Minimally invasive treatments grab BPH spotlight

New approaches preserve ejaculation, may eliminate need for medication

Lisette Hilton / UT Correspondent

Minimally invasive surgical options took front and center this year when the AUA published its revised guideline on the surgical management of male lower urinary tract symptoms secondary to BPH.

The revised guideline includes recommendations for the UroLift and Rezum devices, which received FDA clearance in 2013 and 2015, respectively.

“In patients who have bothersome symptoms and have prostates of 30 to 80 grams, the UroLift and Rezum are reasonable options,” said guideline co-author Steven A. Kaplan, MD, professor of urology at the Icahn School of Medicine at Mount Sinai in New York and director of New approaches preserve ejaculation, may eliminate need for medication

Please see BPH, on page 40

UroLift System
- Uses permanent transprostatic implants to open the prostatic urethra by compressing the prostate parenchyma

Rezum System
- Uses sterile water vapor thermal therapy to ablate obstructive prostate tissue

AquaBlation/AquaBeam System
- Combines real-time imaging, autonomous robotics, and waterjet ablation for targeted removal of prostate tissue

Prostatic Artery Embolization
- Microscopic beads are used to block blood flow to specific areas of the prostate, depriving cells of oxygen

AUA GUIDELINE RECOMMENDATIONS

Recommended for treatment of prostates <80 grams with side lobe enlargement and absence of obstructive middle lobe

Recommended for treatment of prostates <80 grams; evidence of longer term retreatment rates remains limited

Recent data not ready for review when AUA panel developed guideline

Not recommended outside the context of a clinical trial

Images (from left) courtesy of NeoTract/Teleflex, Boston Scientific, PROCEPT BioRobotics, Embolx

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In this interview, Andrew Portis, MD, of HealthEast Kidney Stone Institute, St. Paul, MN, discusses his experience with ureteral access sheaths and describes an algorithm for their selection and use.

Q&A
Andrew Portis, MD
UAS BEST PRACTICES

For the full article, please turn to page 32
MAKE NOCTIVA THE ONE

for your patients who awaken 2 or more times per night to urinate

Specifically engineered to provide the lowest effective and safe dose of desmopressin on the market.

Significantly reduced nighttime urine production

Gave patients over 4 hours of uninterrupted sleep

Significantly increased the number of nights with 0 or 1 void

IMPORTANT SAFETY INFORMATION

WARNING: HYPONATREMIA

See full prescribing information for complete boxed warning.

- NOCTIVA can cause hyponatremia. Severe hyponatremia can be life-threatening, leading to seizures, coma, respiratory arrest, or death.
- NOCTIVA is contraindicated in patients at increased risk of severe hyponatremia. See Important Safety Information below for full contraindications.
- Ensure serum sodium is normal before starting or resuming NOCTIVA. Measure serum sodium within 7 days and approximately 1 month after initiating therapy or increasing the dose, and periodically during treatment. More frequently monitor patients ≥65 years of age and those at increased risk of hyponatremia.
- If hyponatremia occurs, NOCTIVA may need to be discontinued.

INDICATIONS AND USAGE

NOCTIVA is a vasopressin analog indicated for the treatment of nocturia due to nocturnal polyuria in adults who awaken at least 2 times per night to void.

Limitation of Use: Not studied in patients younger than 50 years of age.
THE SIMPLICITY OF

ONE spray
ONE nostril
ONE time a night

With NOCTIVA™ (desmopressin acetate) Nasal Spray, you can give your patients relief tonight and better functioning tomorrow.¹

Order samples at NoctivaHCP.com/UT

CONTRAINDICATIONS
NOCTIVA is contraindicated in patients with the following conditions: hyponatremia or a history of hyponatremia, polydipsia, primary nocturnal enuresis, concomitant use with loop diuretics or systemic or inhaled glucocorticoids, estimated glomerular filtration rate <50 mL/min/1.73 m², syndrome of inappropriate antidiuretic hormone secretion (SIADH), during illnesses that can cause fluid or electrolyte imbalance, congestive heart failure (New York Heart Association Class II-IV), and uncontrolled hypertension.

WARNINGS AND PRECAUTIONS
• Fluid retention: Not recommended in patients at risk of increased intracranial pressure or history of urinary retention. Monitor volume status in patients with NYHA Class I congestive heart failure.
• Nasal conditions: Discontinue in patients with concurrent nasal conditions that may increase absorption, until resolved.

ADVERSE REACTIONS
Common adverse reactions in clinical trials (incidence >2%) included nasal discomfort, nasopharyngitis, nasal congestion, sneezing, hypertension, back pain, epistaxis, bronchitis, and dizziness.

DRUG INTERACTIONS
Monitor serum sodium more frequently when NOCTIVA is concomitantly used with drugs that may cause water retention and increase the risk for hyponatremia.

USE IN SPECIFIC POPULATIONS
• Pregnancy: Use of NOCTIVA is not recommended.
• Pediatric: Do not use NOCTIVA for primary nocturnal enuresis in children.

To report SUSPECTED ADVERSE REACTIONS, contact Avadel at 1-877-638-4579 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Please see full Brief Summary on the following pages.

NOCTIVA™ (desmopressin acetate) Nasal Spray

The following is a brief summary. Please consult Full Prescribing Information for complete details.

**WARNING: HYPONATREMIA**

- NOCTIVA can cause hyponatremia. Severe hyponatremia can be life-threatening, leading to seizures, coma, respiratory arrest, or death.
- NOCTIVA is contraindicated in patients at increased risk of severe hyponatremia, such as patients with excessive fluid intake, illnesses that can cause fluid or electrolyte imbalances, and in those using loop diuretics or systemic or inhaled glucocorticoids.
- Ensure serum sodium concentrations are normal before starting or resuming NOCTIVA. Measure serum sodium within 7 days and approximately 1 month after initiating therapy or increasing the dose, and periodically during treatment. More frequently monitor serum sodium in patients 65 years of age and older and in patients at increased risk of hyponatremia.
- If hyponatremia occurs, NOCTIVA may need to be temporarily or permanently discontinued.

**INDICATIONS AND USAGE**

NOCTIVA is indicated for the treatment of nocturia due to nocturnal polyuria in adults who awaken at least 2 times per night to void.

Nocturnal polyuria was defined in the NOCTIVA clinical trials as nighttime urine production exceeding one-third of the 24-hour urine production.

Before starting NOCTIVA:
- Evaluate the patient for possible causes for the nocturia, including excessive fluid intake prior to bedtime, and optimize the treatment of underlying conditions that may be contributing to the nocturia.
- Confirm the diagnosis of nocturnal polyuria with a 24-hour urine collection, if one has not been obtained previously.

Limitation of Use: NOCTIVA has not been studied in patients less than 50 years of age.

**CONTRAINDICATIONS**

NOCTIVA is contraindicated in patients with the following conditions due to an increased risk of severe hyponatremia:
- Hyponatremia or a history of hyponatremia [see Warnings and Precautions]
- Polydipsia
- Primary nocturnal enuresis [see Use in Specific Populations]
- Concomitant use with loop diuretics [see Warnings and Precautions]
- Concomitant use with systemic or inhaled glucocorticoids [see Warnings and Precautions, Drug Interactions]
- Renal impairment with an estimated glomerular filtration rate (eGFR) below 50 mL/min/1.73 m² [see Use in Specific Populations]
- Known or suspected syndrome of inappropriate antidiuretic hormone (SIADH) secretion
- During illnesses that can cause fluid or electrolyte imbalance, such as gastroenteritis, salt-wasting nephropathies, or systemic infection
- NOCTIVA is contraindicated in patients with the following conditions because fluid retention increases the risk of worsening the underlying condition:
  - Congestive heart failure (New York Heart Association Class II to IV) [see Warnings and Precautions]
  - Uncontrolled hypertension

**WARNINGS AND PRECAUTIONS**

**Risk of Hyponatremia:** NOCTIVA can cause hyponatremia. [see Boxed Warning and Adverse Reactions]. Severe hyponatremia can be life-threatening if it is not promptly diagnosed and treated, leading to seizures, coma, respiratory arrest, or death.

NOCTIVA is contraindicated in patients at increased risk of severe hyponatremia, such as those with excessive fluid intake, those who have illnesses that can cause fluid or electrolyte imbalances, and in those using loop diuretics or systemic or inhaled glucocorticoids [see Boxed Warning, Contraindications, and Drug Interactions].

Before starting or resuming NOCTIVA, ensure that the serum sodium concentration is normal. Consider the 0.83 mcg dose as the starting dose for patients who may be at risk for hyponatremia.

When NOCTIVA is administered, fluid intake in the evening and nighttime hours should be moderated to decrease the risk of hyponatremia. Monitor the serum sodium concentration within 7 days and approximately 1 month of initiating NOCTIVA or increasing the dose, and periodically thereafter. The frequency of serum sodium monitoring should be based on the patient’s risk for hyponatremia. For example, more frequent monitoring is recommended for patients 65 years of age or older or those on concomitant medications that can increase the risk of hyponatremia, such as tricyclic antidepressants, selective serotonin reuptake inhibitors, nonsteroidal anti-inflammatory drugs (NSAIDs), chlorpromazine, carbamazepine, and thiazide diuretics [see Drug Interactions].

If hyponatremia occurs, NOCTIVA may need to be temporarily or permanently discontinued, and treatment for the hyponatremia instituted, depending on the clinical circumstances, including the duration and severity of the hyponatremia.

**Fluid Retention:** NOCTIVA can cause fluid retention, which can worsen underlying conditions that are susceptible to volume status. Therefore, NOCTIVA is contraindicated in patients with New York Heart Association Class II to IV congestive heart failure or uncontrolled hypertension [see Contraindications]. In addition, NOCTIVA is not recommended in patients at risk for increased intracranial pressure or those with a history of urinary retention, and should be used with caution (e.g., monitoring of volume status) in patients with New York Heart Association Class I congestive heart failure.

**Concurrent Nasal Conditions:** Discontinue NOCTIVA in patients with concurrent nasal conditions that may increase systemic absorption of NOCTIVA (e.g., atrophy of nasal mucosa, and acute or chronic rhinitis), because the increased absorption may increase the risk of hyponatremia. NOCTIVA can be resumed when these conditions resolve.

**ADVERSE REACTIONS**

The following adverse reaction is described elsewhere in the labeling:
- Hyponatremia [see Boxed Warning and Warnings and Precautions]

**Clinical Trials Experience:** Because clinical trials are conducted under widely varying conditions, the adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Two randomized, double-blind, placebo-controlled, multicenter trials conducted in adults 50 years of age and older evaluated the efficacy and safety of NOCTIVA nasal spray compared to placebo. At baseline, 1,045 patients treated with NOCTIVA 0.83 mcg or 1.66 mcg, or placebo, had nocturia due to nocturnal polyuria, waking at least 2 times per night to urinate. Nocturnal polyuria was defined as nighttime urine production exceeding one-third of the 24-hour urine production. The mean age of the patients studied with nocturia due to nocturnal polyuria was 67 years with 42% between 50 and 64 years of age, and 58% aged 65 years and older. Fifty-seven percent were men and 43% were women. Caucasians comprised 79%, Blacks 12%, Hispanics 6%, and Asians 2% of the trial population.

During these trials, serious adverse reactions were reported in 2%, 2%, and 3% of patients with nocturia due to nocturnal polyuria treated with NOCTIVA 0.83 mcg, NOCTIVA 1.66 mcg, and placebo, respectively. There was one case of hyponatremia in the 1.66 mcg group and one case in the placebo group classified as serious adverse reactions.

Adverse Reactions Leading to Discontinuation: Among patients with nocturia due to nocturnal polyuria, the discontinuation rate due to adverse reactions was 4.0% with NOCTIVA 0.83 mcg, 4.4% with NOCTIVA 1.66 mcg, and 2.3% with placebo. Table 1 displays the most common adverse reactions leading to discontinuation in patients with nocturia due to nocturnal polyuria.

**Table 1: Most Common Adverse Reactions (>2 Incidences) Leading to Discontinuation in Patients With Nocturia Due to Nocturnal Polyuria in 2 Double-Blind, Placebo-Controlled Clinical Trials**

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>NOCTIVA 1.66 mcg (n=341)</th>
<th>NOCTIVA 0.83 mcg (n=354)</th>
<th>Placebo (n=340)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyponatremia/Blood Sodium Decreased</td>
<td>4 (1.2%)</td>
<td>3 (0.9%)</td>
<td>1 (0.3%)</td>
</tr>
<tr>
<td>Nasal Discomfort</td>
<td>2 (0.6%)</td>
<td>0</td>
<td>3 (0.9%)</td>
</tr>
<tr>
<td>Nasal Congestion</td>
<td>2 (0.6%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Atrial Fibrillation</td>
<td>2 (0.6%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Dizziness</td>
<td>0</td>
<td>2 (0.6%)</td>
<td>1 (0.3%)</td>
</tr>
<tr>
<td>Dysuria</td>
<td>1 (0.3%)</td>
<td>2 (0.6%)</td>
<td>0</td>
</tr>
</tbody>
</table>

**Most Common Adverse Reactions:** Table 2 summarizes the most common adverse reactions reported by patients with nocturia due to nocturnal polyuria. This table shows adverse reactions reported in at least 2% of patients treated with NOCTIVA and at a higher incidence with the 1.66 mcg dose than with placebo.
Table 2: Common Adverse Reactions (Reported by ≥2% of NOCTIVA-Treated Patients and at a Higher Incidence With the 1.66 mcg Dose Than With Placebo) in 2 Double-Blind, Placebo-Controlled Clinical Trials in Patients With Nocturia Due to Nocturnal Polyuria

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
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<th>Placebo (n=349)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nasal Discomfort</td>
<td>20 (5.9%)</td>
<td>12 (3.4%)</td>
<td>17 (4.9%)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>13 (3.8%)</td>
<td>8 (2.3%)</td>
<td>10 (2.9%)</td>
</tr>
<tr>
<td>Nasal Congestion</td>
<td>10 (2.9%)</td>
<td>5 (1.4%)</td>
<td>5 (1.4%)</td>
</tr>
<tr>
<td>Sneezing</td>
<td>9 (2.6%)</td>
<td>8 (2.3%)</td>
<td>5 (1.4%)</td>
</tr>
<tr>
<td>Hypertension/Blood Pressure Increased</td>
<td>9 (2.6%)</td>
<td>6 (1.7%)</td>
<td>4 (1.1%)</td>
</tr>
<tr>
<td>Back Pain</td>
<td>8 (2.3%)</td>
<td>4 (1.1%)</td>
<td>3 (0.9%)</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>7 (2.1%)</td>
<td>7 (2.0%)</td>
<td>4 (1.1%)</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>7 (2.1%)</td>
<td>3 (0.8%)</td>
<td>3 (0.9%)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>6 (1.8%)</td>
<td>7 (2.0%)</td>
<td>5 (1.4%)</td>
</tr>
</tbody>
</table>

No overall changes were observed in the safety profile during the open-label, uncontrolled extension trial with up to 126 weeks of follow-up.

Table 3: Hyponatremia in 2, Double-Blind, Placebo-Controlled Clinical Trials in Patients With Nocturia Due to Nocturnal Polyuria

Table 4: Hyponatremia, Based on Age, in 2 Double-Blind, Placebo-Controlled Clinical Trials in Patients With Nocturia Due to Nocturnal Polyuria

Table 4: Hyponatremia in 2, Double-Blind, Placebo-Controlled Clinical Trials in Patients With Nocturia Due to Nocturnal Polyuria

Table 4: Hyponatremia, Based on Age, in 2 Double-Blind, Placebo-Controlled Clinical Trials in Patients With Nocturia Due to Nocturnal Polyuria

OVERDOSAGE

Signs of overdose may include effects from hyponatremia such as seizure, altered mental status, cardiac arrhythmias, and worsening edema. Other signs of overdose may include oliguria and rapid weight gain due to fluid retention. In case of overdose, NOCTIVA should be discontinued immediately, serum sodium should be assessed, and appropriate medical treatment initiated.

PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Hypertension: Inform patients that NOCTIVA can cause hypertension, which may be life-threatening. Inform patients to monitor blood pressure at home and report any significant changes.

Drug Interactions: NOCTIVA is contraindicated in patients with a history of nasal allergy or on medications that may cause antihistamine effects. NOCTIVA is not recommended for use in patients with a history of nasal allergy or on medications that may cause antihistamine effects.

Drugs Administered Intranasally: The drug interaction potential between NOCTIVA and other intranasally administered drugs has not been studied. NOCTIVA is not recommended for use in patients who require treatment with other drugs via the nasal route.
Data shift thinking on nocturia’s causes, treatment

Gopal H. Badlani, MD

Dr. Badlani, a Urology Times editorial consultant, is professor of urology at Wake Forest Baptist Medical Center, Winston-Salem, NC.

