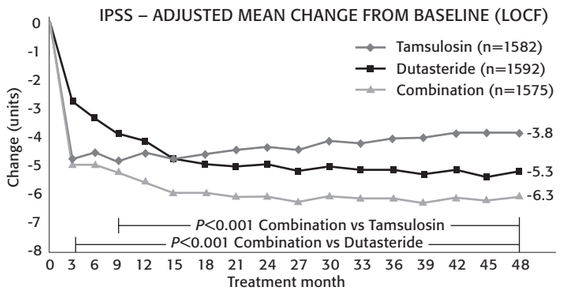
and bothersome symptoms similar to ABs but generally takes three to six months to see the affects. In six to twelve months the prostate should shrink approximately 25% yielding a reduction in PSA on average of approximately 50%.[24] The rationale for reducing prostate size is based on the fact that prostate volume increases by a mean of approximately 3.5% to 5% annually in men with BPH over 50 years of age in clinical trials up to 4.5 years. As the prostate grows it constricts the urethra resulting in variable levels of obstruction and/or irritative urinary symptoms. In severe cases, urine flow is completely obstructed. In a 4-year controlled clinical study, 12% of men with symptomatic BPH receiving an alpha blocker alone (n=1611) progressed to AUR or BPH-related surgery.[25]

**TABLE 7.** 5-ALPHA REDUCTASE INHIBITORS

| 5ARIs BLOCK CONVERSION OF TESTOSTERONE TO DIHYDROTESTOSTERONE | |
|---|---|
| Blockage of pathway 2 | Blockage of pathway 1 and 2 |
| Finasteride 5 mg daily | Dutasteride 0.5 mg daily |

Although it was initially thought that monotherapy with 5ARIs would suffice, better results have been seen with combination therapy using an AB and a 5ARI in two major studies using the different medications.[26] Figure 3 is an example of the beneficial results of combination therapy. Current thinking is that the patient should start on combination therapy (if they have an enlarged prostate) and stay on combination therapy.

**FIGURE 3.** EFFECTS OF MONO THERAPY AND COMBINATION THERAPY ON INTERNATIONAL PROSTATE SYMPTOM SCORE (IPSS)




With inhibition of the conversion of testosterone to dihydrotestosterone side effects which may occur with use of the 5ARIs include: diminished ejaculatory volume, erectile dysfunction, decreased libido and gynecomastia.[15]

Unlike ABs that produce results within two to four weeks, 5ARIs may take three to six months. A benefit of using combination therapy is that the AB should produce some initial symptom relief. Patients should be educated on what to do if they experience worsening of symptoms while on combination therapy. If minimal or no response is noted, then the provider must consider the patient to have a prostate refractory to therapy, or possibly OAB.

### STEP 4.

Patients showing little to no response to behavioral modification along with mono or combination pharmacological therapy should be considered for OAB or referred to a specialist.

### DISCUSSION OF QUESTION 5

The correct answer is A, yes. Let's consider that the patient has one of two situations in which both treatment of OAB and BPH is appropriate. First, he has urgency, frequency and nocturia treated with an antimuscarinic, but still has a weak flow. Two, his stream is improved with the AB or AB/5ARI, but he still has bothersome urgency, frequency and nocturia. Both of these scenarios are outlined in figure 1. Although there is no formal guidance for the use of antimuscarinics with Abs and/or 5ARIs, the provider may be able to elicit symptoms of both storage and irritative voiding symptoms and treat appropriately.[4,26,27]

### SUMMARY

We have presented a case of male LUTS. Although generally thought to be caused by an obstructing prostate, the fact remains that the bladder can also be the source of the problem. Understanding normal genitourinary function allows the provider to identify abnormal activity. Flow and volume voided are essential in the patient history. A history of poor flow is more indicative of the prostate being behind the symptoms, whereas, decreased volumes and frequent voids are consistent with bladder problems.

Using a logical, conscientious approach LUTS can be treated effectively and safely in the office of the PCP.

*Supported by educational grants from Pfizer and Astellas.*

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CONTINUING MEDICAL EDUCATION PROJECT:

# Lower Urinary Tract Symptoms in Males: OAB vs BPH

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Disclosure record for Matt Toren Rosenberg, M.D.
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Astellas: Consultant or Advisor; GlaxoSmithKline: Consultant or Advisor; Pricara: Consultant or Advisor; Allergan: Consultant or Advisor; Forest: Meeting Participant or Lecturer; Pfizer: Consultant or Advisor; Watson: Consultant or Advisor; Bayer: Consultant or Advisor; Endo Pharma: Consultant or Advisor; Dong-A-Pharmtech: Consultant or Advisor; Purdue: Consultant or Advisor

American Urological Association Education and Research, Inc.

