweight, which increases the risk of UI fourfold. Obesity accounts for 15 percent to 20 percent of UI cases. BMI is one of the top modifiable risk factors for UI, along with oral estrogen use, stroke, and diabetes. Being

overweight is associated with both types of UI (stress and urgency). If weight is a risk factor for UI, weight loss might be an effective treatment. Case studies and cohort studies showed that surgical weight loss decreased UI prevalence in the study populations by 50 to 100 percent and decreased the frequency and severity of UI. In a randomized controlled trial, a low-calorie liquid diet intervention caused weight loss and was accompanied by a decrease in UI symptoms compared to the control.

Based on these data, 338 overweight or obese women experiencing at least 10 UI episodes per week were recruited to participate in the PRIDE study, which consisted of 6 months of lifestyle intervention or control. Lifestyle intervention included diet, exercise, and behavioral modification (modeled on the Diabetes Prevention Program (DPP) and Look HEAD interventions). The control group received a structured education program on general health. Women were randomized to either the control or weight-reduction groups. After 6 months, the weight-reduction group was further randomly divided into a motivation-based maintenance group that used UI to motivate participants to maintain weight loss, or a traditional, skills-based maintenance group; all PRIDE participants were then followed for an additional 12 months. The primary outcome was the change in UI episode frequency at 6 months, based on patient self-report diaries. The study population had a mean age of 53 years and was 20 percent African American. The average weight was 96 kilograms (211.6 lb), and the initial UI frequency was 25 episodes per week. The type of UI was distributed as follows: stress (22 percent), urge (43 percent), or mixed (33 percent).

At 6 months, the intervention group lost 8 percent of initial body weight, compared to 1.6 percent in the control group. The greater weight loss in the intervention group was accompanied by a significantly greater decrease in total UI episodes and SUI episodes, but not in UUI episodes, compared to the control group. The proportion of participants who experienced a clinically significant reduction in the frequency of any incontinence episodes of 70 percent or greater at 6 months was higher in the weight-loss group. At 18 months, there was still a significant although smaller difference in weight loss between the two groups; while there was no longer a significant difference between the two groups in UI improvement overall, women in the weight loss group were significantly more likely to report a 70 percent or greater improvement in weekly UI episodes at 12 months (total and SUI) and 18 months (UUI). The benefit of the weight loss intervention for UI was thus maintained through at least 12 months; there was no difference between the motivation versus skill-based strategy for weight maintenance. When analyzing the relationship between weight loss and UI improvement among all PRIDE participants at 18 months, there was a definite “dose response” between greater weight loss and UI improvement: there was a strong association between greater weight loss and a decrease in UI episode frequency, as well as in a greater than 70 percent reduction in total and urge UI. Seventy-five percent of women who lost at least 5 percent of their baseline weight—a number with clinical significance for seeing improvements in cardiovascular and other conditions—reported being at least moderately satisfied with improvements in urine leakage. The maximum effect on UI was achieved by 5 to 10 percent weight loss. A decrease in urinary incontinence might be another benefit among the extensive health improvements associated with moderate weight reduction.

The mechanism by which the lifestyle intervention treatment works is not understood. There was no association between the change in weight or waist circumference and urodynamic parameters. However, some interesting changes were observed—for example, weight loss of at least 5 percent or decrease of at least 5 cm in waist circumference was accompanied by increased bladder capacity. Many secondary measures were recorded and are awaiting analysis.

An additional study funded by NIDDK that has allowed investigation of weight loss and UI is the Action for Health in Diabetes (Look AHEAD) study, a randomized controlled trial of the long-term impact of an

intensive lifestyle intervention to achieve weight loss versus diabetes support and education on cardiovascular events and other outcomes in obese persons with type 2 diabetes. UI was the most prevalent complication associated with diabetes among women in the Look AHEAD study. In an ancillary study, at 1 year, the lifestyle intervention program significantly decreased prevalence and incidence of overall and stress UI. Another NIDDK study, the Longitudinal Assessment of Bariatric Surgery (LABS) study, examined the effect of bariatric (weight loss) surgery on severe obesity and related health outcomes. Nearly half the female participants had at least weekly UI at baseline. At 3 years post-surgery, the median weight loss was 30 percent, and UI remission occurred in 70 percent of patients.