Waking up at night to urinate is by far the most bothersome lower urinary tract symptom. It is clear now that nocturia has a distinct pathophysiology from daytime urinary frequency with some overlapping causes. However, its impact on quality of life and health is profound. It disproportionately affects the elderly, physically disabled, and those overweight. Although the incidence in women may be slightly higher (almost 30% in a recent study using the NHANES database [see page 7]), it is present in men as well. During my early years in urology, nocturia was the index that determined if an older man underwent TURP. Today it is clear that urologic causes are way down the list of etiologies.

Fluid shift from the lower extremities resulting in higher urine output is a common cause that can be improved with leg elevation in the evening and restricting intake 2 hours prior to bedtime. Additionally, if the patient takes a diuretic in the morning, changing the time to late afternoon may reduce output at night. Thus, a frequency and volume chart at night compared to the day is by far the most useful diagnostic tool. A medical history is critical, including the presence of sleep apnea, cardiopulmonary conditions, recurrent lower extremity edema, and sleep-cycle disturbance. Drugs such as diuretics and lithium can cause excessive output.

One might be surprised that obstetric history was found to have no association with nocturia in the NHANES study, since urinary symptoms are affected by the obstetrical history. The postulate here is the significant time interval between the obstetrical event and the age where nocturia is a bother leads to a recall bias.

Lack of effective medical therapy has frustrated many patients, but physicians, and still desmopressin was used by <5% in one study (World J Urol Oct 4, 2018 [Epub ahead of print]) for fear of electrolyte imbalance, particularly in the elderly. Now a new nasal spray formulation has a shorter half-life and is perhaps safer.

Reduced bladder capacity and incomplete emptying in men, particularly due to obstruction, is easier to treat, whereas medical causes such as sleep apnea, diabetes, and renal disease require a significant effort on the patient’s part.

Catastrophic events such as falls and fractures while getting up at night are a major burden in the elderly, and in the REDUCE trial sub-analysis, “Nocturia was associated with increased mortality risk (hazard ratio [HR]=1.72, 95% CI 1.13-2.55) independent from demographics and medical comorbidities” (Prostate Cancer Prostatic Dis Sept. 13, 2018 [Epub ahead of print]).

Waking up at night can be frustrating for many patients, especially if it takes a while to drift back into dreamland, which leaves them tired and sleep-deprived the next day. To paraphrase singer Alison Krauss: I don’t look for bliss, just contentment of a good night’s sleep!
Nearly 30% of U.S. women report significant nocturia

John Schieszer
UT Correspondent

SAN FRANCISCO—Nocturia appears to be highly prevalent in the United States, with almost 30% of all women reporting significant nocturia, according to new data reported at the AUA annual meeting in San Francisco.

Researchers mined data from the National Health and Nutrition Examination Survey (NHANES) database and found that among all women surveyed, 28.8% reported significant nocturia.

The authors analyzed data on 7,620 women and found that nocturia rates increased with increasing age (p<.0001). In addition, among those women who underwent childbirth, delivery type had no association with nocturia (p=.23).

The investigators conducted a multivariable analysis and found that only increasing age (odds ratio [OR]: 1.8), African-American race (odds ratio: 2.35), body mass index ≥30 (odds ratio: 1.5), urge incontinence (OR: 1.6), and poor overall health (OR: 1.48) were associated with increased rates of nocturia.

“Urge incontinence and poor health status correlated with nocturia,” said study author Timothy Byler, MD, assistant professor of urology at SUNY Upstate Medical University, Syracuse, NY. “In terms of medical comorbidities associated with nocturia, depression, hypertension, and arthritis were highly associated.”

Obstetrical history not associated

Dr. Byler, who presented the study findings, said obstetrical history was found to have no association with nocturia. Factors not associated with nocturia were hysterectomy, prolapse, oophorectomy, menopause, and delivery type. He said the findings, while intriguing, are limited by their retrospective nature.

“There are certain limitations due to recall bias and survey bias,” said Dr. Byler.

Nocturia can be one of the most bothersome lower urinary tract symptoms that can significantly affect quality of life. In both men and women, nocturia has been associated with decreased overall health, but little evidence exists on the prevalence of nocturia in U.S. females.

“There is a lot of focus on male nocturia and treatment for it, but there is not a lot in the literature on female nocturia and how common it is,” Dr. Byler said in an interview with Urology Times.

Dr. Byler and his colleagues wanted to look at prevalence and identify factors associated with significant nocturia. They examined the NHANES database and looked at females surveyed during the years 2009-2014. Nocturia information was obtained from a questionnaire and for this study, the authors defined significant as those women who urinated two or more times per night. The team investigated demographic characteristics, urinary incontinence history, and gynecologic/obstetrical history.

“Dr. Byler said the Boston Area Community Health Study estimated 28 million U.S. adults regularly experienced significant nocturia (two or more times per night). In just loss of productivity based on that number, it is projected the costs at more than $61 million in 2008, according to Dr. Byler.”

“Urge incontinence and poor health status correlated with nocturia. In terms of medical comorbidities associated with nocturia, depression, hypertension, and arthritis were highly associated.”

TIMOTHY BYLER, MD

He said conditions associated with nocturia in adults include an increased risk for mortality, increased risk in falls, increased risk in depression, a decreased risk in quality of life, and a risk for decreased work productivity. He said the disease states associated with nocturia include endocrine disorders and obstructive sleep apnea.

Based on their findings, the authors concluded that nocturia is prevalent in the U.S. in women and may need to be discussed more commonly.

“IT may have associations with other medical issues and concerns, and we should remember to query women about nocturia. We should try to address it more,” Dr. Byler said.

In Brief / For up-to-date news, visit urologytimes.com

PELVIC FLOOR EXERCISES HELP WITH DETRUSOR OVERACTIVITY

Pelvic floor muscle (PFM) contractions can reduce the severity of contractions of the detrusor muscle of the bladder in patients with overactive bladder, including those with and without multiple sclerosis, according to a recent study.

The study, published in American Journal of Physical Medicine & Rehabilitation (Oct. 18, 2018 [Epub ahead of print]) suggests that pelvic floor muscle contractions may reinforce a key “voluntary reflex” controlling urination.

The authors, led by Adelia Lúcio, PhD, of HUMAP-UFSM, Campo Grande, Brazil, performed urodynamic studies in two groups of women. Eighteen patients had OAB symptoms related to multiple sclerosis. Another 17 patients had idiopathic OAB.

In the experimental procedure, the women were instructed to perform a 15-second PFM contraction during a period of detrusor muscle overactivity. The study focused on overactivity of the detrusor muscle.

The results confirmed that contracting the pelvic floor muscles led to reduction in the pressure produced by detrusor overactivity. Although the decrease in detrusor muscle pressure with PFM contraction was significant in both groups, the effect was larger in patients with idiopathic OAB. For this group, the median decrease in detrusor overactivity was 69%, compared to 34% in the patients with multiple sclerosis.

CLINICAL UPDATES

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Clinical Updates

OAB patients continue medical therapy unnecessarily

Sacral neuromodulation monotherapy efficacious as third-line treatment

Cheryl Guttman Krader
UT Contributing Editor

SAN FRANCISCO—Findings of a retrospective review of patients treated with sacral neuromodulation (SNM) for overactive bladder (OAB) speak to the modality’s efficacy as third-line therapy, but also point to a need to better understand why some patients continue concurrent medical therapy, said Katherine Amin, MD, at the AUA annual meeting in San Francisco.

In a study that included data from 78 patients followed for a median of approximately 16 months after the SNM procedure, the authors found that 64 patients (82.1%) stopped and never restarted their OAB medications. Comparisons with the group of individuals who continued to consistently fill an OAB medication prescription for 1 year or more showed the two cohorts differed significantly only in age, with the patients remaining on medical therapy being older than their counterparts utilizing SNM alone (74.5 vs. 64.9 years, p=.004).

“Considering that symptom improvement and patient satisfaction were equivalent in the groups that discontinued and remained on OAB medications, we believe that SNM can successfully treat OAB and avoid the adverse effects of OAB medications.”

Other comparisons showed the two groups were similar with respect to body mass index, sex, SNM revision rate, urodynamic parameters, patient-perceived percentage of improvement, and Patient Global Impression of Improvement (PGI-I) score.

“Considering that symptom improvement and patient satisfaction were equivalent in the groups that discontinued and remained on OAB medications, we believe that SNM can successfully treat OAB and avoid the adverse effects of OAB medications, which may include detrimental cognitive effects with long-term usage of agents with anticholinergic activity,” said Dr. Amin, fellow in female pelvic reconstructive medicine and surgery at Virginia Mason, Seattle.

Reasons for medication use unclear

“Further study is needed to understand the reasons why some patients continued on their OAB medications. Perhaps their condition is extremely refractory to treatment or maybe they were not adequately informed about the potential to stop their medications. Meanwhile, at our institution we are trying to ensure that patients are fully counseled so that they realize they may have the opportunity to discontinue their medication after SNM surgery,” said Dr. Amin, working with Alvaro Lucioni, MD, and colleagues.

Patients undergoing SNM during the study period were excluded from the analysis if they had the procedure for urinary retention or subsequently underwent SNM removal. Data about patient demographics, baseline characteristics, and improvement after SNM were extracted from the patients’ electronic medical records. Information on medication use was identified using an external prescription database.

“The prescription database at our institution allows for complete tracking of when patients refill their medications,” Dr. Amin said.

Patients were categorized as remaining on concurrent medication therapy if they filled a prescription for an OAB medication for at least 11 consecutive months in the first year after SNM. Of the 10 patients remaining on concurrent medication therapy, seven were using an anticholinergic agent, one patient was on a beta-3 agonist, and two patients had filled prescriptions for both types of medications.

The majority of patients included in the study were female. For the overall population, mean body mass index was about 29 kg/m², and mean maximum cystometric capacity was 320 mL. Detrusor overactivity was present in 75% of patients remaining on concurrent therapy and 48% of those who utilized SNM alone, but the difference between groups was not statistically significant.

SNM revision was performed in 10% to 11% of patients in the two groups.

At last follow-up, mean PGI-I score was 2 (much better) in the patients who used SNM alone versus 3 (a little better) in the concurrent group. Mean patient-perceived percentage of improvement was 60% in the SNM-alone group and 30% in the concurrent group. The between-group difference was not statistically significant for either endpoint.

<table>
<thead>
<tr>
<th>TABLE OUTCOMES FOR SNM WITH/WITHOUT MEDICAL THERAPY</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean Patient Global Impression of Improvement</strong></td>
</tr>
<tr>
<td>- Sacral neuromodulation only: 2 (much better)</td>
</tr>
<tr>
<td>- Sacral neuromodulation and concurrent medical therapy: 3 (a little better)</td>
</tr>
<tr>
<td><strong>Mean patient-perceived percentage of improvement</strong></td>
</tr>
<tr>
<td>- Sacral neuromodulation only: 60%</td>
</tr>
<tr>
<td>- Sacral neuromodulation and concurrent medical therapy: 30%</td>
</tr>
</tbody>
</table>

Source: Katherine Amin, MD

MIXED UI TREATMENT APPROACHES COMPARED

In women with mixed urinary incontinence, a combined conservative and surgical treatment approach provided significant improvements versus surgical treatment alone, according to results of a randomized clinical trial.

Compared to women who received a midurethral sling alone, women who received the sling plus perioperative behavioral/pelvic floor exercise had improved quality of life and decreased need for retreatment at 12 months, it was reported at the International Continence Society annual meeting in Philadelphia.

For more about this study, and for related content, go to www.urologytimes.com/overactive-bladder.
Non-head MRI found safe in patients undergoing SNM

Efficacy of treatment not affected by scan, data show

Laird Harrison
UT Correspondent

SAN FRANCISCO—The therapeutic efficacy of sacral neuromodulation (SNM) was not affected by non-head magnetic resonance imaging (MRI) scans in a recent study.

“We evaluated 11 patients, and in this study we were able to demonstrate the safety of lumbosacral MRI with implanted SNM devices,” Juan M. Guzman-Negron, MD, a second-year fellow in female pelvic medicine and reconstructive surgery at Cleveland Clinic, told Urology Times.

Historically, the use of MRI in patients with SNM devices has been contraindicated, said Dr. Guzman-Negron, working with Howard B. Goldman, MD, and colleagues. The findings were presented at the AUA annual meeting in San Francisco and subsequently published in the Journal of Urology (May 29, 2018 [Epub ahead of print]).

Currently, the FDA has only approved a 1.5 Tesla MRI head scan in patients implanted with the InterStim II Neurostimulator. But few studies have examined the risk, other than a handful of retrospective studies that have shown no significant adverse events, Dr. Guzman-Negron said.

“In this study we were able to demonstrate the safety of lumbosacral MRI with implanted SNM devices.”

JUAN M. GUZMAN-NEGRON, MD

“Most studies were in the head and neck,” he said. “Our study focused more on the lumbar area, which places the sacral neuromodulation device closest to the center of the body transmit coil, increasing the likelihood of radiofrequency energy transmission and heating compared to scans of other body regions.”

To assess the risk, Dr. Guzman-Negron and colleagues first exposed a phantom model implanted with SNM to 1.5 Tesla lumbosacral and pelvic MRI scans and found that the risk of harmful heating was very low. To further investigate, the authors identified 11 patients with SNM implants who required lumbosacral 1.5 Tesla MRI.

They were all between 18 and 99 years of age, with a median of 75 years. Eight of the patients were women. All were implanted with a functioning InterStim II implantable pulse generator as a treatment for urgency urinary incontinence. All underwent lumbosacral 1.5 Tesla MRI. In six of them, the indication was lower back pain. The authors recorded stimulus settings and electrode impedances from the devices before and after the patients underwent MRI.

Discomfort, warmth end after scan

One patient reported discomfort at the site of the implantable pulse generator during the MRI, but the discomfort disappeared after the scan. Two patients reported warmth at the site of the implantable pulse generator during the MRI, but also said that sensation ended with the scan.

None of the patients experienced stimulation or movement at the implantable pulse generator site, or any paresthesia.

Impedances and battery life only showed minimal changes during implantable pulse generator interrogation post MRI. Likewise, the authors found no changes in threshold amplitudes for sensation and localization of stimulation.

There were no worsening scores in Urogenital Distress Inventory and Incontinence Impact Questionnaires 1 month after MRI. None of the patients reported a negative Patient Global Impression of Improvement score 1 month after MRI. Only one patient could recall pain, discomfort, movement, or abnormal stimulus during the MRI scanning.

Urologists planning MRI scans for patients with SNM implants should always consult with their respective hospital radiology department, Dr. Guzman-Negron recommended.

Only one patient could recall pain, discomfort, movement, or abnormal stimulus during the MRI scanning.
Rechargeable neuromodulation system found efficacious
Clinically significant reductions in OAB symptoms seen at 1-year follow-up

Andrew Bowser
UT Correspondent

PHILADELPHIA—One year after implantation, a miniaturized, rechargeable sacral neuromodulation system remains a safe and effective treatment for overactive bladder, according to results of a European post-marketing clinical follow-up study presented at the International Continence Society annual meeting in Philadelphia.

Among patients with a clinical response 1 month after implantation, most went on to have clinically and statistically significant reductions in overactive bladder symptoms at 1 year, according to investigator Bertil F.M. Blok, MD, PhD, of the department of urology at Erasmus Medical Center, Rotterdam, the Netherlands.

“This rechargeable sacral neuromodulation system may provide significant cost saving, and reduction in patient risk and physician burden, by eliminating frequent replacement surgeries,” Dr. Blok said.

Dr. Blok reported. Quality of life also significantly improved at 1 year, and 91% of subjects said they were satisfied with the device.

Recharging was easy, according to 91% of subjects. One hundred percent said the duration and frequency of recharging was acceptable; 70% recharged every 2 weeks, on average, while 30% recharged every week.

Serious device adverse events were not seen in the study, Dr. Blok said, although 10 subjects had undesirable stimulation that resolved with reprogramming, and one patient had pain at the implantable pulse generator site that resolved with reprogramming.

One patient had a lead migration, and three subjects were explanted due to an infection related to the procedure or lack of efficacy.

In terms of procedural complexity, implantation of the lead is “exactly the same” as the non-rechargeable sacral neuromodulation device, but implantation of the battery is simpler, Dr. Blok said.

“You place the battery lateral from the incision, and you only have to make a pocket with one finger, and then that’s enough,” he said.

Dr. Blok reported a financial disclosure related to Axonics Modulation Technologies, and noted that the company provided funding for him to attend the ICS meeting.