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**LEARNING OBJECTIVES:**

1. Correctly identify lower urinary tract symptoms (LUTS) in a male
2. Differentiate overactive bladder (OAB) symptoms from those of benign prostatic hyperplasia (BPH)
3. Understand the importance of urinary flow and volume voided in evaluation of LUTS
4. Develop a treatment plan for OAB and BPH

## 52 year old Male with Urinary Urgency, Frequency and Nocturia…

Two 52 year old patients, husband and wife in otherwise good health, present to your practice with urinary urgency, frequency and nocturia. Assuming that no abnormalities are noted on physical examination or laboratory review most providers will tend to conclude that the female has OAB and the male suffers from BPH. Why is it that these two patients with similar symptoms would commonly receive different initial therapy? Since obstruction is unlikely in a female, OAB is a logical assumption. However, in the male patient, though the initial empiric diagnosis of BPH may be correct, the fact remains that not all cases of male LUTS equate to BPH.

*Let's go back on the evaluation of the male to see if there are some clues to the etiology of his LUTS.*

As mentioned, this is a healthy 52 year old male with urinary frequency, urgency and nocturia. Upon further history he reports a good stream with what seems to be low volumes. He states that these symptoms have been progressive over the last few years. His primary concern is that he fears he may have an episode of incontinence if he cannot find a restroom in a timely manner. He further states that he is presenting at the urging of his wife who is tired of his frequent nighttime trips to the bathroom that disrupt her sleep.

His past medical history is remarkable for hyperglycemia which has been diet-controlled and hypertension. His only surgery was a vasectomy and he has no allergies. Medications include Lisinopril 10 mg per day. Review of systems is otherwise unremarkable aside from those symptoms mentioned earlier. He states he drinks 6 cups of coffee per day, has never smoked and only drinks alcohol socially. Family history is remarkable for his father having poorly controlled diabetes treated with insulin.

### PHYSICAL EXAMINATION

| | |
|---|---|
| Vital Signs | T: 98.3, BP: 120/78, HR: 65, RR: 16 |
| General | Well developed, well nourished |
| Cardiac | Regular rate and rhythm, no murmurs |
| Chest | Clear to auscultation in all fields |
| Abdomen | Soft, non tender, no masses, no hernia |
| Genitourinary | Circumcised phallus with normal meatus , no discharge noted, normal testes |
| Rectal | Normal sphincter tone, no impacted stool, smooth non tender prostate, guaiac negative |
| Extremities | No cyanosis, varicosities or edema, normal distal pulses |
| Back | No tenderness noted |

### LABORATORY EVALUATION

| | |
|---|---|
| Fasting blood glucose | 98 mg/dl |
| Prostate specific antigen | 1.7 ng/ml |
| Renal function | Not indicated by current guidelines |
| Urinalysis | Normal for all parameters |
| Urine cytology | Only indicated in presence of hematuria. Could be considered if patient at high risk (eg. Smoker) |

**QUESTION 1:** What further tests or information would be of use?
A. Bladder diary
B. Post void residual
C. Urodynamic testing
D. Cystoscopy
E. A and B

**QUESTION 2:** What is the most probable diagnosis?
A. Benign prostatic hyperplasia
B. Overactive bladder
C. Urinary tract infection
D. Normal changes of aging
E. Excessive fluid intake

**QUESTION 3:** What are your treatment options?
A. Refer to a specialist
B. Discussion and implementation of behavioral changes only
C. Pharmacological therapy alone
D. Surgical intervention
E. Behavioral changes with consideration of medications

**QUESTION 4:** Would your treatment plan change if the same patient presents with a weakened or poor urinary flow and only minimal irritative symptoms?
A. No change in treatment plan necessary
B. Immediate referral to Urologist
C. Treat benign prostatic hypertrophy in addition to overactive bladder
D. Treat for benign prostatic hypertrophy and gauge response
E. Additional testing required