Dr. Subak closed by noting that areas for future research include examining the epidemiology of the association between UI and body composition and conducting ancillary studies on existing data sets that include measures of weight, body composition, activity, and UI. There is a need to understand to what extent physical activity is associated with UI and if increased activity is associated with improved UI, as well as a need to understand the mechanism by which weight loss improves UI. Future UI clinical trials could address the importance of weight loss strategy (type of behavioral, pharmacological or surgical weight loss), combining weight loss with other approaches to therapy, and ways to provide more women with UI access to treatment. UI may be a motivator for lifestyle changes leading to weight loss.

***Discussion***

*Impact of medical history, demographics:* In response to a participant question, Dr. Subak affirmed that vaginal delivery is a major risk factor for developing UI and that this was observed in the PRIDE cohort, but a history of vaginal delivery did not affect outcomes. There was also no difference in the study results by race/ethnicity.

*Implementing PRIDE findings in practice:* A participant commented that patients are resistant to accept the notion that weight loss will affect their UI symptoms, despite the evidence. Dr. Subak and others noted that physicians should continue to discuss the relationship between weight and UI, even when they receive a negative reaction. Change often occurs after similar messages cumulatively affect an individual's behavior. However, it is not clear whether resolution of UI is a powerful motivator for losing weight.

*UUI versus SUI prevalence:*
A participant observed that obese women in PRIDE had a higher than expected incidence of UUI. Dr. Subak noted that this might be an artifact of the study (i.e., the availability of surgical options for SUI could have created a recruitment bias, increasing participation of incontinent women with more UUI). Older epidemiology studies suggest that SUI is more common, but newer epidemiology suggests that UUI is, in fact, more common.

*Weight loss intervention:* In response to a participant question, Dr. Subak noted that, in the weight-loss intervention group, most participants lost weight, with some losing greater than 10 percent of baseline weight. This was an intensive approach, with a lot of participant time commitment. However, it may not matter how patients lose weight; research may be able to show that UI symptoms can improve with weight loss regardless of the method.

Notably, the lifestyle intervention was administered via small groups (10 to 15 women), and there were cohort dynamics within these weight-loss intervention groups, with some group dynamics being stronger than others. The group assignment was a controlled factor in all analyses.

## GROUP DISCUSSION

*All Participants*

Dr. Bavendam thanked the speakers for their excellent presentations. She commented that UI has a big impact on QOL, but it is far more than a QOL issue. UI is associated with a decrease in physical activity, which in turn is associated with many other medical conditions. Dr. Bavendam asked the participants to reflect on the presentations, as the discussion period provided an opportunity to voice any comments or reactions. The Summit participants provided the following comments:

- There is a lack of interaction between physicians and both continence nurse specialists and physical therapists to help patients with UI. Physical therapists and continence nurses design individualized treatments for their patients, discussing dietary management, exercise, weight loss, and pelvic floor muscle training. Behavioral therapy needs to be emphasized as a first line therapy before considering surgery. This message has not reached enough physicians. Physicians rarely refer their patients to physical therapy or continence nurse specialists.

- There is also an economic issue in supporting women to make the necessary lifestyle changes. Insurance companies do not reimburse nutritional changes and other lifestyle interventions. Patients may be reluctant to pay out of pocket, and this represents a significant obstacle for clinics that emphasize lifestyle changes.

- Education is also lacking. Women should be educated about practices that may help manage UI or maintain the gains they made in surgery. Education about pelvic floor health is needed.

- Treatment of UI is inherently interdisciplinary, and it would be useful to bring all the different skills and resources to where patients receive most of their care so that they do not have to visit many different specialists.