More than 50% of patients stop botulinum treatment
Treatment discontinuation seen despite improvement after two injections

Laird Harrison
UT Correspondent

SAN FRANCISCO—Over half of patients stop intradetrusor botulinum toxin injections within 10 years, mostly due to lack of clinical efficacy, researchers say.

Secondary inefficiency occurs in one-third of patients who show improvement after the first two injections, according to Jean-Nicolas Cornu, MD, PhD, professor of urology at Charles Nicolle Hospital in Rouen, France, who presented the research at the AUA annual meeting in San Francisco.

“When you have neurogenic bladder and detrusor overactivity, [botulinum toxin] cannot be considered a lifelong treatment,” he told Urology Times.

Intradetrusor injections of abobotulinumtoxinA (Dysport) and onabotulinumtoxinA (Botox) are effective in the short term, but few studies have followed patients for a longer term.

To fill that gap, Dr. Cornu and his colleagues retrospectively analyzed records on all patients treated with abobotulinumtoxinA or onabotulinumtoxinA for neurogenic detrusor overactivity in three tertiary reference centers between 2002 and 2007. They excluded patients with a history of augmentation cystoplasty prior to the first injection of botulinum toxin.

The 140 patients were evenly divided between males and females. Sixty-four had spinal cord injuries, 46 had multiple sclerosis, 14 spina bifida, five supratentine diseases, and 11 had other spinal diseases.

Seventy patients received abobotulinumtoxinA for the first injection, and 62 received onabotulinumtoxinA. Ninety-three had involuntary detrusor contraction. The average volume of their first uninhibited contraction was 184.8 mL. Their average maximum cystometric capacity was 301
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*Based on a tertiary clinical literature search performed 11/2014. 89 peer-reviewed articles were accepted according to Inclusion/Exclusion criteria, of which 80% (71 articles) showed favorable outcomes in support of Hem-o-lok Clips. Data on file, Teleflex Incorporated, Report #MLIB-000588.
†Data on file (2013 internal study), Teleflex Incorporated, Report #DI01591. Testing conducted on porcine carotids, sample size = 33, p≤ 0.05. Clinical performance cannot be extrapolated from the data. Testing pressures range beyond physiological pressures.
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TURP duration linked with complication rate

Laird Harrison
UT Correspondent

SAN FRANCISCO—Transurethral resection of the prostate (TURP) is safest when performed in under 60 minutes and should not be performed for longer than 120 minutes, researchers say.

The study supports the conventional wisdom about the procedure, said Christopher B. Riedinger, MD, a fourth-year resident who works with attending surgeon Norm Smith, MD, at the University of Chicago.

“We mostly confirmed what we thought,” Dr. Riedinger said. He presented the research at the AUA annual meeting in San Francisco.

Around the world, 1.2 million men undergo surgery for BPH or lower urinary tract symptoms per year, with TURP the most common procedure, said Dr. Riedinger.

Complication rates are improving with advances in instrumentation and perioperative care, yet a “dogma” persists that the procedure should be done in under an hour, he said. To see whether this tradition is supported by actual complication rates, Dr. Riedinger and his colleagues analyzed the American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP) from 2006 to 2016 for patients undergoing TURP, as defined by CPT codes 52601 and 52630.

They excluded patients whose cases were classified as an emergency, who were diagnosed with preoperative sepsis, or who underwent a con-current procedure. That left them with 31,813 TURPs.

They separated these patients into five groups based on operative time: 0 to 30 minutes (8,163 patients), 30.1 to 60 minutes (12,932 patients), 60.1 to 90 minutes (6,790 patients), 90.1 to 120 minutes (2,517 patients), and greater than 120 minutes (1,411 patients).

Longer surgery, more complications

They found an overall complication rate of 9.00%, which increased with longer surgical duration (p<0.001).

The odds ratio of having any complication was 1.1 in the 30.1- to 60-minute group, 1.3 in the 60.1- to 90-minute group, 1.6 in the 90.1- to 120-minute group, and 2.1 in the >120-minute group.

Patients whose American Society of Anesthesiologists classification was at least 4 were more likely to have fast procedures.

General anesthesia was used in 62.4% of the procedures in the 0- to 30-minute group. Another 33.8% had spinal anesthesia and 3.8% had some other type of anesthesia. The proportion getting general anesthesia increased with the duration of the procedure, reaching 79.8% in the group whose TURP took more than 2 hours.

The risk of needing a transfusion (p<0.001) and reoperation (p<0.001) also increased with the operative time in a linear fashion.

The risk of deep vein thrombus or pulmonary embolism was highest in the group whose surgery took longer than 2 hours, and was lowest in the groups whose surgery took 30.1 to 90 minutes (p<0.021).

The risk of sepsis or septic shock remained relatively constant, below 1%, for all the duration groups except the group whose TURP took longer than 2 hours, whose risk was 1.8%. Controlling for age, comorbidities, American Society of Anesthesiologists class, race, year of surgery, and type of anesthesia administered did not affect this association.

The risk of transfusion remained significantly increased across all groups, while each of the above complications remained significantly increased for surgeries lasting longer than 120 minutes.

BOTULINUM

continued from page 10

mL, and average maximum detrusor pressure was 53.5 cm H2O.

After 5 years, 63.9% were still receiving the injections. At 7 years, that proportion dropped to 59.1% and at 10 years it was down to 49.1%.

Spina bifida only contributing factor

The authors looked at factors that might contribute to discontinuation, including gender, neurologic condition, duration from neurologic disease onset, maximal detrusor pressure, and volume of the first uninhibited detrusor contraction. Only spina bifida emerged as a statistically significant factor; patients with this condition were more likely to discontinue.

In 28% of discontinuations, the patient decided to stop despite what appeared to be a satisfactory outcome. In 27%, the reason for discontinuation was secondary failure. In 17%, it was primary failure. In 14%, improvements not related to botulinum toxin were the reason. In 12%, the reason was progression of the neurologic condition. And in 2%, it was an adverse event.

Thirty-six percent of the patients turned to antimuscarinics after giving up on botulinum toxin. Twenty-eight percent had augmentation cystoplasty. Eleven percent had an ileal conduit, 6% suprapubic tube, 3% sacral neuromodulation, and 2% sphincterotomy. For 14%, the subsequent treatment was unknown.

Dr. Cornu reported consultant fees or travel grants from Allergan, Astellas, Boston Scientific, Bouchara-Recordati, Coloplast, Cousin Biotech, Medtronic, Mundipharma, Pfizer, Pierre Fabre Médicaments, SAP, and Takeda. He has been an investigator for Astellas, GT Urological, Medtronic, Ipsen, Coloplast, Cousin Biotech, and Allergan.
PCa care in elderly costs Medicare $1.2 billion

Andrew Bowser
UT Correspondent

Diagnosing and treating localized prostate cancer in men 70 years of age and older has cost Medicare an estimated 3-year total of $1.2 billion, according to results of a retrospective cohort study.

Those costs could be slashed by $120 million if all men with Gleason scores of 6 or lower pursued initial conservative management, said study author Justin Trogdon, PhD, associate professor of health policy management at the University of North Carolina, Chapel Hill.

“The evidence was there for the lack of health benefits, but we thought we could really drive the message home if we pointed out that, by the way, we’re spending a lot of money on this,” Dr. Trogdon said of the rationale for the study in an interview with Urology Times.

The study, published in JAMA Oncology (Sept. 13, 2018 [Epub ahead of print]), was based on an analysis of the Surveillance, Epidemiology, and End Results (SEER)-Medicare linked database. Looking at the period between 2004 and 2007, the authors identified nearly 50,000 men who had initial conservative management, defined as no treatment within 12 months of diagnosis.

They found that the median cost per patient within 3 years of diagnosis was $14,453 (interquartile range [IQR], $4,887-$27,899). Most of the cost was due to treatment, at a median of $10,558 (IQR, $1,990-$23,718). However, 3-year median total cost per patient was just $1,914 for patients with a Gleason 6 or lower score who had initial conservative management.

In their report, they referenced the Prostate Cancer Intervention versus Observation Trial (PIVOT), which suggested there is no survival benefit to radical prostatectomy versus observation in older men with localized prostate cancer. They also noted studies showing how treatment of localized prostate cancer results in increases in sexual dysfunction, bowel problems, and other adverse outcomes.

“All told, the $1.2 billion 3-year cost to Medicare represented a substantial sum in these older men who were unlikely to die of prostate cancer, Dr. Trogdon and co-authors concluded.

Published guidelines continue to recommend against PSA screening in men 70 years of age and older, said Dr. Trogdon and colleagues.

In their report, they referenced the Prostate Cancer Intervention versus Observation Trial (PIVOT), which suggested there is no survival benefit to radical prostatectomy versus observation in older men with localized prostate cancer. They also noted studies showing how treatment of localized prostate cancer results in increases in sexual dysfunction, bowel problems, and other adverse outcomes.

“This is one of those decisions that’s pretty cut clear. Screening and treating men for prostate cancer in men 70 years of age and older, said Dr. Trogdon.

One solution is to adhere more strictly to the guidelines and not screen these older men in the first place, Dr. Trogdon suggested. If patients are screened, however, putting them on active surveillance and not immediately treating could be a strategy that takes into account both the potential costs of care and potential harms of treatment, he added.

The situation may be improving, given the increasing recognition of prostate cancer overdiagnosis, according to Dr. Trogdon and co-investigators. In a review of more recent SEER data covering the 2009-2013 period, they found declines in prostate cancer incidence and treatment that they said would shave off about $200 million, bringing the total 3-year cost to about $1 billion.

Based on that decrease, the total 3-year cost to Medicare would have declined by $200 million to $1 billion, according to Dr. Trogdon.

“I think in general, the trend is potentially moving in the right direction, but we’ve still got quite a way to go,” Dr. Trogdon said.

Agent identifies sites of PCa recurrence

Imaging tool leads to treatment changes in 59% of patients scanned

Lisette Hilton
UT Correspondent

Imaging with 18F-fluciclovine positron emission tomography/computed tomography identified sites of disease recurrence in a majority of prostate cancer patients with biochemical recurrence and led to changes in treatment course in 59% of men scanned, according to a recent study (J Urol Sept. 1, 2018 [Epub ahead of print]). Armored with information from 18F-fluciclovine PET/CT (Axumin), urologists and patients with suspected biochemical recurrence of prostate cancer could make more informed decisions about treatment. Researchers do not yet know if the information provided by the scan changes outcomes from treatment.

“The dilemma with biochemical recurrence is that urologists, radiation therapists, and medical oncologists have to make an educated guess as to where the recurrence is. We would use things like the quickness with which the PSA recurred after therapy, or the PSA velocity, to infer whether that recurrence is somewhere locally, in the prostate or metastatic bed, or distantly, meaning metastatic to lymph nodes or the bone. The problem is that kind of guesswork was frequently inaccurate,” said Gerald L. Andriole, MD, professor and chief of urologic surgery at Washington University School of Medicine in St. Louis and lead author of the LOCATE trial, a prospective, multicenter, open-label study done at 15 U.S. sites.

“Now we have this imaging study that can show us where the site of recurrence is in most patients. And that can allow us to do smarter, more targeted therapies,” Dr. Andriole said.

Dr. Andriole and co-authors studied use of 18F fluciclovine, an FDA-approved molecular imaging agent for use in PET imaging in men with suspected prostate cancer recurrence, in 213 patients thought to have biochemical recurrence. They found 18F fluciclovine PET/CT was positive in 57% of patients, leading to often-major changes in treatment for more than half of the patients studied. Among the changes, three-quarters of the 60 patients who were going to have androgen deprivation therapy (ADT) changed post-scan to non-systemic salvage treatment.

Please see IMAGING AGENT, on page 19
**METS? NO METS? START XTANDI.**

Regardless of metastatic status, XTANDI offers your patients with CRPC the confidence of proven efficacy when PSA is rising* during LHRH therapy†

*PSA level ≥ 2 ng/mL with at least 2 consecutive rises despite castrate testosterone levels (≤ 50 ng/dL).²

Visit [XtandiNewData.com](http://XtandiNewData.com) for new clinical trial results

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**Indication and Important Safety Information**

**Indication**

XTANDI (enzalutamide) is indicated for the treatment of patients with castration-resistant prostate cancer (CRPC).

**Important Safety Information**

**Warnings and Precautions**

**Seizure** occurred in 0.4% of patients receiving XTANDI in clinical studies. In a study of patients with predisposing factors for seizure, 2.2% of XTANDI-treated patients experienced a seizure. Patients in the study had one or more of the following pre-disposing factors: use of medications that may lower the seizure threshold; history of traumatic brain or head injury, cerebrovascular accident or transient ischemic attack, Alzheimer’s disease, meningioma, or leptomeningeal disease from prostate cancer, unexplained loss of consciousness within the last 12 months, history of seizure, presence of a space occupying lesion of the brain, history of arteriovenous malformation, or history of brain infection. It is unknown whether anti-epileptic medications will prevent seizures with XTANDI. Advise patients of the risk of developing a seizure while taking XTANDI and of engaging in any activity where sudden loss of consciousness could cause serious harm to themselves or others. Permanently discontinue XTANDI in patients who develop a seizure during treatment.

**Posterior Reversible Encephalopathy Syndrome (PRES)**

In post approval use, there have been reports of PRES in patients receiving XTANDI. PRES is a neurological disorder which can present with rapidly evolving symptoms including seizure, headache, lethargy, confusion, blindness, and other visual and neurological disturbances, with or without associated hypertension. A diagnosis of PRES requires confirmation by brain imaging, preferably MRI. Discontinue XTANDI in patients who develop PRES.

**Hypersensitivity** reactions, including edema of the face (0.5%), tongue (0.1%), or lip (0.1%) have been observed with XTANDI in clinical trials. Pharyngeal edema has been reported in post-marketing cases. Advise patients who experience any symptoms of hypersensitivity to temporarily discontinue XTANDI and promptly seek medical care. Permanently discontinue XTANDI for serious hypersensitivity reactions.

**Ischemic Heart Disease** in the placebo-controlled clinical studies, ischemic heart disease occurred more commonly in patients on the XTANDI arm compared to patients on the placebo arm (2.7% vs 1.2%). Grade 3-4 ischemic events occurred in 1.2% of patients on XTANDI versus 0.5% on placebo. Ischemic events led to death in 0.4% of patients on XTANDI compared to 0.1% on placebo. Monitor for signs and symptoms of ischemic heart disease. Optimize management of cardiovascular risk factors, such as hypertension, diabetes, or dyslipidemia. Discontinue XTANDI for Grade 3-4 ischemic heart disease.

**Falls and Fractures** in the placebo-controlled clinical studies, falls occurred in 10% of patients treated with XTANDI compared to 4% of patients treated with placebo. Fractures occurred in 8% of patients treated with XTANDI and in 3% of patients treated with placebo. Evaluate patients for fracture and fall risk. Monitor and manage patients at risk for fractures according to established treatment guidelines and consider use of bone-targeted agents.

**Embryo-Fetal Toxicity** Safety and efficacy of XTANDI have not been established in females. XTANDI can cause fetal harm and loss of pregnancy when administered to a pregnant female. Advise males with female partners of reproductive potential to use effective contraception during treatment with XTANDI and for 3 months after the last dose of XTANDI. XTANDI should not be handled by females who are or may become pregnant.

**Adverse Reactions**

The most common adverse reactions (≥ 10%) that occurred more frequently (≥ 2% over placebo) in the XTANDI patients from the randomized placebo-controlled trials were asthenia/fatigue, decreased appetite, hot flush, arthralgia, dizziness/vertigo, hypertension, headache and weight decreased. In the bicalutamide-controlled study, the most common adverse reactions (≥ 10%) reported in XTANDI patients...
XTANDI significantly prolonged metastasis-free survival\(^\dagger\) in patients with nonmetastatic CRPC and significantly extended overall survival and radiographic progression-free survival in patients with metastatic CRPC

**Nonmetastatic CRPC:** Median metastasis-free survival was 3 years (36.6 months [95% CI, 33.1-NR]) with XTANDI + LHRH therapy\(^\dagger\) vs 14.7 months (95% CI, 14.2-15.0) with placebo + LHRH therapy\(^\dagger\) (HR = 0.29 [95% CI, 0.24-0.35]; P < 0.0001)\(^1\)

- As seen in the PROSPER trial: a multinational, randomized, double-blind phase 3 trial that enrolled 1401 patients with nonmetastatic CRPC who progressed on LHRH therapy\(^\dagger\). Eligibility criteria included PSA doubling time ≤ 10 months and no prior chemotherapy\(^2\)

**Metastatic CRPC:** 23% reduction in the risk of death with XTANDI + LHRH therapy\(^\dagger\) vs placebo + LHRH therapy\(^\dagger\) (HR = 0.77 [95% CI, 0.67-0.88]) and 83% reduction in the risk of radiographic progression or death vs placebo + LHRH therapy\(^\dagger\) (HR = 0.17 [95% CI, 0.14-0.21]; P < 0.0001)\(^1\)

- As seen in the PREVAIL trial: a multinational, randomized, double-blind phase 3 trial that enrolled 1717 patients with metastatic CRPC who progressed on LHRH therapy\(^\dagger\). Eligibility criteria included no prior chemotherapy\(^1\)

**References:**
2. Pfizer. XTANDI. Data on File.

**Drug Interactions**

**Effect of Other Drugs on XTANDI**
Avoid strong CYP2C8 inhibitors, as they can increase the plasma exposure to XTANDI. If co-administration is necessary, reduce the dose of XTANDI.