**QUESTION 5:** Can you treat for both OAB and BPH together?
A. Yes
B. No

### DISCUSSION

This patient presents with history, physical exam, and laboratory findings consistent with OAB. Though this condition is most often associated with female patients, it is a prevalent cause of LUTS in the male population along with BPH.[1] In fact, OAB affects approximately 33 million Americans, with equal prevalence in men and women of about 16-17%.[2] Kaplan, et al showed that the majority of men under 50 years of age with LUTS do not, in fact, have BPH and that their symptoms are likely attributable to another cause.[3] Unfortunately, if the patient is treated for the wrong diagnosis and the prescribed therapy does not resolve the symptoms they may suffer needlessly or even undergo unnecessary prostate surgery.[4] The impact of OAB is highly significant as untreated patients are at increased risk of falls (and subsequent fractures), decreased quality of life, depression and impaired activities of daily living.[1,5] The correct pharmacologic treatment of LUTS, no matter the underlying cause, has been shown to be economically effective.[6,7]

As the first, and sometimes the only, provider that these patients may see, the Primary Care Provider (PCP) is in a unique position to offer counseling, education and treatment.[8] To do this, the PCP must look beyond the idea that LUTS in the male always equates to BPH, and could, in fact be something else.

## DISCUSSION OF QUESTION ONE

The correct answer is E, information from the bladder diary and a post void residual would be useful at this juncture. However, before further discussion on the tests, it is important to understand how the symptoms are guiding the differential diagnosis. This patient is presenting with lower urinary tract symptoms of urgency, frequency, and nocturia without symptoms of urinary tract obstruction. LUTS can be urologically based, which includes the prostate and the bladder, or medically based. The goal of a comprehensive history and physical and laboratory evaluation is to seek out any potential causes. For example, diabetes causing polyuria and polydipsia, a urinary tract infection or just an unfortunate habit of drinking excessive fluids. In addition, medications may cause diuresis, alter normal sphincter control or mimic other urinary symptoms. (Table 1)

**TABLE 1.** MEDICATIONS THAT CAN CAUSE LUTS

| | |
|---|---|
| Sedatives | Confusion, secondary incontinences |
| Alcohol, Caffeine, Diuretics | Diuresis |
| Anticholinergics | Impair detrusor contractility, voiding difficulty, overflow incontinence |
| α – Agonists | Increased outlet resistance, voiding difficulty |
| ß - Blockers | Decreased urethral closure, stress incontinence |
| Calcium-Channel Blockers | Reduce bladder smooth muscle contractility |
| Angiotensin Converting Enzyme | Induce cough, stress urinary incontinence |
| First generation antihistamines | Increase outlet resistance |
| Cholinesterase inhibitors | Precipitate urge incontinence |
| Opiods | Constipation |

If no reversible causes are found, then we can turn our focus to the bladder and the prostate to see if they are functioning in a normal fashion. Understanding normal function is paramount to identifying abnormal function. Normal bladder function is to store approximately 300-500 ml of urine before emptying with adequate warning of a gentle urge sensation. Normal prostate function (in addition to creation of fluid for seminal emission) is to allow free urinary flow and not obstruct. Question 1 addresses the tests that may be of assistance when determining normal versus abnormal function. It is important to note that if the flow is poor we should think obstruction and no further tests are needed (this will be discussed later). However, this patient denies obstructive symptoms and complains of symptoms that are irritative in nature. (Table 2)

**TABLE 2.** LUTS ASSOCIATED WITH THE BLADDER AS OPPOSED TO THE PROSTATE

| STORAGE/IRRITATIVE (BLADDER) | VOIDING/OBSTRUCTIVE (PROSTATE) |
|---|---|
| Urgency | Hesitancy |
| Frequency | Poor flow/weak stream |
| Nocturia | Intermittency |
| Urge incontinence | Straining to void |
| Stress incontinence | Terminal dribble |
| Mixed incontinence | Prolonged urination |
| Overflow incontinence | Urinary retention |

At this point we need to assess how the bladder is functioning. For example, is the patient having urgency and frequency as a result of incomplete voiding? Is the patient voiding frequently of large amounts which would not be a problem of the bladder, but rather reflective the volume of fluid coming to the bladder from the kidneys.