- UI is not a homogeneous disease. Every patient may present a different etiology that requires personalized treatment.

- Obesity has been normalized in this country; it is not politically correct to discuss obesity. This is a problem because it makes it difficult to educate patients about the benefits of weight loss.

- Women often have unrealistic expectations of their treatment. The disconnect between treatment reality and expected outcomes often leads to disappointment. Communication and education about reasonable expectations is needed.

- Men also suffer from incontinence, but there may need to be differences in how they are treated. For example, men do not respond well to group weight-loss strategies. They tend to do better when managing their weight individually.

- Physical therapists specializing in pelvic health issues can be found on the following website: www.womenshealthapta.org. Another resource is the North American Menopause Society (www.menopause.org), which lists providers trained in incontinence issues. Prevention and nonsurgical treatment should be at the forefront of initial management for incontinence.

- A participant noted that, from a treatment perspective, women are not simple; rather, they are multidimensional and complicated. Women need to be informed about their bodies, which change throughout the lifespan. Continuing conversations between women and their primary care professionals and nurses are required to navigate complicated health issues. Health professionals should develop nuanced questions to identify UI symptoms.

- Women in their 70s and 80s are much different than women in their 50s. It is important to consider these differences in designing trials and interpreting results. An attendee noted that the benefit of educating older women about the benefits of UI treatments will be amplified as they pass the information to their daughters. A classic geriatric principle is that many small changes will create multiple benefits, and this applies to incontinence as well. Treating women with UI likely will yield additional health benefits.

Dr. Bavendam thanked the participants for their reflections and the excellent discussion.

## BREAKOUT GROUPS

Dr. Bavendam explained that the participants would be divided into two breakout groups with different perspectives: that of non-surgeons (i.e., noninvasive healers, reference group) and surgeons. The task for the non-surgeon and surgeon breakout groups would be to develop key messages from the completed research (one or two per study) that should drive change in the field and to identify future research needs. The messages should be targeted to health care colleagues. All of the treatments are effective; the key is to differentiate which treatments work best in which situations.

Dr. Bavendam presented a model of UI as a journey that begins when a woman notices the first symptoms. As the symptoms continue or increase in severity, the woman recognizes that something is wrong, adapts to the symptoms, considers talking to a health care provider, adapts again, and then seeks specialty care when the burden of symptoms is too large to handle. Dr. Bavendam noted that it would be helpful to intervene earlier in the process to provide women with information about UI self-care and primary care options. Screening is another important issue.

Dr. Bavendam encouraged the participants to consider several questions during the breakout sessions:

1. Do we need better treatments?
2. Do we need better patient selection for current treatments?
3. Do we need standardized regimens for sequencing treatments?
4. What is the role of patient preference in starting treatments?

“Profiling” an individual patient with respect to causes and contributing factors for UI is another important concept for consideration. Many factors contribute to incontinence, including anatomy (ranging from normal to prolapse), innervation (ranging from normal to absent), and muscle function (ranging from normal to disuse atrophy). Two patients might present with the same symptoms, but their comorbidities, behaviors, and personal tendencies might vary widely. A primary care physician has limited time, and the primary action is to identify symptoms, address comorbidities, and prescribe a first-line treatment or self-care. Initiating women on the path to improvement is an important objective for clinical, research and health care payers.

In addition to developing key messages for colleagues, Dr. Bavendam asked the participants to consider the research needs to increase the number of women with UI who are successfully treated. She noted that the breakout groups should consider short, medium, and long time frame activities. She asked each group

to identify and sequence the top five future research priorities, noting that it is time to get started and make a difference.

Dr. Bavendam explained that the breakout groups would meet for 1 hour and 40 minutes before presenting their findings on key messages and research priorities to the whole group during the report back. Science writers would capture the key points during the discussion. The breakout groups broke for their task of developing main messages to clinician colleagues and determining the priorities for future research needs in the field. Dr. Marcel Salive, National Institute on Aging, moderated Breakout Group 1: Non-surgeons, and Dr. Ziya Kirkali, NIDDK, moderated Breakout Group 2: Surgeons.