Avoid strong CYP3A4 inducers as they can decrease the plasma exposure to XTANDI. If co-administration is necessary, increase the dose of XTANDI.

**Effect of XTANDI on Other Drugs**
Avoid CYP3A4, CYP2C9, and CYP2C19 substrates with a narrow therapeutic index, as XTANDI may decrease the plasma exposures of these drugs. If XTANDI is co-administered with warfarin (CYP2C9 substrate), conduct additional INR monitoring.

**Lab Abnormalities:**
In the two placebo-controlled trials in patients with mCRPC, Grade 1-4 neutropenia occurred in 15% of XTANDI patients (1% Grade 3-4) and 6% of placebo patients (0.5% Grade 3-4). In the placebo-controlled trial in patients with nmCRPC, Grade 1-4 neutropenia occurred in 8% of patients receiving XTANDI (0.5% Grade 3-4) and in 5% of patients receiving placebo (0.2% Grade 3-4).

**Hypertension:**
In the two placebo-controlled trials in patients with mCRPC, hypertension was reported in 11% of XTANDI patients and 4% of placebo patients. Hypertension led to study discontinuation in < 1% of patients in each arm. In the placebo-controlled trial in patients with nmCRPC, hypertension was reported in 12% of patients receiving XTANDI and 5% of patients receiving placebo.

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Castration-resistant prostate cancer is defined as disease progression on androgen deprivation therapy (LHRH therapy or prior bilateral orchiectomy).\(^4\)

CI, confidence interval; HR, hazard ratio; LHRH, luteinizing hormone-releasing hormone; NR, not reached; PSA, prostate-specific antigen.

\(^{1}\)The primary endpoint of the study was metastasis-free survival, defined as the time from randomization to whichever of the following occurred first 1) loco-regional and/or distant radiographic progression per BICR (blinded independent central review) or 2) death up to 112 days after treatment discontinuation without evidence of radiographic progression.\(^2\)

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WARNINGS AND PRECAUTIONS
Seizure
Seizure occurred in 0.4% of patients receiving XTANDI in clinical studies. In these trials, patients with predisposing factors for seizure were generally excluded. Seizure occurred from 13 to 604 days after initiation of XTANDI. Patients experiencing seizure were permanently discontinued from therapy and all seizure events resolved.

In a single-arm trial designed to assess the risk of seizure in patients with pre-disposing factors for seizure, 8 of 366 (2.2%) XTANDI-treated patients experienced a seizure. Three of the 8 patients experienced a second seizure during continued treatment with XTANDI after their first seizure resolved. It is unknown whether antiepileptic medications will prevent seizures with XTANDI. Patients in the study had one or more of the following pre-disposing factors: the use of medications that may lower the seizure threshold (<54%), history of traumatic brain or head injury (<28%), history of cerebrovascular accident or transient ischemic attack (<24%), and Alzheimer’s disease, meningoia, or leptomenigeal disease from prostate cancer, unexplained loss of consciousness within the last 12 months, past history of seizure, presence of a space occupying lesion of the brain, history of arteriovenous malformation, or history of brain infection (all <5%). Approximately 17% of patients had more than one risk factor.

Advise patients of the risk of developing a seizure while receiving XTANDI and of engaging in any activity where sudden loss of consciousness could cause serious harm to themselves or others. Permanently discontinue XTANDI in patients who develop a seizure during treatment.

Posterior Reversible Encephalopathy Syndrome (PRES)
There have been reports of posterior reversible encephalopathy syndrome (PRES) in patients receiving XTANDI. PRES is a neurological disorder which can present with rapidly evolving symptoms including seizure, headache, lethargy, confusion, blindness, and other visual and neurological disturbances, with or without associated hypertension. A diagnosis of PRES requires confirmation by brain imaging, preferably magnetic resonance imaging (MRI). Discontinue XTANDI in patients who develop PRES.

Hypersensitivity
Hypersensitivity reactions, including edema of the face (0.5%), tongue (0.1%), or lip (0.1%) have been observed with enzalutamide in four randomized clinical trials. Pharyngeal edema has been reported in post-marketing cases. The risk of LAST NAME should be closely monitored by periodic medical and laboratory evaluations. The risk of LAST NAME should not be handled by females who are of reproductive potential to use effective contraception and may not reflect the rates observed in clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. Four randomized controlled clinical trials enrolled patients with CRPC that had progressed on ADT. The median duration of treatment was 8.3 months with XTANDI and 3.0 months with placebo. During the trial, 48% of patients on the XTANDI arm and 46% of patients on the placebo arm received glucocorticoids.

Ischemic Heart Disease
In the combined data of three randomized, placebo-controlled clinical studies, ischemic heart disease which occurred more commonly in patients on the XTANDI arm compared to patients on the placebo arm (2.7% vs 1.2%). Grade 3-4 ischemic events occurred in 1.2% of patients in the XTANDI arm compared to 0.5% in the placebo arm. Ischemic events led to death in 0.4% of patients in the XTANDI arm compared to 0.1% in the placebo arm.

Monitor for signs and symptoms of ischemic heart disease. Optimize cardiovascular risk factors, such as hypertension, diabetes, or dyslipidemia. Discontinue XTANDI for Grade 3-4 ischemic heart disease.

Falls and Fractures
Falls and fractures occurred in patients receiving XTANDI. Evaluate patients for fracture and fall risk. Monitor and manage patients at risk for fractures according to established treatment guidelines and consider use of bone-targeted agents. In the combined data of three randomized, placebo-controlled clinical studies, falls occurred in 10% of patients treated with XTANDI compared to 4% of patients treated with placebo. Falls were not associated with loss of consciousness or seizure. Fractures occurred in 8% of patients treated with XTANDI and in 3% of patients treated with placebo. Grade 3-4 fractures occurred in 2% of patients treated with XTANDI and in <1% of patients treated with placebo. The median time to onset of fracture was 337 days (range: 2 to 996 days) for patients treated with XTANDI. Routine bone density assessment and treatment of osteoporosis with bone-targeted agents were not performed in the studies.

Embryo-Fetal Toxicity
The safety and efficacy of XTANDI have not been established in females. Based on animal reproductive studies and mechanism of action, XTANDI can cause fetal harm and loss of pregnancy when administered to a pregnant female. Advise males with female partners of reproductive potential to use effective contraception during treatment with XTANDI and for 3 months after the last dose of XTANDI. XTANDI should not be handled by females who are or may become pregnant.

ADVERSE REACTIONS
Clinical Trial Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates reported in clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Four randomized controlled clinical trials enrolled patients with CRPC who had progressed on androgen deprivation therapy (gNRH therapy or prior bilateral orchiectomy). Three trials were placebo-controlled and one trial was bicalutamide-controlled. Patients received XTANDI 160 mg (2784 patients) or placebo orally once daily (1708 patients) or bicalutamide 50 mg orally once daily (189 patients). All patients continued androgen deprivation therapy (ADT).

The most common adverse reactions (>10%) that occurred more frequently (>2% over placebo) in the XTANDI-treated patients from the randomized placebo-controlled clinical trials were asthenia/fatigue, decreased appetite, hot flush, arthralgia, and disturbance in attention.

ER/2 shows adverse reactions reported in AFFIRM that occurred at a ≥2% higher frequency in the XTANDI arm compared to the placebo arm.

Table 1. Adverse Reactions in AFFIRM

<table>
<thead>
<tr>
<th></th>
<th>XTANDI N = 800</th>
<th>Placebo N = 399</th>
</tr>
</thead>
<tbody>
<tr>
<td>General Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthenia/Weakness</td>
<td>9.0%</td>
<td>4.4%</td>
</tr>
<tr>
<td>Peripheral Edema</td>
<td>1.0%</td>
<td>0.8%</td>
</tr>
<tr>
<td>Musculoskeletal and Connective Tissue Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Back Pain</td>
<td>5.3%</td>
<td>2.4%</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>2.1%</td>
<td>1.8%</td>
</tr>
<tr>
<td>Musculoskeletal Pain</td>
<td>1.3%</td>
<td>0.3%</td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>5.5%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>7.5%</td>
<td>0.5%</td>
</tr>
<tr>
<td>Spinal Cord Compression</td>
<td>4.5%</td>
<td>3.8%</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>0.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Impairment Disorders</td>
<td>1.8%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Hypersomnia</td>
<td>1.8%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Infections and Infestations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper Respiratory Tract Infection</td>
<td>6.5%</td>
<td>0.3%</td>
</tr>
<tr>
<td>Lower Respiratory Tract and Lung Infection</td>
<td>4.8%</td>
<td>1.3%</td>
</tr>
<tr>
<td>Psychiatric Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>6.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Anxiety</td>
<td>4.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Renal and Urinary Disorders</td>
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<td></td>
</tr>
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<td>Hematuria</td>
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<td>1.0%</td>
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<tr>
<td>Pollakiuria</td>
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<td>Injuries, Poisoning and Procedural Complications</td>
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<tr>
<td>Fall</td>
<td>0.3%</td>
<td>1.3%</td>
</tr>
<tr>
<td>Non-pathologic Fractures</td>
<td>1.4%</td>
<td>0.8%</td>
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<tr>
<td>Skin and Subcutaneous Tissue Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pruritus</td>
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<tr>
<td>Respiratory Disorders</td>
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</tr>
<tr>
<td>Epistaxis</td>
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<td>1.3%</td>
</tr>
</tbody>
</table>

1. Includes asthenia and fatigue.
2. Includes dizziness and vertigo.
3. Includes amnesia, memory impairment, cognitive disorder, and disturbance in attention.
4. Includes nephromegaly, upper respiratory tract infection, sinusitis, rhinitis, pharyngitis, and laryngitis.
5. Includes pneumonia, lower respiratory tract infection, bronchitis, and lung infection.
PREVAIL (NCT01212991): XTANDI versus Placebo in Chemotherapy-naive Metastatic CRPC
PREVAIL enrolled 1717 patients with metastatic CRPC who had not received prior cytotoxic chemotherapy, of whom 1715 received at least one dose of study drug. The median duration of treatment was 17.5 months with XTANDI and 4.6 months with placebo. Grade 3-4 adverse reactions were reported in 44% of XTANDI-treated patients and 37% of placebo-treated patients. Discontinuations due to adverse events were reported for 6% of XTANDI-treated patients and 6% of placebo-treated patients. The most common adverse reaction leading to treatment discontinuation was fatigue/asthenia, which occurred in 1% of patients on each treatment arm.

Table 2. Adverse Reactions in PREVAIL

<table>
<thead>
<tr>
<th>Reaction</th>
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<th>Placebo N = 844</th>
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<td><strong>Grade 1-4 (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>General Disorders</td>
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<tr>
<td>Asthenic Conditions</td>
<td>47</td>
<td>33</td>
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<tr>
<td>Peripheral Edema</td>
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<td>8.2</td>
</tr>
<tr>
<td><strong>Musculoskeletal and Connective Tissue Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Back Pain</td>
<td>29</td>
<td>22</td>
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<tr>
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<tr>
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<tr>
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<td>9.4</td>
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<td><strong>Vascular Disorders</strong></td>
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<td></td>
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<tr>
<td>Hot Flush</td>
<td>18</td>
<td>7.8</td>
</tr>
<tr>
<td>Hypertension</td>
<td>14</td>
<td>7.2</td>
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<tr>
<td><strong>Nervous System Disorders</strong></td>
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<td>Headache</td>
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<td>3.7</td>
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<td>3.1</td>
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<td>6.5</td>
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<td><strong>Infections and infestations</strong></td>
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<tr>
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<tr>
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Table 2. Adverse Reactions in PREVAIL (continued)

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<td><strong>Grade 1-4 (%)</strong></td>
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<tr>
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<tr>
<td>Muscle-Connective Tissue Disorders</td>
<td></td>
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<tr>
<td>Back Pain</td>
<td>19</td>
<td>2.7</td>
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<td></td>
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<td>1.3</td>
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<td><strong>Respiratory Disorders</strong></td>
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<tr>
<td>Diarrhea</td>
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<tr>
<td><strong>Infections and infestations</strong></td>
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<td></td>
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<tr>
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<tr>
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<td>Insomnia</td>
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<td>5.3</td>
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<td>2.1</td>
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<tr>
<td>Metabolism and Nutrition Disorders</td>
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<tr>
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<td>3.0</td>
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<tr>
<td>Loss</td>
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<td>8.5</td>
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<tr>
<td>Reproductive System and Breast Disorders</td>
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Table 3. Adverse Reactions in PREVAIL (continued)

<table>
<thead>
<tr>
<th>Reaction</th>
<th>XTANDI N = 871</th>
<th>Bicalutamide N = 844</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Grade 1-4 (%)</strong></td>
<td></td>
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</tr>
<tr>
<td>General Disorders</td>
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<tr>
<td>Asthenic Conditions</td>
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<td>33</td>
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<tr>
<td>Peripheral Edema</td>
<td>12</td>
<td>8.2</td>
</tr>
<tr>
<td><strong>Musculoskeletal and Connective Tissue Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Back Pain</td>
<td>29</td>
<td>22</td>
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<tr>
<td>Arthralgia</td>
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<td><strong>Nervous System Disorders</strong></td>
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<td>Headache</td>
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<td>Dysgeusia</td>
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<td>3.1</td>
</tr>
<tr>
<td><strong>Restless Legs Syndrome</strong></td>
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<td>Upper Respiratory Tract Infection</td>
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<tr>
<td>Lower Respiratory Tract and Lung Infection</td>
<td>7.9</td>
<td>4.7</td>
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<td><strong>Psychiatric Disorders</strong></td>
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</tr>
<tr>
<td>Insomnia</td>
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<td><strong>Renal and Urinary Disorders</strong></td>
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<td>Hematuria</td>
<td>8.8</td>
<td>3.8</td>
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<tr>
<td><strong>Injury, Poisoning and Procedural Complications</strong></td>
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</tr>
<tr>
<td>Fall</td>
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<td>5.3</td>
</tr>
<tr>
<td>Non-Pathological Fracture</td>
<td>8.8</td>
<td>2.1</td>
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<tr>
<td>Metabolism and Nutrition Disorders</td>
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<tr>
<td>Decreased Appetite</td>
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<td>3.0</td>
</tr>
<tr>
<td>Loss</td>
<td>12</td>
<td>8.5</td>
</tr>
<tr>
<td>Reproductive System and Breast Disorders</td>
<td>3.4</td>
<td>1.4</td>
</tr>
</tbody>
</table>

PROSPER (NCT02003924): XTANDI versus Placebo in Non-metastatic CRPC Patients
PROSPER enrolled 1401 patients with non-metastatic CRPC, of whom 1395 received at least one dose of study drug. Patients were randomized 2:1 and received either XTANDI at a dose of 160 mg once daily (N = 930) or placebo (N = 465). The median duration of treatment at the time of analysis was 18.4 months (range: 0.0 to 42 months) with XTANDI and 11.1 months (range: 0.0 to 43 months) with placebo.

Table 4. Adverse Reactions in PROSPER

<table>
<thead>
<tr>
<th>Reaction</th>
<th>XTANDI N = 930</th>
<th>Placebo N = 465</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Grade 1-4 (%)</strong></td>
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<td></td>
</tr>
<tr>
<td>Metabolism and Nutrition Disorders</td>
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<tr>
<td>Decreased Appetite</td>
<td>9.6</td>
<td>3.9</td>
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<td>Nervous System Disorders</td>
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<td>Dizziness</td>
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<td>Headache</td>
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<td>Cognitive and Attention Disorders</td>
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<td>Constipation</td>
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<td>6.9</td>
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<td>General Disorders and Administration Site Conditions</td>
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<td></td>
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<tr>
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<td>4.7</td>
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<td><strong>Psychiatric Disorders</strong></td>
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<td></td>
</tr>
<tr>
<td>Anxiety</td>
<td>2.9</td>
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</table>

Laboratory Abnormalities
In the AFFIRM and PREVAIL studies in metastatic CRPC, Grade 1-4 neutropenia occurred in 15% of patients receiving XTANDI (1% Grade 3-4) and in 6% of patients receiving placebo (0.5% Grade 3-4).