The correct answer for question one is E, both checking a bladder diary and a post void residual are appropriate. By asking the patient to produce a bladder diary, one can quantify voiding frequency and volumes, as well as identify behavioral problems as opposed to ones of pathologic origin. It is also notable that by keeping a diary the patient will become aware of their habits and find opportunities for improvement. The diary can also help monitor treatment.[9] Checking a post void residual (PVR) is used to confirm that the patient is not having irritative symptoms from incomplete emptying that may be a symptom of a neurogenic bladder or severe obstruction. Whereas, it is true that most PCP's will not have a device to scan the bladder in the office, they will have access to a standard ultrasound unit at a local hospital or diagnostic center. If the PVR is less than 50 ml, the chance that they have a significant obstruction or a neurogenic bladder is highly unlikely.[4] The PCP should feel very confident that treating OAB in a patient with low PVR is safe and will not result in urinary retention.

There is no need for urodynamic testing unless the patient has an identified neurologic issue or is refractory to therapy. A cystoscopy will not provide further information and should only be performed in patients with hematuria or who are refractory to therapy. One can consider a cystoscopy as an option in high risks patients (i.e. those with a history of smoking).

## DISCUSSION OF QUESTION TWO

The answer is B, overactive bladder. The patient's symptoms are most consistent with bladder irritation (urgency, frequency and nocturia) and as noted by his diary, he is voiding frequently of small amounts.

BPH is unlikely as he is not presenting with typical symptoms of prostatic obstruction (hesitancy, double voiding, dribbling or interrupted flow) and he actually has a good flow. So what defines a good flow? It is difficult to offer an absolute measurement for "good flow", but it can be described as a smooth, arc-shaped curve with high amplitude, as opposed to a "poor flow" which would be weak, flat, asymmetric or interrupted with multiple peaks.[4] Most men will understand this terminology and can reference it in description of their own habits.

In regards to the other options in the question, we have confirmed the absence of infection with the urinalysis and LUTS is not a normal change of aging and should not be tolerated in the symptomatic patient.[4]

The issue of excessive volume intake is of interest. We did identify that the patient drinks quite a bit a coffee and this could exacerbate his symptoms at times. However, he still needs to void when his bladder is not close to being full, as demonstrated by bladder diary. Regardless of the chosen treatment plan, the PCP may suggest watching the fluid intake as it may make the symptoms worse.

## DISCUSSION OF QUESTION THREE

The correct answer is E, behavioral changes with consideration of medications. Similar to other disease states, behavioral modifications is the cornerstone of therapy. Whether it is learning to time voids, limit fluids or stand at the toilet long enough to make sure one empties to completion, awareness and alteration of habits becomes very useful.[10] Again the bladder diary plays a key role in identification of potentially modifiable habits. Diet can also play a role. Studies have shown that an increased intake of high energy foods (food containing a large amount of caffeine) and protein may be a risk factor for LUTS.[11] Likewise, a diet rich in vegetables and beta carotene, lutein and vitamin C may help symptoms.[12]

When considering pharmacological therapy one must still implement the behavioral modifications. Burgio et al conducted a crossover study among older women with urge incontinence (UI) to compare the effects of behavioral therapy, drug therapy, and their combination on patients' baseline frequency of UI episodes. Patients receiving behavioral therapy alone in the initial study phase had a 57% reduction in the frequency of UI, which increased to an 89% reduction after the addition of drug therapy. Similarly, patients receiving drug therapy alone in the initial phase had a 73% reduction in the frequency of UI, which increased to an 84% reduction after the addition of behavioral therapy. The authors concluded that combination therapy yields better outcomes.[13]

In regard to pharmacologic management of OAB, antimuscarinics are the first line of drug therapy. (Tables 3 and 4) As all antimuscarinics have been proven effective , the choice should be based on efficacy, dose flexibility, adverse event profiles and drug interactions.[14] There are both immediate release and extended release medications.[15] The extended release medications have a better tolerability than their immediate release counterparts. Though the exact mechanism of action of these drugs is unknown, it is thought that they may work on the efferent or afferent pathways. In the US there are multiple compounds to choose from, 2 are topical and the rest are oral. Of the oral medications, most are hepatically metabolized and one is renally excreted.