## REPORT BACK

The two groups reported back in reverse order, with Breakout Group 2: Surgeons reporting first.

### Surgeons Breakout Session Report Back

Dr. Albo reported back from the surgeons' breakout session, including the take-home messages related to each study that were developed by the surgeons. The key messages included the following:

1. BACH: There are modifiable risk factors for UI and ethnic differences in health care-seeking behaviors. The concept of remission is intriguing, but it must be investigated further before being promoted as a message to avoid misinterpretation.
2. ATLAS: For patients with predominant SUI, it is reasonable to try a pessary alone or in combination with behavioral therapy.
3. BE-DRI: Adding behavioral therapy to antimuscarinics improves continence rates at 2 months. Behavioral therapy provides no additional benefit to keep patients off medication. It is impressive that after a short course of one anticholinergic women might be able to stop medication; another study is needed to investigate this further.
4. SISTEr: Both procedures lead to high levels of patient satisfaction. The higher efficacy of the autologous sling should be balanced with the issue of increased voiding dysfunction. Patient expectations need to be examined.
5. TOMUS: Either MUS procedure is a safe and effective option for uncomplicated patients with predominant SUI.
6. PRIDE: Modest weight loss improves incontinence.
7. ABC: onabotulinumtoxinA and solifenacin are both effective options. OnabotulinumtoxinA is more cost-effective at 9 months, and urinary retention rates are low and short in duration.

The surgeons' breakout group identified the following research priorities:

1. Investigate why individuals are not seeking care and the factors preventing patients from receiving care.
2. Study the function of normal and abnormal urethra, bladder, and pelvic muscle throughout developmental stages to better understand basic pathophysiology.
3. Develop tools to measure specific abnormalities.
4. Determine whether early intervention improves outcomes and reduces costs.
5. Develop an outpatient procedure for SUI (e.g., stem cell injections, a small sling).
6. Conduct a trial to compare MUS (mesh) and fascial (non-mesh) slings.
7. Investigate the efficacy of perioperative interventions (e.g., vitamin D).

#### *Discussion*

One message from the surgical trials is that none of the devices are free of complications; up to one-third of treatments fail. Better treatments are needed, and an improved understanding of the causes of UI will help to develop better treatments that target a variety of causes. A participant opined that the MUS is not the best procedure, and researchers are investigating new pathophysiological mechanism-based treatments (e.g., regenerative medicine, cell-based therapy).

UI is a major reason why older adults enter nursing homes. A useful avenue of research would be to investigate the efficacy of botulinum toxin in patients prior to nursing home admittance. The ABC trial enrolled patients older than 68 years, and several patients were older than 80 years, but the safety of onabotulinumtoxinA for older women should be assessed further.

Early intervention can be accomplished by incorporating a question about UI symptoms into a standard primary care form so that patients can be identified early and given the opportunity to enroll in prevention programs. Evidence could be developed for screening, but screening is expensive and there must be post-screening options for individuals identified with UI. It would be helpful to know whether intervention at age 30 prevents UI at age 50, similar to how intervening on blood pressure reduces cardiovascular disease 20 years later. It is easier to treat a patient with fewer symptoms, but it is harder to demonstrate a significant difference in a clinical trial. The public education component of UI also should be considered.

**Non-surgeons Breakout Session Report Back**

Dr. Marjorie Bowman reported back from the non-surgeons breakout session. The messages that the group decided needed to be conveyed to clinicians and to the public included the following:

1. There is a need to set realistic expectations about the possible range of improvement.
2. A variety of treatment options are available.
3. Misinformation is a significant problem, and education begins by dispelling myths about UI.
4. Increasing awareness of pelvic health through education campaigns and stigma reduction is important. A public figure could help accomplish this.
5. Screening for UI is important, but there are significant obstacles for clinicians which cannot be solved at the present meeting.
6. Tying UI to other campaigns and issues, such as nocturia or falls, could be a way to raise awareness.
7. UI is an important “vital sign” for healthcare providers to know about because it is associated with comorbidities and is a symptom of other potential health problems.