Table 5. Laboratory Abnormalities in PROSPER

<table>
<thead>
<tr>
<th>Reaction</th>
<th>XTANDI N = 930</th>
<th>Placebo N = 465</th>
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<tbody>
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<td><strong>Grade 1-4 (%)</strong></td>
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<tr>
<td>Neutropenia</td>
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<tr>
<td>Chemistry</td>
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<tr>
<td>Hypomagnesemia</td>
<td>26</td>
<td>21</td>
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</tbody>
</table>

In PREVAIL, higher frequency in the XTANDI arm compared to the placebo arm.
Drugs That Inhibit CYP2C8

Co-administration of a strong CYP2C8 inhibitor (gemfibrozil) increased the composite area under the concentration-time curve (AUC) of enzalutamide plus N-desmethyl enzalutamide by 2.2-fold. Co-administration of XTANDI with strong CYP2C8 inhibitors should be avoided if possible. If co-administration of XTANDI with a strong CYP2C8 inhibitor cannot be avoided, reduce the dose of XTANDI.

Effect of XTANDI on Drug Metabolizing Enzymes

Enzalutamide is a strong CYP3A4 inducer and a moderate CYP2C9 and CYP2C19 inducer in humans. At steady-state, XTANDI reduced the plasma exposure to midazolam (CYP3A4 substrate), warfarin (CYP2C9 substrate), and omeprazole (CYP2C19 substrate). Concomitant use of XTANDI with narrow therapeutic index drugs that are metabolized by CYP3A4 (e.g., alfentanil, cyclosporine, diltiazem, ergotamine, fentanyl, imipramine, quinidine, sirolimus and tacrolimus), CYP2C9 (e.g., phenytoin, warfarin) and CYP2C19 (e.g., S-mephenytoin, clopidogrel) should be avoided, as enzalutamide may decrease their plasma exposure. If co-administration with warfarin cannot be avoided, conduct additional INR monitoring.

Lactation

XTANDI is excreted in human milk. A single oral 30 mg/kg enzalutamide administration on postnatal day 14, enzalutamide and/or its metabolites were present in milk at a Cmax that was 4.0 times higher than concentrations in the plasma and occurred 4 hours after administration.

Females and Males of Reproductive Potential

Contraception

Based on animal studies, XTANDI may impair fertility in males of reproductive potential. Based on findings in animal reproduction studies, male fertility may be impaired by treatment with XTANDI. In a 26-week study in rats, atrophy of the prostate and seminal vesicles was observed at ≥ 30 mg/kg/day (equal to the human exposure based on AUC). In 4-, 13-, and 39-week studies in dogs, hydroperoxigenase and atrophy of the prostate and epididymides were observed at ≥ 4 mg/kg/day (0.3 times the human exposure based on AUC).

Pregnancy

Risk Summary

The safety and efficacy of XTANDI have not been established in females. Based on animal reproductive studies and mechanism of action, XTANDI can cause fetal harm and loss of pregnancy. There are no human data on the use of XTANDI in pregnant females. Co-administration of enzalutamide in pregnant mice during organogenesis caused adverse developmental effects at doses lower than the maximum recommended human dose (see Data). XTANDI should not be handled by females who are or may become pregnant.

Animal Data

In an embryo-fetal developmental toxicity study in mice, enzalutamide caused developmental toxicity when administered at oral doses of 10 or 30 mg/kg/day throughout the period of organogenesis (gestational days 6-15). Findings included embryo-fetal lethality (increased post-implantation loss and resorptions) and decreased anogenital distance at ≥ 10 mg/kg/day, and cleft palate and absent patellae bone at 30 mg/kg/day. Doses of 30 mg/kg/day caused maternal toxicity. The doses tested in mice (1, 10 and 30 mg/kg/day) resulted in systemic exposures (AUC) approximately 0.04, 0.4 and 1.1 times, respectively, the exposures in patients. Enzalutamide did not cause developmental toxicity in rabbits when administered throughout the period of organogenesis (gestational days 6-18) at dose levels up to 10 mg/kg/day (approximately 0.4 times the exposures in patients based on AUC).

In a pharmacokinetic study in pregnant rats with a single oral 30 mg/kg enzalutamide administration on gestation day 14, enzalutamide and/or its metabolites were present in the fetuses at a Cmax that was approximately 0.3 times the concentration found in maternal plasma and occurred 4 hours after administration.

OVERDOSAGE

In the event of an overdose, stop treatment with XTANDI and initiate general supportive measures taking into consideration the half-life of 5.8 days. In a dose escalation study, no seizures were reported at < 240 mg daily, whereas 2 seizures were reported, 1 each at 360 mg, 480 mg, and 600 mg daily. Patients may be at increased risk of seizure following an overdose.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

Administration of enzalutamide to male and female rats transgenic mice by oral gavage daily for 26 weeks did not result in increased incidence of neoplasms at doses up to 20 mg/kg/day.

Enzalutamide did not induce mutations in the bacterial reverse mutation (Ames) assay and was not genotoxic in either the in vitro mouse lymphoma thymidine kinase (TK) gene mutation assay or the in vivo mouse micronucleus assay.

Based on nonclinical findings in repeat-dose toxicity studies, which were consistent with the pharmacological activity of enzalutamide, male fertility may be impaired by treatment with XTANDI. In a 26-week study in rats, atrophy of the prostate and seminal vesicles was observed at ≥ 30 mg/kg/day (equal to the human exposure based on AUC). In 4-, 13-, and 39-week studies in dogs, hydroperoxigenase and atrophy of the prostate and epididymides were observed at ≥ 4 mg/kg/day (0.3 times the human exposure based on AUC).

Risk Summary

The safety and efficacy of XTANDI have not been established in females. Based on animal reproductive studies and mechanism of action, XTANDI can cause fetal harm and loss of pregnancy. There are no human data on the use of XTANDI in pregnant females. In an animal reproductive studies (studies in non-metastatic CRPC, hypertension was reported in 11% of patients receiving XTANDI and 4% of patients receiving placebo. Medical history of hypertension was balanced between arms. Hypertension led to study discontinuation in 1% of patients in each arm. In the PROSPER study in non-metastatic CRPC, hypertension was reported in 12% of patients receiving XTANDI and 3% of patients receiving placebo.

Post-Marketing Experience

The following additional adverse reactions have been identified during post-approval use of XTANDI. Because these reactions were reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate the frequency or establish a causal relationship to drug exposure. Body as a Whole: hypersensitivity (edema of the face, tongue, lip, or pharynx). Gastrointestinal Disorders: vomiting. Neurological Disorders: posterior reversible encephalopathy syndrome (PRES). Skin: Subcutaneous Tissue Disorders: rash.
more research is needed to confirm the clinical value of a high PEER value for diagnosis of CD117-positive ROs, Dr. Kauffman told Urology Times. “We need larger numbers, and more importantly, we need external validation from other institutes,” he said.

Dr. Kauffman and colleagues first identified PEER as a potential clinical variable that could improve preoperative differentiation of renal tumor biopsies in a retrospective analysis of 93 RO or chromophobe RCC tumors that were resected between 2003 and 2012. They found some clinical variables, including tumor size and age, were associated with chromophobe RCC.

However, the most reliable variable turned out to be the CT peak signal intensity in a tumor, especially when expressed as a ratio of tumor to cortex. The authors further observed that differences in tumor-cortex signal intensity between RO and chromophobe RCC were greatest when using an early contrast phase, as opposed to a delayed phase. All of the RO tumors were relatively hyperenhancing with a tumor:cortex PEER of 0.50 or greater, according to their report. Conversely, the chromophobe RCCs were relatively hypoenhancing, at a PEER of 0.50 or less—except for four cases with a PEER over 0.50, all of which turned out to be CD117-negative.

Subsequently, Dr. Kauffman and co-investigators looked at PEER prospectively in 22 additional tumors that were specifically CD117-positive, and the CT enhancement measure once again correctly classified all of them as RO or chromophobe RCC.

**Inter-observer reproducibility excellent**

The prospective inter-observer reproducibility was excellent for PEER scoring, with an intraclass correlation coefficient of 0.97, and perfect for assignment of RO versus chromophobe RCC, at 1.0, according to the study authors. “It was very encouraging that this tool showed a very high reproducibility among our own different observers,” Dr. Kauffman said. “They had different levels of radiologic expertise, and despite that, their independent scoring of every tumor was remarkably similar.”

The study was supported in part by a grant from the National Cancer Institute.
Clinical Updates

Study: Germline mutation prevalence high in RCC subset

Findings suggest certain patients should be referred for genetic counseling

Out of 74 patients with non-clear cell RCC, nine (12.2%) had RCC-associated germline mutations.

Eight potentially actionable mutations

Out of 74 patients with non-clear cell RCC, nine (12.2%) had RCC-associated germline mutations, while in the 177 patients with clear cell RCC, only three (1.7%) had such mutations (p=0.001).

Eight out of nine of those germline mutations in the non-clear cell RCC subset were potentially actionable. Those included seven mutations in FH, which is diagnostic of the hereditary syndrome hereditary leiomyomatosis and RCC (HLRCC), and one in MET.

For patients with FH mutations diagnostic of HLRCC, clinical practice guidelines now recommend treatment with bevacizumab (Avastin) plus everolimus (Afinitor) or erlotinib (Tarceva), and in a phase II biomarker study, presence of a germline MET mutation was associated with response to MET/VEGFR2 inhibitor treatment in patients with papillary RCC, Dr. Carlo and co-authors reported.

DOES FRAILTY PREDICT FOR COMPLICATIONS AFTER BLADDER CANCER SURGERY?

Measures of frailty and comorbidity failed to offer predictive information regarding postoperative complications in a study of patients with bladder cancer undergoing radical cystectomy. Better stratification accord remains an unmet need in the field.

"Despite significant refinements in surgical techniques, radical cystectomy remains a highly morbid operation, and greater than one-half of patients experience complications during their hospital stay and after discharge," wrote study authors led by Yair Lotan, MD, of the University of Texas Southwestern Medical Center in Dallas. Earlier research has been done attempting to predict post–radical cystectomy outcomes using tools such as the American Society of Anesthesiologists (ASA) Physical Status Classification, the Charlson Comorbidity Index (CCI), and others.

More recently, there has been suggestion that measures of frailty might be correlated with post–radical cystectomy outcomes. The new study assessed whether the modified Frailty Index, as well as the CCI and ASA classifications, can predict complications following the operation. The results were published in Cancer (Oct. 6, 2018 [Epub ahead of print]). To read more about this research, go to bit.ly/frailtybladderca.

Andrew Bowser
UT Correspondent

Patients with advanced non-clear cell renal cell carcinoma (RCC) have a high prevalence of germline mutations, including some that could be used to guide therapy, researchers reported in JAMA Oncology (2018; 4:1228-35).

More than 20% of the non-clear cell RCC patients had a hereditary mutation, and about half of those were in specific genes, FH and MET, that could be used to direct systemic treatment or to indicate eligibility for clinical trials, said researcher Maria I. Carlo, MD, a clinical geneticist and medical oncologist at Memorial Sloan Kettering Cancer, New York.

"These findings suggest that regardless of family history, patients with advanced non-clear cell RCC should be referred to a cancer geneticist to at least consider germline testing," Dr. Carlo said in an interview with Urology Times.

"There is still more research to be done to clarify which subgroups of non-clear cell should be referred, but I think it’s definitely reasonable to have a discussion with all patients with non-clear cell RCC, knowing you’ll have a higher prevalence of mutations."

MARIA I. CARLO, MD

According to co-author Robert Motzer, MD, those results suggest all non-clear cell RCC patients should be referred for genetic counseling.

"Beyond a rare inherited condition called von Hippel-Lindau syndrome, as well as a few other uncommon disorders, we haven’t previously known that kidney cancer had this strong hereditary component," Dr. Motzer said in an article on the Memorial Sloan Kettering blog, On Cancer (bit.ly/RCCblog).

"In the modern era of oncology, with near-ubiquitous sequencing of tumor DNA, increasing numbers of germline variants in cancer-related genes may be found," wrote commentary authors Patrick G. Pilić, MD, and Kathleen A. Cooney, MD.

However, a team approach that includes genetic counseling, treatment planning, and cancer prevention will be needed to interpret the genetic findings ethically and appropriately, wrote Dr. Pilić, of the University of Texas MD Anderson Cancer Center in Houston, and Dr. Cooney, of the Huntsman Cancer Institute in Salt Lake City.

Dr. Carlo reported a consulting or advisory role with Pfizer.
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Special to Urology Times

While many efforts in cancer detection and treatment have led to improved morbidity and mortality outcomes, that is not necessarily the case with bladder cancer. In fact, despite improved patient awareness, driven by advocacy groups like the Bladder Cancer Advocacy Network (BCAN) and well-defined guidelines for diagnosis and treatment (AUA/SUO, NCCN), the 5-year survival rates for bladder cancer have remained largely unchanged since the 1990s.

There may be multiple reasons for this, but one major cause to consider is the continued poor compliance with established guidelines. In fact, multiple studies have shown that despite having well-established guidelines and increased patient awareness of bladder cancer, compliance remains low.

A study by Schrag et al found that only 40% of patients were compliant with the recommended schedule of bladder cancer surveillance (J Natl Cancer Inst 2003; 95:588-97). Chanie et al found significant underutilization of care in patients with high-grade, nonmuscle-invasive bladder cancer (NMIBC), with only one case of comprehensive compliance out of 4,545 eligible patients (Cancer 2011; 117:539-401). A more recent study conducted within the Veterans Affairs system by Han et al and presented at the Veterans Affairs Urological Forum at the 2018 AUA annual meeting concluded that one-third of veterans with high-risk NMIBC do not receive the recommended surveillance regimen, defined as one cystoscopy every 4 months for the first 2 years after diagnosis.

While possible causes to consider for the poor compliance were identified, such as provider and patient attitudes and perception of risk, direct analysis of any patient component was not possible in these studies as there were no follow-up mechanisms in place to survey patients. Having the opportunity to question patients about their experience could perhaps provide a more thorough understanding about poor compliance from the patient’s perspective. This in turn could also play an important role in the ongoing shift to value-based medicine, not only in improving outcomes but also in improving patient satisfaction.

The other end of the scope

Cystoscopy has been the gold standard for bladder cancer detection for over 100 years. Over time, the technique and equipment have evolved, but the mechanism for direct bladder observation has remained basically the same, i.e. direct visualization of the bladder mucosa. While effective, it is also invasive and is at least in part responsible for patient non-compliance.

A recent patient survey conducted by BCAN addressed a number of questions and concerns that could help lead to a better understanding of patients’ poor compliance with surveillance guidelines.

The BCAN survey was completed by over 1,000 participants, more than 900 of whom were surveillance patients in the United States. A $10 gift card was offered as incentive to minimize survey participant bias. A primary objective of the survey was to assess patients’ attitudes about cystoscopy and to quantify their feelings across four primary measures: discomfort, pain, anxiety, and embarrassment. Attitudes and feelings were self-reported by surveillance patients on a continuum ranging from mild to severe for each of the four measures. While less than 30% of U.S. patients experienced moderate to severe embarrassment, results were higher for discomfort, pain and anxiety (figure).

In summary, across these measures, up to 65% of U.S. patients have experienced moderate to severe discomfort, pain, or anxiety. Qualitative comments offered by survey participants further reinforce the negative experience of cystoscopy and support that the invasiveness of cystoscopy could contribute to non-compliance with the guideline-recommended surveillance protocol.

In a follow-up section, patients were given access to information about urine biomarker testing and its potential utility in the surveillance setting (Urol Oncol 2017; 35:531.e15-531.e22). Patients were then asked if after two or three cystoscopies revealing no tumor recurrence, would they be willing to use a urine biomarker test to reduce the frequency of cystoscopies as part of their ongoing surveillance.

In summary, only 12% of U.S. patients were not interested in trying to use a urine biomarker test to reduce the frequency of cystoscopy once they had two to three negative cystoscopies post-resection. More than one-half of participants would be interested in the potential of using a urine biomarker test to reduce the frequency of cystoscopy as part of their ongoing surveillance, lending support to the idea that a noninvasive option could promote improved surveillance compliance.

Flott et al recently identified the importance of a patient-centric approach to improving the patient experience in urologic cancer care (J Clin Oncol 2017; 10[15]:39-46). While the BCAN survey is not a prospective patient-reported outcomes measure, it does provide insight into the patient experience that may be contributing to poor compliance with surveillance guidelines.