**TABLE 3.** IMMEDIATE RELEASE ANTIMUSCARINICS

| DRUG | DOSING | DOSE | METABOLISM |
|---|---|---|---|
| Oxybutynin IR | 2 – 4 times per day | 5 mg | Hepatic |
| Tolterodine IR | Twice per day | 1 -2 mg | Hepatic |
| Trospium Chloride | Twice per day | 20 mg | Renal |

**TABLE 4.** EXTENDED RELEASE ANTIMUSCARINICS

| DRUG | DOSING | DOSE | METABOLISM |
|---|---|---|---|
| Darifenacin | Daily | 7.5 mg, 15 mg | Hepatic |
| Fesoterodine | Daily | 4 mg, 8 mg | Hepatic |
| Oxybutynin ER | Daily | 5 – 30 mg | Hepatic |
| Oxybutynin TDS | Twice per week | 3.9 mg | Hepatic |
| Oxybutynin 10% gel | Daily | 100 mg | Hepatic |
| Solifenacin | Daily | 5 mg, 10 mg | Hepatic |
| Tolterodine ER | Daily | 5 mg | Hepatic |
| Trospium Chloride | Daily | 60 mg | Renal |

The most common side effects of the antimuscarinics include dry mouth, constipation, headache and blurred vision.[16] These common side effects are generally tolerable, however, the balance of tolerability and efficacy should be discussed with each patient. It is important to note that antimuscarinics are contraindicated in patients with urinary or gastric retention or uncontrolled narrow-angle glaucoma. (PDR)

Follow up for patients starting antimuscarinic therapy should occur within two to four weeks after initiation.[4] This is also a good time to consider checking PVR to ensure that volume is not increasing.[17] The risk of urinary retention, though studies have proven to be low overall, is highest during the first month of treatment. Not all patients will respond to starting doses, so be prepared to titrate medication as studies have shown that greater than 50% of patients will increase dose with improved efficacy if given the option.[18] It is advisable to try several medications before considering the patient refractory to therapy and referring off to a specialist.

There have been no indications for referral noted in this particular patient.[4] (Table 5) However, if the provider is uncomfortable initiating treatment, referral is appropriate.

**TABLE 5.** WHEN TO UTILIZE THE SPECIALIST

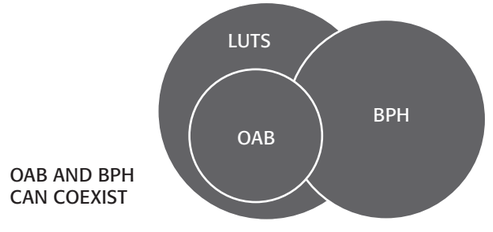
| INDICATION FOR REFERRAL |
|---|
| History of recurrent urinary tract infections or other infection |
| Microscopic or gross hematuria |
| Prior genitourinary surgery |
| Elevated prostate-specific antigen |
| History of genitourinary trauma |
| Abnormal prostate exam |
| Suspicion of neurological cause of symptoms |
| Meatal stenosis |
| Pelvic Pain |
| Uncertain diagnosis or patient choice |

Surgical intervention is certainly outside of the realm of the PCP and should be considered for the patients refractory to conservative therapy or those who prefer to avoid medications.

## DISCUSSION OF QUESTION FOUR

The correct answer is D, treat benign prostatic hyperplasia and gauge response. As we recall the information given earlier on prostate function, a poor flow is highly predictive of an obstructive cause. This is not to say that you can't have both OAB and BPH symptoms presenting together (Figure 1), however, it is most prudent to treat the more problematic issue first to see how symptoms respond.[4]

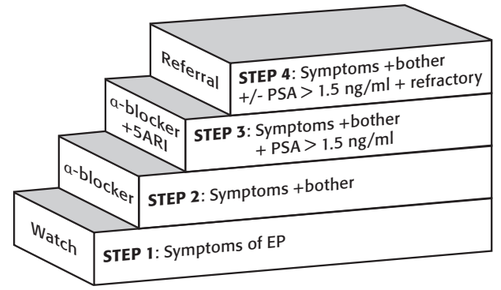
**FIGURE 1.** RELATIONSHIP OF OAB, BPH AND LUTS




Similar to the treatment of OAB, BPH therapy begins with behavioral modification.[19] After that, the options include alpha-blockers (ABs), 5 alpha-reductase inhibitors (5ARIs) or combination of the two.