The non-surgeons breakout group identified the following research priorities:

1. Test the effectiveness of direct-to-consumer interventions.
2. Study the personal choices of female healthcare providers to determine what they believe is effective.
3. Investigate the long-term effects of treatments, including potential changes in the brain and pelvis that would ameliorate UI.
4. Conduct trials of common CAM treatments that are being used to treat UI.
5. Conduct secondary analysis of existing data and add supplements to existing trials.
6. Conduct more trials focusing on more vulnerable patients (age being one of many factors).
7. Investigations to better understand patient centered outcomes and motivate women to seek evaluation and treatment

***Discussion***

There is synergy and overlap between the surgeons and non-surgeons groups. Both groups agreed that investigating the effectiveness of direct-to-consumer treatments is important.

One participant noted that it would be useful to divide the study population of older vs. younger patients, because the pathophysiology could be different between the two groups. Older patients have very specific needs and safety considerations that younger patients do not. In addition, as the population around the world ages (China, for example, has a rapidly aging population), the special needs of older patients will become more important. NIH could investigate these needs by supporting international studies.

Another participant asked whether there is additional information about mechanisms and the pathophysiology of UI. How obesity relates to UI—the role of weight and inflammatory markers—remains to be understood.

It is also unknown whether long-term changes are reversible or not.

It was noted that the translational aspect is missing from mechanistic studies.

There is a need to advocate for incontinence and bladder issues as an important medical problem, to increase funding and accelerate research and translational work in this field.

## ESTABLISH WRITING GROUP

*Tamara Bavendam, M.D., M.S., NIDDK, NIH, Bethesda, MD*

Dr. Bavendam commented that the outcome of the meeting's discussions would be referenced within NIDDK, and she asked the participants if they thought that the key messages could be consolidated into a peer-reviewed manuscript worthy of publication. A participant commented that a publication would be a beneficial product to mark the 10-year anniversaries of the UITN and PFDN.

Several participants expressed support for the idea of presenting the status and future of clinical research on UI in women, contingent on whether the meeting discussion can be condensed into a coherent and compelling narrative. A review describing the six published studies would be a good way to increase the visibility of the topic and might help to attract research funding. The expert opinions voiced during the meeting could form the foundation of a research framework for the next 10 years, including the most important, paradigm-shifting scientific challenges to engage.

Dr. Bavendam acknowledged that developing a manuscript is an aspirational goal. She suggested that the participants review the meeting summary following completion. If several attendees are interested in developing a manuscript, Dr. Bavendam will establish a writing group to explore the feasibility of publication.

## CLOSING COMMENTS AND ADJOURNMENT

*Tamara Bavendam, M.D., M.S., NIDDK, NIH, Bethesda, MD*

Dr. Kirkali provided an update on the Symptoms of Lower Urinary Tract Dysfunction Research Network (LURN). The Network has been established, and investigators at six sites are developing protocols for self-reported measures for LUTS. Network objectives include successful treatments for LUTS and a

better understanding of the sensory aspects of LUTS. One goal of the Network is to better phenotype individuals through protocol development, as correct diagnoses enable individuals to receive better treatments.

Dr. Bavendam expressed appreciation for the interaction and participation of the attendees, many of whom represent a variety of federal agencies, . Dr. Bavendam stated that the speakers had done an excellent job summarizing their work. She said that the meeting represented a good first step toward identifying research needs. Dr. Bavendam explained that the notes from the meeting will be distributed to the participants for their feedback, and the attendees agreed that their email addresses could be shared with each other. Dr. Bavendam expressed appreciation for the participants' enthusiasm and energy and adjourned the meeting.

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