With the advent of more sensitive urine biomarker tests that can offer enhanced risk stratification and the opportunity to reduce the frequency of cystoscopy, a shared decision-making process with each individual patient may well help to improve compliance, outcomes, and overall patient satisfaction. With the potential for value-based medicine on the horizon, this approach could be just what the doctor, and the patient, ordered.
Should radiotherapy be offered for metastatic prostate Ca?

Phase III data indicate benefit only for a subset of patients

The management of primary tumors in the setting of metastases has remained an active area of investigation for several malignancies, including genitourinary cancers. A large randomized controlled trial was conducted at 117 hospitals in Switzerland and the United Kingdom (STAMPEDE-Trial) to determine the benefit of radiation therapy (RT) to the prostate, in addition to androgen deprivation therapy (ADT), in men with newly diagnosed metastatic prostate cancer (Lancet Oct. 18, 2018 [Epub ahead of print]). According to Parker et al, there was no improvement in the overall survival for the entire group, but survival improvement was noted in a subset of patients by adding RT to the standard of care ADT.

The investigators randomly assigned 2,061 patients to either receive standard of care ADT (1,029 men; control group) or ADT plus RT (1,032 men; radiotherapy group). Standard of care was lifelong ADT alone, but during the trial, upfront docetaxel (Taxotere) use was permitted (given to 18% of men). RT was delivered either as daily (55 Gy in 20 fractions over 4 weeks) or weekly (36 Gy in six fractions over 6 weeks) treatment. The primary outcome was overall survival in the entire study population, seeking a 25% relative reduction in death from any cause. Secondary outcomes included failure-free survival, progression-free survival, metastatic progression-free survival, prostate cancer-specific survival, and symptomatic local event-free survival (including urinary tract infection).

The researchers also documented the metastatic burden in 94% of men during the study. High metastatic volume, defined as four or more bony or visceral metastases, was noted in roughly 58% while all remaining 42% were classified as having low-volume metastases. Median PSA before ADT was quite high at 97 ng/mL, and the groups were quite comparable in terms of the usual clinical parameters.

There was no improvement in overall survival from the addition of RT to ADT when compared with controls receiving only ADT. After a median follow-up of 37 months, 391 patients had died in the control group (median survival, 46 months) with 370 deaths in the radiotherapy group (median survival, 48 months; stratified log-rank test $p=0.451$; HR: 0.92, 95% CI: 0.80-1.06; $p=0.266$). The median failure-free survival improved in the RT group compared to the control group (17 months vs. 13 months; HR: 0.76, 95% CI: 0.68-0.84; $p<0.001$).

When analyzed based on metastatic burden, overall survival was improved in patients with low-volume metastases who received RT and ADT when compared with the controls who received ADT (with or without docetaxel) as their initial treatment (HR: 0.68, 95% CI: 0.52-0.90; $p=0.007$). The 3-year median survival was 73% in control group and 81% in the RT group. Similarly, the failure-free survival was improved in patients with low metastatic burden who received RT (HR: 0.59, 95% CI: 0.49-0.72; $p<0.001$).

One or more “symptomatic local events” were reported by 432 patients (42%) in the control group and 450 patients (44%) in the RT group. There was no difference in the time to first symptomatic local event. The most common events were urinary catheterization (3%) and UTI (5%-7%), with 52% of the patients in each group requiring ureteral stents or transurethral resection of the prostate. In patients receiving RT, grade 1-4 bladder toxicity was noted in 68% while grade 1-4 bowel toxicity was noted in 55%. There was somewhat lower toxicity noted with the weekly RT treatment schedule when compared to the daily treatment.

Intriguing results, but caution needed

The authors suggest that radiotherapy in the subgroup of men with low metastatic burden should now be considered standard, but it’s important to remember that the study was not designed to evaluate the radiotherapy treatment benefit in these men. While the analysis yielded intriguing results, the conclusion based on subgroup analysis should be viewed with caution. The total number of deaths in the low-volume metastases cohort was relatively low in both the RT group (90/410, 22%) and the control group (116/409, 28%), with absolute difference of 6%. This would suggest that more events (ie, deaths) and longer follow-up may be needed to assess the benefit of RT in this subgroup of men.

The radiation dose used in this trial is lower than what is used in clinical practice. Could higher dose of RT result in improved survival and better local control? Other local therapy options such as prostatectomy were not included in this trial. There is clinical evidence to suggest that surgery should be as effective as RT in this setting. Another challenge is the numerous definitions used in the literature to define low-volume, or oligometastatic, disease and the most appropriate imaging studies to detect metastases.

Many of these questions regarding the type, duration, and benefits of local therapy in men with metastatic prostate cancer will likely be answered through several ongoing clinical trials such as SWOG 1802 (ClinicalTrials.gov Identifier: NCT03678025). In the meantime, hopefully these data are not viewed as license to indiscriminately offer local therapy, either RT or surgery, to men with metastatic prostate cancer.
How to bill for hospital consults without physical exam

Charging by time permissible with appropriate documentation

Q: What is the best way to charge for a consult at the hospital that does not require a significant physical exam? For example, I was asked to see an old Medicare patient of mine who was in urinary retention following a major surgery. My billing department told me that I could not charge without documenting a physical exam.

A: You have a very important question for urologists. First and foremost, your billing department is correct. A Level 1 initial hospital care code requires a detailed physical exam (at least four exam points for the affected organ system, in this case the genitourinary system, and at least four exam points in other organ systems).

Without the required history and physical exam, we recommend using the subsequent hospital care code that is satisfied by your documentation of the physical exam. For future consults that do not require a significant amount of physical exam, we recommend charging by time, if over 50% of the time has been spent in counseling the patient and coordinating care.

For hospital consults that do not require a significant amount of physical exam, we recommend charging by time, if over 50% of the time has been spent in counseling the patient and coordinating care.

- specific total time indicating the time spent with the patient, and the floor time as indicated above
- time spent in counseling the patient or include the statement that “over 50% of the time was spent in counseling and coordinating care”
- issues/data discussed with the patient.

The average time to accomplish a Level 1 recorded in the CPT book is 30 minutes. This is considered an average time and not a “threshold” time. If you spend less than 30 minutes, you can still charge this code (99221).

Q: My biller said she heard at one of your seminars that we did not need to append a −25 modifier to an E/M charge in conjunction with 51798. This does not seem to be correct. I specifically remember being told many years ago that we had to attach a −25 modifier to any E/M code when billing with 51798 (Measurement of post-voiding residual urine and/or bladder capacity by ultrasound, non-imaging).

A: Many years ago, what you were told was correct. All of the 5XXXX codes were either 0-, 10-, or 90-day globals. Charging an E/M service with any CPT code from the Surgery section would require the appropriate modifier, and −25 is the most appropriate in the majority of cases.

However, as time changes, so do Medicare rules. Your biller is correct at this time. When billing Medicare, you do not need a −25 modifier attached to the E/M when billing with 51798 (Measurement of post-voiding residual urine and/or bladder capacity by ultrasound, non-imaging).

For Medicare patients, do not add the −25 modifier to an E/M code when billing in conjunction with an XXX global procedure. In addition to the above, 51794, all laboratory services (including urinalyses), and imaging procedures are listed as XXX global services.

The exception to that rule are the few XXX procedures/services that include E/M services in the bundled service list under the NCCI edits. An example of an XXX global procedure that requires a modifier for an E/M code reported on the same date is 96402 (Chemotherapy administration, subcutaneous or intramuscular, hormonal-anti-neoplastic).

If you check the bundling matrix in AUAcodingtoday.com, you will be able to see if a modifier is required for E/M code by entering all codes to be charged that date and clicking “analyze codes.”

Please see CONSULTS, page 26
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How to predict performance in value-based pay models

Use CMS QRUR information to understand your practice’s costs

I
n September 2018, the Centers for Medicare & Medicaid Services (CMS) announced that the Quality and Resource Use Reports (QRURs) and Physician Quality Reporting System (PQRS) Feedback Reports will no longer be available after the end of 2018. These reports offer valuable insight into urologists’ performance compared to peers and benchmarks in two programs (Value-Based Payment Modifier, PQRS) that have been transitioned into the Merit-based Incentive Payment System (MIPS). If you have not already done so, you should download these reports from the CMS website (bit.ly/QRUR/ BM) before the end of 2018.

Encouraging patients to maintain a relationship with a PCP is a good strategy for patient care coordination as well as ensuring that costs are allocated to your TIN only when your providers really are the most responsible for these patients’ care and costs.

CONSULTS

continued from page 24

The bundling matrix will indicate whether an E/M code needs a modifier for either an NCCI bundle or a global period bundle.

Q: I have a two-part question for you. First, if you perform a laparoscopic pyeloplasty, can you bill 50605 as well as for stent placement through a ureterotomy? My hospital system is saying they are bundled, but I don’t think they are. Second, when I do a ureteroureterostomy, I feel code 50605 should be allowed, but they keep denying my coding. Can you help me to set the record straight?

A: Regarding your first question, the description of 50544—Laparoscopy, surgical; pyeloplasty—does not include insertion of a stent in the description. Nor is there a different code that would include both the stent insertion and pyeloplasty. Therefore, from a CPT coding perspective, it is appropriate to look for a code that would describe the insertion of a stent to report in addition to the laparoscopic pyeloplasty.

Unfortunately, CPT does not include a code for laparoscopic insertion of stent. Expanding the search, we find two potential codes that could be considered: 50605 (Ureterotomy for insertion of indwelling stent, all types) and 30949 (Unlisted laparoscopy procedure, ureter). Choosing which code to use is a bit of debate. Code 50605 does not specify approach in the description. The AUA has recommended in other cases for circumstances in which there is no existing laparoscopic code for the procedure performed, with payer notification, a code considered to be traditionally provided with open approach but without a specified approach in the descriptor can be reported for the service. Note that payer notification is recommended prior to reporting the service. Many groups are successfully reporting in this manner.

However, for those instances where the payer prefers the use of the unlisted code or in circumstances in which the compliance program for the billing entity requires reporting of the unlisted code specifying approach, the unlisted code with reference to the compatible open code should be reported.

Neither of the codes is considered bundled with the pyeloplasty code in the National Correct Coding Initiative (NCCI) bundling edits. Therefore, you should charge separately for the insertion of the stent when medically necessary. It should be noted that not all payers conform to NCCI bundling edits; as such, you may encounter some payers that will not allow separate payment for the stent insertion.

Finally, NCCI edits change quarterly. This answer was correct at the time of publication, but you will need to make sure that edits do not change for future billings. Note: As we have stated many times before, documentation for all procedures should support the medical necessity for performing that procedure at that encounter. If medical necessity cannot be supported, the procedure should not be charged.

Addressing your second question, the description of 50760 (Ureteroureterostomy) does not include insertion of the stent. The two codes are bundled in the NCCI, but could be unbundled with the modifier. However, since the stent is being inserted because of the procedure and is related to the procedure, there is not a good modifier that will pull you out of the bundle. We would recommend that you not bill for the insertion of the stent separately.

While the payment adjustments from these 2016 programs have already occurred in 2018, the QRUR in particular contains actionable information for your practice. Furthermore, my interpretation of recent reports from CMS indicate that the patient- and physician-level detail available in the 2016 QRUR may not be forthcoming under MIPS reporting (Cost Category). This article, then, will focus on how to use your 2016 report to understand your practice’s “costs” and how to begin to influence those costs.

How are patients attributed to your practice?
The Cost Category for MIPS includes the same two measures found in your 2016 QRUR: Total Per Capita Costs for All Attributed Beneficiaries (TPCC) and Medicare Spending Per Beneficiary. Please see QRUR, page 27
QRUR
continued from page 26

From the mean, you should examine your supplemental tables in detail to determine why and form a plan to lower those costs to the extent you can (more on this later).

Tables 5B (Beneficiaries and Episodes Attributed to Your TIN for the MSPB Measure) and 5D (MSPB Costs, by Episode and Service Category) are probably the most important tables to review.

Next, open Table 2A (Beneficiaries Attributed to Your TIN for the Cost Measures). Here, you will find a list of all beneficiaries attributed to your TIN; the reason for attribution, the number of services incurred by providers in your TIN and outside your TIN, and whether the patient was hospitalized.

Action(s) you should take: Look at the Basis for Attribution column. If you have any step 1 patients, then it may be because your NP or PA is billing under their specialty type rather than your physicians’ (incident to). If all your patients are step 2, then you can assume that these patients did not see a PCP in 2016. Encouraging patients who were readmitted to the hospital within 30 days to see if they were preventable admissions.

Bottom line: This set of reports presents an opportunity to understand which physicians, facilities, and diagnoses have been associated with higher cost. Potential actions include raising awareness about costs of care, shifting referral patterns to lower cost facilities/physicians, implementing a workflow to ensure that patients with chronic conditions see a PCP at least once a year, and addressing how your practice controls urology-related ED visits that might result in hospitalization. While the information is somewhat dated (2016), this author believes the QRUR is predictive of a practice’s success under MIPS and future value-based reimbursement generally.

Table 3B shows detailed cost information by category of service and inside and outside your TIN for TPCC.

Action(s) you can take: Using a spreadsheet or basic business intelligence tool, link this table to Table 2A and Table 2C using the patient identifier as the link/key. From these joined data, analyze costs by category and group into those you can control (in your TIN, categories you control such as major procedures) and those you cannot. Look for expensive outliers in your practice.

Table 4A-4D address attributed beneficiaries with chronic conditions, and there is no direct correlate for urologists in the Cost Category of MIPS. The information does serve as another reminder that patients with any non-urologic chronic condition should see a PCP and not be attributed to your TIN under the TPCC in Cost Category of MIPS.

Finally, Tables 5B (Beneficiaries and Episodes Attributed to Your TIN for the MSPB Measure) and 5D (MSPB Costs, by Episode and Service Category) are probably the most important tables to review. Linking these tables on the beneficiary will reveal detail on costs by provider, facility, diagnosis, and category. These are the costs that your TIN can influence.

Action(s) you can take: Using a spreadsheet, identify low- and high-cost providers, hospitals, and diagnoses. Use these apples-to-apples comparisons to steer patients to low-cost facilities where appropriate. Examine the charts of patients who were readmitted to the hospital within 30 days to see if they were preventable admissions.

Bottom line: This set of reports presents an opportunity to understand which physicians, facilities, and diagnoses have been associated with higher cost. Potential actions include raising awareness about costs of care, shifting referral patterns to lower cost facilities/physicians, implementing a workflow to ensure that patients with chronic conditions see a PCP at least once a year, and addressing how your practice controls urology-related ED visits that might result in hospitalization.

The information is somewhat dated (2016), this author believes the QRUR is predictive of a practice’s success under MIPS and future value-based reimbursement generally.
As 2019 nears, focus on these financial planning tasks

Take time to review emergency fund, max out retirement account contributions

Q: What are some financial planning tasks I should focus on before year end?
A: The quickly approaching year end presents the perfect opportunity to review and possibly adjust your financial planning strategies. A lot can happen in a year, and you should be updating your accounts and checking in on where you stand with many of the goals you set at the beginning of the year.

Check on the status of your emergency fund. Did you need to dip into it at all this year? Have your necessary expenses changed? It’s always a good idea to review the balance of the account as well as your budget to see if additional funds need to be added to bolster the account. The general rule of thumb for emergency funds is to have 3 months of necessary expenses if you are a dual-income household and 6 months to a year if you are a single-income household.

Max out your retirement accounts. You have until the tax filing date next spring to make a 2018 contribution to an individual retirement account (IRA), but 401(k) and 403(b) contributions are only deductible when made in the same calendar year. The 2018 contribution limit is $18,500 for 401(k)s and 403(b)s and $5,500 for IRAs. If you are over age 50, catch-up contributions may be available as well.

Use the remaining money in your Flexible Spending Accounts. If you still have money set aside in a flexible spending account for health care or dependent care expenses, it is important to try and use those funds before the end of the year or risk forfeiting the money. Some employers offer a grace period into the spring of the next year or a $500 flexible spending account carry-over from 1 year to the next, but most do not.

Make contributions into your children’s 529 accounts. College costs continue to rise, and it is important to start saving early if you hope to reach your college funding goals. Additionally, in some states, a state income tax deduction is offered to residents who contribute to their 529 plan. In some cases, the tax savings can be substantial.

Review the balance of your emergency fund as well as your budget to see if additional funds need to be added to bolster the account.

Designate those individuals to whom you wish to gift assets. The annual gift tax exclusion is $15,000 for 2018 ($30,000 for married couples). You can gift this amount to any number of individuals without having to pay gift tax or have it count against your lifetime gift and estate tax exemption.

Make charitable donations. Giving to charity can be a very powerful tax-savings tool. Check and see if you have any appreciated investment assets that you could gift instead of cash. This way, you avoid paying capital gains taxes on those investments and are able to claim a deduction for the full value of the donated asset. When the charitable organization sells it, there’s no tax to them. Be aware, however, that under the new tax law, you may need to donate a substantial amount of assets to be eligible for a charitable deduction on your taxes.