In 2010, Rosenberg , et al. proposed a stepwise approach to the treatment of BPH which was dependent upon level of perceived patient bother and prostate size (as determined by PSA).[20] (Figure 2)

**FIGURE 2.** STEPS: SIMPLIFIED TREATMENT OF THE ENLARGED PROSTATE




### STEP 1.

Before any intervention is offered, bother must be ascertained. If a patient chooses watchful waiting then he should be made aware that BPH is a progressive disease and that patients with an enlarged prostate are at higher risk of worsening flow, acute urinary retention and need for surgery in the future.[21]

### STEP 2.

A symptomatic patient (one with bother) is generally ready to accept treatment. A small prostate (<30 grams) can be treated with an AB alone, whereas the larger prostate (>30 grams) would do better with combination of an AB and a 5ARI.[20] Unfortunately, even an experienced provider will have difficulty gauging prostate size with a finger examination and most PCP's will not have the ability to readily measure a prostate with ultrasound. In 1999, Roehrborn wrote a seminal piece showing that PSA can be used as a surrogate marker for prostate size and that a level of 1.5 ng/ml in any age male equates to a minimal size of 30 grams.[22] In Step 2, a bothered patient with a small prostate is started on an AB alone.

ABs work via inhibition of α1-adrenergic mediated contraction of the prostatic smooth muscle, thereby relieving bladder outlet obstruction.[23] These medications generally improve flow and reduce bothersome symptoms within days to weeks. It is important to note that ABs do not affect prostate size or interfere with the natural progression of the disease. There are uroselective and non-uroselective ABs. (Table 6).

**TABLE 6.** ALPHA BLOCKERS

| NON - UROSELECTIVE | UROSELECTIVE |
|---|---|
| Terazosin 1, 2, 5, 10 mg daily | Tamsulosin 0.4 mg daily |
| Doxazosin 1, 2, 4, 8 mg daily | Alfuzosin 10 mg daily |
| | Silodosin 8 mg daily |

Though all the medications have potential side effects, the incidence is decreased with the uroselective agents. The potential side effects include: asthenia, fatigue, dizziness, postural hypotension, congestion, rhinitis and abnormal ejaculation.[15]

Follow up for patients on AB should be within two to four weeks as this is a sufficient length of time for the medication to take effect.[4] If minimal or no response is noted, then the provider must consider the patient to have a prostate refractory to therapy, or possibly OAB.

### STEP 3.

A symptomatic patient with a large prostate as indicated by PSA > 1.5 ng/ml (prostate > 30 g) may be treated with a combination AB and 5ARI. Utilization of ABs has already been described in the prior section. 5ARIs work by blocking the conversion of testosterone to dihydrotestosterone (DHT), blocking DHT both shrinks and prevents further growth of the prostate.(Table 7) Reduction in size improves flow

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## QUESTION RESPONSES

| Q# | A | B | C | D | E |
|---|---|---|---|---|---|
| 1 | Ⓐ | Ⓑ | Ⓒ | Ⓓ | Ⓔ |
| 2 | Ⓐ | Ⓑ | Ⓒ | Ⓓ | Ⓔ |
| 3 | Ⓐ | Ⓑ | Ⓒ | Ⓓ | Ⓔ |
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## PROGRAM EVALUATION

**Scale:** P=Poor F=Fair G=Good VG=Very Good E=Excellent

| | | P | F | G | VG | E |
|---|---|---|---|---|---|---|
| **LEARNING OBJECTIVES** | | | | | | |
| 1 | Correctly identify lower urinary tract symptoms (LUTS) in a male | ① | ② | ③ | ④ | ⑤ |
| 2 | Differentiate overactive bladder (OAB) symptoms from those of benign prostatic hyperplasia (BPH) | ① | ② | ③ | ④ | ⑤ |
| 3 | Understand the importance of urinary flow and volume voided in evaluation of LUTS | ① | ② | ③ | ④ | ⑤ |
| 4 | Develop a treatment plan for OAB and BPH | ① | ② | ③ | ④ | ⑤ |
| **CONTENT** | | **P** | **F** | **G** | **VG** | **E** |
| 5 | To what extent this activity is fair and balanced. | ① | ② | ③ | ④ | ⑤ |
| 6 | Likelihood that you will implement change in your practice based on information from this activity. | ① | ② | ③ | ④ | ⑤ |
| 7 | Your OVERALL rating of this activity. | ① | ② | ③ | ④ | ⑤ |
| **PRACTICE** | | **P** | **F** | **G** | **VG** | **E** |
| 8 | I am better equipped to differentiate OAB and BPH. | ① | ② | ③ | ④ | ⑤ |
| 9 | I am better equipped to prescribe behavioral changes in place of or to complement other therapies. | ① | ② | ③ | ④ | ⑤ |
| 10 | How will you use the information presented to improve the care of your patients? | | | | | |

**SIGNATURE** **DATE**