These are just a handful of financial issues to consider as we approach year end. Your financial and legal advisers can run through a more comprehensive checklist of planning options based on your personal circumstances.

Q: My 401(k) has a vesting schedule. What does vesting mean?
A: Many employer-sponsored retirement plans have a vesting schedule to incentivize employees to remain with the company long term. Vesting refers to ownership and means that, even if your employer made matching contributions, you may not fully own those assets yet. While you are always 100% vested in the salary deferral contributions you make to the plan, ownership of employer contributions is gained over time.

Vesting schedules may be graded, giving you increased ownership of employer contributions each year. For example, after 1 year of service you may be 20% vested and after year two, 40%, and so on until you are 100% vested. Graded schedules can be no longer than 6 years.

Alternatively, the plan may have a cliff vesting schedule. Just like it sounds, this provision means that for a certain period of time, you won’t be vested at all. Then, like going off a cliff, you become 100% vested all at once. If your employer selects a cliff vesting schedule, the cliff can be no longer than 3 years of service. With either type of vesting schedule, the definition of service can vary, so be sure to read the plan document.

Financial tips

- You have until the tax filing date next spring to make a 2018 contribution to an individual retirement account, but 401(k) and 403(b) contributions are only deductible when made in the same calendar year.
- Under the new tax law, you may need to donate a substantial amount of assets to be eligible for a charitable deduction on your taxes.
- Vesting for 401(k) plans may be on a graded schedule, giving you increased ownership of employer contributions each year, or on a cliff schedule, meaning that after a period of time, you become 100% vested all at once.
Preventing and addressing dishonesty in the workplace continues to challenge my physician practice clients. Recently, a client suffered an extreme example of how workplace dishonesty can cause harm. Her scary story is unfortunately familiar to many providers out there.

The situation began with a visit from a payer’s fraud department. The investigators reviewed patient charts with my client, the practice owner, and hinted at fraudulent billing and other improprieties. She could not understand the investigators’ claims and did not recognize the patient names at issue.

She began by looking for the patients’ names in the system. We immediately realized the charts were modified, deleted, or nonexistent. When the individual who handles IT for the practice was contacted for help—let’s call him Bart—he became nervous and uneasy. Bart was terminated immediately when it became clear he had played some role in the issue at hand.

Bart exclusively handled the practice’s administration, provider billing, bill paying, check deposits, vendor contracts, payroll, and other key activities. Bart disappeared the day this happened and has not been seen or heard from since. There is evidence that he continued to access the practice’s servers to delete and modify records remotely even after his departure.

My client brought in an IT and forensic specialist to address the issues Bart created, as he was also the only one at the practice with passwords, system access, and any knowledge of the IT setup. After reviewing payroll records, it appeared that Bart established fake vendors that payroll funneled thousands of dollars to biweekly. My client had not detected the payments since all payroll and other financial activities had been left in Bart’s hands. We also determined Bart had obtained credit cards in the practice’s name and racked up bills for friends and family—all paid at the expense of the practice.

Since Bart handled all paperwork for the practice, my client did not question anything Bart asked her to sign. Bart was able to open bank accounts, take out loans, and otherwise use the practice’s credit, identity, and revenue.

Because all the mail in the office also went through Bart, my client also found there were many unpaid bills, including those for malpractice insurance, general liability insurance, provider license renewals, and health insurance premiums. Even worse, the very insurance my client might have turned to for coverage of Bart’s fraudulent activities lapsed.

Since Bart handled all the billing, it is still unclear how much of it was fraudulent. We do know that Bart reviewed the original payer audit request and responded without the practice’s knowledge, triggering the investigation.

I continue to assist my client in trying to address financial and legal issues. This should be a lesson to all practice owners to take proactive steps to protect themselves. At a minimum, they should:

- Complete a background check on everyone who is hired. Bart had a criminal history, which could have been easily detected.
- Never assign one employee complete oversight of any particular function within the practice. Make sure there is more than one person for every task and regular oversight and/or audit for any employee with significant financial, IT, or billing responsibilities.
- Always have access to passwords, bank accounts, and be trained in other major practice responsibilities.
- Conduct regular financial audits. This could mean reviewing the income and expenses with your accountant monthly or some other approach.
- Look for red flags. In this case, Bart did not let anyone else touch his computer or handle billing. He got anyone who he did not “like” fired. He was the only one allowed to open mail, handle checks, or pay vendors. He always took his laptop home with him. Controlling conduct like this should be a red flag for practice owners.

In this case, the police and FBI were informed of Bart’s activities, and the payer is helping the practice figure out what occurred.

There are many more steps that a practice can take to protect itself. I suggest talking with legal and financial advisers to make sure your practice has adequate safeguards in place. Let this client’s experience serve as a warning to physician practices everywhere.
How to streamline your practice’s workflows and processes

Identifying issues and embracing a team approach can lead to positive change

SUSANNE MADDEN, MBA, PCMH CCE
Ms. Madden is president and CEO of the Verden Group, a consulting firm. She is a contributor to Urology Times sister brand Physicians Practice, where this article was first published.

It’s Monday morning. Your phones are ringing off the hook, patients are getting squeezed into the schedule any place your staff can find, and it’s looking like it’s going to be another exhausting day.

Make sure that you are solving the right problem by digging in to the root cause of the issue.

But does it really have to be like this? Busy offices rarely have the time to pause, evaluate workflows, and attempt to improve efficiencies across the practice. However, unless you make that time, things are likely to stay the same and you’ll repeat those exhausting Mondays over and over.

Where to start
First, start with the most obvious issues. For example, figure out what is the single, most recurring annoyance in your practice. Is it being over-scheduled? Patients not getting timely call-backs? The same questions coming up time and again from patients? Narrowing it down to an item or two that you’d like to improve is essential to making any progress at all. Try to do too much at once and you will likely fail, as time is limited and more pressing obligations will always keep popping up.

Second, put together a small team of people to work on the problem and set aside 30 to 45 minutes a week to work on it. Tapping into those on the “front lines” of the issue often reveals quick solutions. Staff usually know what needs to be fixed and how to fix it, but either haven’t been empowered to do so themselves or simply haven’t had the time to focus on implementing the solution.

Third, make sure that you are solving the right problem by digging in to the root cause of the issue. I find that working with the “5 Why’s” process (bit.ly/The5whys) and the “How, How” diagram (bit.ly/HowHowdiagram) is very effective at getting to the underlying cause of a problem, and working through how to implement a solution.

A variety of process improvement tools can assist you in any area of process improvement: from the more complex Six Sigma methodology to working with an A3 problem solving tool—but the best process improvement projects are usually those where the easiest process for your team is used, and they can hone their improvement skills over time from there.

Implementing your changes
Once you’ve established the problem, its cause, and how you can change it, you need to implement those changes in your practice.

Start by drafting a staff memo that accomplishes two things: it ensures that your new process gets captured and disseminated to the staff, and it can be used as part of your training materials going forward. As you perfect more and more processes, that library of literature will grow.

Don’t expect miracles overnight. Staff need time to get used to a process change, particularly if it changes the flow of what they do.

The memo should lay out a few components. It should identify the nature of the problem, quantify why it’s a problem, and state exactly what the team has proposed as the solution. Then ask that everyone support the change, and let them know that you will be measuring the outcome.

Slow and steady wins the race
Don’t expect miracles overnight. Staff need time to get used to a process change, particularly if it changes the flow of what they do. The key to ensuring that changes will stick is to measure the progress and reinforce the new process any place that you find it is not being implemented routinely. Staff need to practice the new way of carrying out a task, and reinforcement is what gets them there.

And don’t forget—always go with the easier changes first. Why? Because having some early “wins” will allow staff to feel confident in deploying new processes, and over time the process of continuous improvement itself can become part of the practice culture. If you try to do too much, too soon, your staff may become overwhelmed and everyone will fail in the endeavor.

It really doesn’t matter whether the issue is administrative or clinical. Identifying a problem, working as a team enabled by process improvement tools to develop a solution, and moving toward implementation is bound to improve how your practice flows.

PHYSICIANS OUTLINE THEIR EHR WORK-AROUNDS

In early August, Centers for Medicare & Medicaid Services Administrator Seema Verma called for an end to physicians using faxes to transmit patient data by 2020. While those outside of medicine wondered why she would want to ban a seemingly obsolete piece of office equipment, many physicians wondered how they would access patient records without it.

So how are doctors getting the patient data they need when they need it? Urology Times sister publication Medical Economics talked to doctors on the front lines—as well as those working on the technology meant to help them—to find out. Learn more at bit.ly/EHRworkarounds.
You chose to be a urologist, now count your blessings

Specialty abounds with unique attributes, opportunities for practitioners

Dr. Baum

Dr. Baum is professor of clinical urology at Tulane University School of Medicine, New Orleans.

Your Voice

Commentary from residents, non-physician providers, and other voices in the field

As I read the journals and look at the job boards, I am pleasantly surprised at the wide range of opportunities available for graduating urology residents.

There's always demand for our services, and that demand will become even greater now that the baby boomers are reaching age 65. In fact, 10,000 people reach age 65 every day. That translates into a lot of work for every American urologist, as most of the aging baby boomers will eventually need our services.

Urology is broad in scope, although the organ systems we treat are relatively small. We have an opportunity to focus on a single, defined area such as urologic oncology, endourology, incontinence, andrology, or robotic surgery. Consequently, if we choose, we can become experts in a defined field or subspecialty.

As I read the journals and look at the job boards, I am pleasantly surprised at the wide range of opportunities available for graduating residents. A newly minted urologist can become an academician, join a large group practice, join a small group of urologists, or even become a solo practitioner. Young urologists can select from a wide variety of geographic locations and can always find something that fits their practice style and lifestyle. We will always be able to find a job.

The call schedule for a urologist is doable compared to that of obstetricians, general surgeons, and orthopedic surgeons. If urologists are experiencing burnout, with some reports as high as 50%, I doubt it is because of an overburdened call schedule.

Many opportunities for entrepreneurship

Our specialty offers multiple opportunities for entrepreneurship and creativity. Most of the new devices and interventions in the field are developed by urologists. We can turn our creative juices to developing new ways of treating urologic diseases more efficiently and with less pain and discomfort.

The current trend of bringing care from the hospital setting to the office setting, where the urologist is more in control of his or her schedule, has been largely advanced by our peers and colleagues.

For those urologists who wish to segue from clinical practice to non-clinical endeavors, there are numerous non-urologic opportunities such as joining the ranks of pharma, becoming a medical director for industry or a hospital, and even going into politics and creating health care policy.

Our specialty enjoys having a good sense of humor. I have never met a urologist who doesn’t have a cute story or joke to share with colleagues and patients. Maybe that’s why we are so happy with our career choice; if you are laughing, you can’t be sad.

In short, the next time you think about what you would do instead of becoming a doctor and especially a urologist, just stop and be thankful you chose urology. You have many reasons to be grateful.
Ureteral access sheaths: Tips on when and how to use

**ANDREW PORTIS, MD**

Dr. Portis is chair of HealthEast Kidney Stone Institute, St. Paul, MN. He is a consultant and investigator for Boston Scientific.

Dr. Portis was interviewed by Urology Times Editorial Consultant Stephen Y. Nakada, MD, the Uehling Professor and founding chairman of urology at the University of Wisconsin, Madison.

**Ureteral access sheaths confer several advantages to the urologist treating a stone patient ureteroscopically. In this interview, Andrew Portis, MD, discusses his experience with sheaths and describes an algorithm for their selection and use.**

**Q:** Please tell us what a ureteral access sheath is and when you would typically use one.

**A:** A ureteral access sheath is basically a means of getting up and down the ureter multiple times while avoiding the need for reintroduction of guidewires to do so. Sheaths range between 10F and 16F in outer diameter.

I use an access sheath on any stone case where I think I’m going to have to make multiple trips up and down the ureter. For urologists like me who prefer to fragment and extract stones, that would include any stone over 4 or 5 mm. It is important to consider stone volume for estimating fragment load rather than just linear dimension.

**Q:** When did you start using an access sheath?

**A:** I started using an access sheath during my fellowship with Dr. Ralph Clayman around 1999-2000. That’s when Applied Medical Resources was coming up with the first really functional access sheath, and Dr. Clayman was involved in the development of that product.

**Q:** What did you perceive as the real tangible benefit aside from the ability to make multiple passes? Were there other advantages you were seeing?

**A:** The advantages included time efficiency, reliability, and the ability to be systematic and standardized in how I did the procedures.

**Q:** Since they vary in size, can you give us a tip or two as to what you do if an access sheath cannot be passed easily over a wire?

**A:** I’ve created an algorithm that can be viewed online (bit.ly/UASalgorithm). The algorithm begins with placing a guidewire into the kidney. I traditionally use a Benson wire first. Occasionally, I’ll find, particularly in men, that the access sheath won’t track well over that. I always place the obturator of the sheath before placing the whole sheath. The obturator will usually track up but sometimes when you add the actual sheath component to it, you’ll get a troublesome step change in durometer (stiffness) and you may have a challenge getting around a prostate.

At that point, I’ll swap out to a super-stiff wire and then I find the assembled access sheath usually tracks up well. But obviously if, according to our algorithm, you’re meeting significant resistance, the solution is just to stop. It’s a matter of recognizing resistance versus kinking.

**When would you typically use a ureteral access sheath?**

**STEPHEN Y. NAKADA, MD**

I use an access sheath on any stone case where I think I’m going to have to make multiple trips up and down the ureter.

**Q:** How do you know the difference between resistance and kinking?

**A:** Kinking is easy because you’ll see the tip deflect in the region of the ureteric orifice on fluoroscopy. For monitoring resistance, I like to keep fingertip pressure on the access sheath as I’m inserting. I get a lot of information regarding the caliber of the ureter initially from using an 8/10 dilator system, so I’ll pass the 8F inner element. If the 8 goes easily, I’ll pass the 10F coaxial sheath over that. If I find resistance with that, unless I’m very confident that I’m going to go after a small stone that can be quickly cleared without a sheath, I stop.

If I have absolutely no resistance with that, I start thinking about using a 12/14F access sheath system. If it just absolutely falls in, which would commonly be the case if a patient is pre-stented, then I might go to a 13/15F sheath system.

**Q:** If you can’t get the access sheath inserted, you said you stop. What do you do then?

**A:** I place a stent and wait 2 weeks for passive ureteral dilation.

**Q:** What do you tell your patients as part of informed consent with regards to that possible outcome?

**A:** We track this. We know that we have a 5% failure rate but it can be difficult to predict. Generally, people who are younger, female, or first-time stone patient would be the ones who might be more challenging. Then you need to differentiate an impacted stone versus a tight ureter. An impacted stone can still allow some careful options to potentially clear. There are very limited second-line strategies to deal with an extremely tight ureter.

**Q:** What are some of the risks of using a sheath regularly?

**A:** The biggest risk that has been brought to our attention is the risk of ureteral trauma, and I think if you follow a stepped approach like we’ve adopted, it’s unusual to see any kind of significant injury. We see a fair number of mucosal splitting cases, and we haven’t seen any clinical sequelae from that. But placing a sheath blindly or forcefully is asking for trouble.

**Q:** If a urologist were to just use sheaths intermittently, what would be the best case for using one?
A: The best case is one in which you need to maximize the trips up and down the ureter. Specifically, this would be for a larger stone (1 cm or greater) with intent to clear. Again, our group is fragmenting stones and clearing, so we’re doing multiple trips almost all the time, but if you’re more of the dusting persuasion, then this may not be as important. Without the access sheath, you have to be very cognizant of increased intrarenal pressure and pyelovenous backflow.

Q: What’s the maximum you would do ureteroscopically?
A: The typical top end, for a patient who didn’t have a contraindication for percutaneous nephrolithotomy, would generally be about 2 cm.

Q: Does stone composition or density play a role in your calculation?
A: If somebody has a really dense stone, where the Hounsfield units are about 1,500, we’d probably start dialing back on what we want to do for the Hounsfield units. I use a 13/15F access sheath if I know I have to clear a lot of stone and I’m confident I can get it in, typically if the patient is pre-stented. In general, it’s best to use the smallest sheath which will allow you to efficiently clear stone and we are increasingly using 11/13F for smaller stones. Since transitioning to digital ureteroscopes, the 10/12F has really become the bottom end which will accommodate our current scopes.

Q: What are some of the risks of using a sheath regularly?
STEPHEN Y. NAKADA, MD

The biggest risk that has been brought to our attention is the risk of ureteral trauma, and I think if you follow a stepped approach like we’ve adopted, it’s unusual to see any kind of significant injury.

ANDREW PORTIS, MD

A: Sometimes those instincts betray you but you don’t have to make decisions based on your instincts. I think we’re well served by the current sheath. We are a referral target for complex stones so extraction because we’re concerned about traumatizing the ureter when removing sharp fragments. By “dialing back,” I mean that I might be very cautious the ureter when removing sharp fragments.

Q: What’s the maximum you would do ureteroscopically?
A: If you can insert a bigger sheath, you’ll be more efficient. There has been some research recently on tamsulosin potentially having an effect in the ureter in allowing insertion of larger sheaths ((J Urol 2018; 199:1622-30; World J Urol May 25, 2018 [Epub ahead of print]). In some of the studies of the use of sheaths with tamsulosin, they’re using a force gauge that actually gives you a real number as opposed to subjective observations. I look forward to those results; that could be a big step forward.

Q: Do you use tamsulosin typically in all of your cases before inserting the access sheath?
A: We don’t have a firm position on tamsulosin yet. I tell patients it’s the “might” drug. It is certainly controversial whether tamsulosin actually helps stones pass. We presented research at the 2018 AUA annual meeting that showed that careful attention to symptom control was more important than tamsulosin. It “might” be beneficial in some circumstances. It “might” make it easier to place an access sheath if you can insert a bigger sheath, you’ll be more efficient. There has been some research recently on tamsulosin potentially having an effect in the ureter in allowing insertion of larger sheaths (J Urol 2018; 199:1622-30; World J Urol May 25, 2018 [Epub ahead of print]). Still, we can’t rule out that tamsulosin “might” be beneficial in some circumstances. It “might” make it easier to place an access sheath but we are still waiting on larger randomized trials.

Q: Do you think the introduction of larger access sheaths will expand the stone sizes that can be tackled ureteroscopically?
A: It “might” make it easier to place an access sheath but we are still waiting on larger randomized trials. It “might” decrease postoperative symptoms from ureteroscopy. Our algorithm generally keeps us out of trouble but ultimately sometimes you just have to make decisions based on your instincts. Sometimes those instincts betray you but you don’t know until after the fact.

Q: What do you think the future is for access sheaths?
A: I think we’re well served by the current sheath. I don’t see a need to change that. As we continue to pay attention to getting patients stone-free, the ability to actively clear stones will remain. I’m optimistic we’ll have better ways to actually remove stone fragments, but ultimately the business we’re in is to render a patient stone-free and if we can do so efficiently and safely, that’s a bonus.

Q: What do you think is the most you would do ureteroscopically?
A: The typical top end, for a patient who didn’t have a contraindication for percutaneous nephrolithotomy, would generally be about 2 cm.

What’s the maximum you would do ureteroscopically?

STEPHEN Y. NAKADA, MD

The typical top end, for a patient who didn’t have a contraindication for percutaneous nephrolithotomy, would generally be about 2 cm.
**Speak Out**  / Interviews with randomly selected urologists on hot-button issues.  
Compiled by Karen Nash.

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**Do you feel appreciated by your patients and the public?**

Generally, yes. I work in both a university hospital and the county hospital, so it’s a mix of different populations of patients. I do cancer, so the majority of patients are very appreciative.

The only caveat is the landscape of health care is changing so dramatically. We try to be independent and solve problems, but we have to wear different hats—cost-effectiveness and productivity, and that stresses out the urologist. It’s not causing bad outcomes, but it may affect the customer service.

So patients have a high regard for us, but when they get that huge bill, they may not like the physician or the hospital.

I believe the public fantasizes a bit in terms of seeing medical shows on TV. They think it’s a glamorous life; it’s actually pretty normal in a very stressful way, because we’re taking care of people’s lives and the quality of their lives.

We may cure cancers, but patients may have to adapt to a new normal, and that is sometimes difficult. Sometimes expectations are not met, or patients’ expectations are different than our expectations, sometimes because of what they see on TV. The expectations of pretreatment may not match expectations post-treatment and that becomes an issue.

It does seem to differ through the generations. Senior patients are much more appreciative. As you mature, I believe you end up having a different perspective.”

*Fernando Kim, MD / Denver*

Being a Veterans Hospital, we have a unique population. We see two extremes among patients, with the vast majority in the middle. On one side are patients who are extremely appreciative of everything that’s done for them. Frequently, these are the guys who have service-related problems who deserve the very best care we can offer. The flip side is, frankly, people who may have a significant number of complaints about care of which the majority are unfounded.

As chief, I receive these complaints. One patient was listed as a white male because his name and everything indicated that. He was actually Hispanic. That was his example of his poor treatment. I tried to correct mistakes done outside of the VA, but he didn’t accept that either. Perhaps part of the VA’s problem is that it’s mostly free; patients may not appreciate what they’re getting.

Delays getting appointments are overblown. It takes 2-3 months to get into my non-VA doctor’s office. Guys are seen here within 2 weeks or so, within days. If care is turned over from the VA and patients can go anywhere, they might come running back to the VA very quickly.”

*Lester N. Krawitt, MD / Las Vegas*

I don’t expect appreciation. We should feel fortunate for any thanks we get from patients, because, as a physician, it’s my job to take care of patients. But I believe patients do appreciate what we do, and it’s nice to receive thanks.

*Sam Bhayani, MD / St. Louis*

My patients are not like the ones on television; I don’t feel we’re asked inappropriate questions or are unappreciated.

I don’t have a metric to compare how my patients’ appreciation has changed over the past 15 to 20 years, but I feel fortunate to be a urologist. We’ve got different medicines, different treatments, and different surgeries. Patients understand how much things have changed and how fortunate they are today with the progress we’ve made.

I remember when we made a 1-foot incision to take out a kidney—patients stayed hospitalized for a week. Now, we make four tiny keyhole incisions and they go home the next day. Patients come in, and their parents had a whole different surgical experience in the ‘80s and ‘90s than they are getting in 2018. They appreciate that.

The public appreciates us too. The public is smart and knows the services we offer. The public has more information than they’ve ever had. They go on the Internet and find things. They get on their cell phones, check their electronic records, and they contact me. I can respond any time. They appreciate not having to drive 2 hours.

I’ve been fortunate to see the changes we’ve had in the last 15 years. Patients go home earlier, feeling better. We have better treatments for cancer. It’s exciting and patients appreciate that.”

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**Four tips to amplify your patient satisfaction surveys**

**Chris Byers**

Patient satisfaction surveys are growing in popularity among health care organizations as the U.S. health system continues its transition to value-based care. If done right, your patient satisfaction survey can be a key player in building a satisfying and cohesive experience for patients.

There’s just one catch: convincing patients to complete your surveys can be tough. To get the most out of your patient satisfaction surveys, follow these four tips:

**Provide a compelling “why.”** Even if your survey takes only 5 minutes to complete, you’re still asking busy people to willingly give up their time.

In the communication accompanying your survey, let patients know that you care about their experience at your facility and will take their feedback seriously. Tell them their feedback plays a vital role in improving quality of care for all patients and make it clear that you want to provide a best-in-class environment and service.

**Keep surveys brief.** It’s best to keep your surveys concise and simple. The longer and more complex a survey is, the less likely people are to participate. Also, if the survey is short and easy to understand, you’ll typically get better, and clearer, feedback from patients.

**Avoid paper surveys.** An online survey is user-friendly and much easier to manage than a paper survey. Patients can complete the survey whenever it is convenient for them, and all submitted data are housed in an organized database for easy analysis.

**Follow up quickly.** Surveys should be sent as soon as possible after the care experience—typically within 48 hours. This allows patients to respond to the survey while their experience is still top of mind.

**Chris Byers** is the CEO of Formstack, an Indianapolis-based company offering an online form and data-collection platform. This article was originally published by *Urology Times* sister publication *Medical Economics*.
IMRT ownership study methodology unsound

To the editor:
The issue of financial incentives in fee-for-service medicine impacting clinical decision-making is an important one; regrettably, the conclusions of Borza et al (“IMRT ownership appears to influence PCa treatment,” October 2018, page 6) rely on antiquated data using flawed methodology that does little to contribute to this discussion—this analysis has been previously refuted in detail when it was initially published (Eur Urol 2018; 73:491-8; Eur Urol 2018; 73:499-501 [comment]).

At its core, the study’s methodology for assigning intensity-modulated radiation therapy ownership to a urologic group is unsound. The authors determined ownership of IMRT based simply on the mention of radiation services on practice websites at a single point in 2012—furthermore, they made no effort to determine the nature of the financial relationship between the group and radiation facility, or whether the groups ceased or commenced radiation services after that time. As such, groups with partial ownership or even no ownership at all (but with co-marketing agreements) would be considered identical to groups with full ownership. Conflicting what may be complex business relationships and then assigning uniform financial motives to clinical decision-making based on a mere website mention lacks academic rigor.

The authors’ definition of single- or multi-specialty group practice (MSG) further compounds these errors. The authors’ definition of an MSG is overly narrow as it based on inclusion of a primary care physician; however, many MSGs are comprised of different medical or surgical specialists without a PCP. Consequently, the authors did not identify a single MSG in the U.S. with ownership of radiation services. Furthermore, the authors did not consider patient preference or appropriateness of treatment. The proportion of patients without identified curative intent was 23.7% and 28.1% in ownership and non-ownership groups, respectively. It would have been important to ascertain the effect that case mix could have had on this small differential.

In addition, the authors did not consider that the mechanics of patient decision-making in integrated urology practices differs substantially from services where multidisciplinary groups are not offered. Integrated urology practices typically include a radiation oncologist in the decision-making process, which has been documented to influence the decision of whether to have surgery or radiation as the initial modality of care for localized prostate cancer (Arch Intern Med 2010; 170:440-50; J Urol 2012; 187:103-8).

Utilization analysis of health care resources must be free of bias, methodologically sound, and relevant to current practice; regrettably, this manuscript meets none of these criteria. Given the relatively small number of urologists nationally and the increasing need for urologic services as our population ages, we have a unique opportunity to work together as a specialty to create novel care paradigms that utilize real data to optimize resource use and enhance outcomes by providing services where they are most effectively and efficiently delivered. The future health and well-being of our specialty, and more importantly our patients, demands it.

Deepak Kapoor, MD / New York

POST-PROCEDURE BPH MEDICATION USE NOT SURPRISING

To the editor:
I read Dr. Steven Kaplan’s “From the Board” commentary, “BPH procedures and med use: Two sides of a coin” (September 2018, page 3), with great interest. The use of LUTS/BPH medications has gained major usage resulting in a drop in the number of surgical procedures. The resulting symptom relief shows mild improvement. However, the obstructive flow factors show minimal increase in urine flow.

We believe that the increased bladder pressures basically remain the same as before treatment and over time probably result in trabeculation and/or hyperactivity. When the patient decides much later to proceed with a surgical approach, a certain amount of bladder dysfunction has already occurred. So it does not surprise us that post-procedure patients require some return to the use of these LUTS/BPH medications.

Ian Nisonson, MD / Miami

CHALLENGING CASE

PERSISTENT URETERAL STONE IN A 76-YEAR-OLD MALE

“A Challenging Cases in Urology” is a new Urology Times section in which residents from the nation’s leading urology programs present their toughest cases and how they ultimately managed them. Cases inform readers of the problem-solving process and provide a lesson from the authors’ experience. In this installment, Michele Fascelli, MD, and Bradley C. Gill, MD, MS, present the case of an elderly male with hypertension, lumbar spinal stenosis, morbid obesity, and erectile dysfunction who presents with acute right-sided worsening of his chronic back pain. A distal right ureteral stone is found on computed tomography imaging and his symptoms respond well to medical therapy, but he later develops severe right flank pain. To read more about this case, as well as other installments in this series, go to www.urologytimes.com/residents-lounge.

Axial CT scan image with distal right ureteral stone that measured 8 mm by 9 mm (red arrow) adjacent to right ureteral stent. Photo courtesy of Michele Fascelli, MD, and Bradley C. Gill, MD, MS.
First patients treated in phase II study of hyperoxaluria agent

Allena Pharmaceuticals, Inc. announced the treatment of the first patients in Study 206, an open-label phase II basket study evaluating ALLN-177 in adults and adolescents with primary hyperoxaluria, or enteric hyperoxaluria with advanced chronic kidney disease and elevated plasma oxalate. ALLN-177 is a first-in-class, non-absorbed, orally administered enzyme that is designed to degrade oxalate within the gastrointestinal tract to treat severe hyperoxaluria. Study 206 is a multicenter, open-label, single-arm study that will enroll between 15 and 20 patients in the U.S. and Europe aged 12 years and older who will be treated with ALLN-177 for 12 consecutive weeks. Subjects will self-administer 5,000 units of ALLN-177 with each meal or snack five times per day. Study endpoints are change from baseline in 24-hour urinary oxalate excretion and plasma oxalate levels. Patients with kidney failure or on dialysis may comprise up to 25% of total enrollment.

Data published from randomized controlled trial of cUTI agent

The Lancet Infectious Diseases has published clinical results from the pivotal randomized controlled trial evaluating cefiderocol for the treatment of complicated urinary tract infection (cUTI) in patients at risk of multidrug-resistant gram-negative infections (Lancet Infect Dis Oct. 25, 2018 [Epub ahead of print]). Results from the study demonstrated treatment with cefiderocol met non-inferiority versus imipenem/cilastatin (IPM/CS) in patients with cUTI at test of cure (TOC), according to Shionogi & Co., Ltd. In the study, 73% (183/252) of patients in the cefiderocol group met the primary endpoint (combination of clinical response and microbiological response at TOC) versus 55% (65/119) in the IPM/CS group, according to Shionogi & Co., Ltd. In the study, 73% (183/252) of patients in the cefiderocol group met the primary endpoint (combination of clinical response and microbiological response at TOC) versus 55% (65/119) in the IPM/CS group, with an adjusted treatment difference of 18.58%. These results in a post-hoc analysis showed that cefiderocol was superior to IPM/CS.

Pivotal trial to evaluate oral agent for polycystic kidney disease

Sanofi is beginning a pivotal clinical trial to study the safety, efficacy, and tolerability of an investigational oral agent called venglustat for certain patients with autosomal dominant polycystic kidney disease (ADPKD). The international trial is enrolling patients who are at risk of rapidly progressive ADPKD. Venglustat is an investigational oral therapy designed to inhibit the abnormal accumulation of glycosphingolipids (GL-1), which plays a role in production of glycosphingolipid production. In genetic mouse models of ADPKD, inhibition of glycosphingolipid production has been shown to reduce kidney cyst growth (Nat Med 2010; 16:788-92). The clinical significance of this is under investigation, according to Sanofi. Venglustat has received Orphan Drug designation in the U.S. for the treatment of ADPKD. The ADPKD clinical trial will be conducted at sites in the U.S., Canada, China, Japan, and several European Union countries.

Cancer subtyping platform may provide bladder Ca biomarkers

GeneCentric Therapeutics presented the first data on the application of its proprietary Cancer Subtyping Platform to bladder cancer and its potential utility to provide drug response biomarkers for the disease. The studies, conducted by GeneCentric scientists in collaboration with researchers at the University of North Carolina Chapel Hill’s Lineberger Cancer Center, assigned four gene expression subtypes based on approximately 2,700 genes from 408 bladder cancer patients in The Cancer Genome Atlas. The researchers then developed a subtype signature based on 60 genes and tested the 60-gene set in two additional data sets. Analysis of the gene signatures suggested additional study of their potential as therapeutic biomarkers independently as well as in combination with other molecular features, according to GeneCentric Therapeutics. For example, subtypes showed differences in the expression profiles of genes that are promising therapeutic targets in bladder cancer, such as FGFR3 and ERBB2. The differences were consistent across multiple data sets. Bladder cancer subtypes also showed variability in immune profiles that is likely to inform the response to immunotherapy. Subtypes were also found to be significantly prognostic for Stage 2 and 3 bladder cancer. The data were presented at the American Society of Clinical Oncology annual meeting in Chicago.

New studies evaluate device’s efficacy in preserving penile length

The Mayo Clinic has initiated two new trials evaluating the efficacy of a new penile traction therapy device (RestoreX) in preserving or improving penile length. The first study is a randomized, controlled trial of 60 men post-prostatectomy who will be assigned to control or one of two treatment arms (traction 30 min. daily x 5 days/week vs. 60 min. daily x 7 days/week). Treatment is initiated at 1 month after prostatectomy and continues until 6 months post-op. All men then enter an open-label phase for 3 months. Primary outcomes are penile length, and secondary outcomes include assessments of sexual function, urinary outcomes, development of Peyronie’s disease, and adverse events. The second study is an open-label trial of 40 men undergoing placement of a penile prosthesis. Men will be offered the option of utilizing traction with RestoreX for 90 minutes daily for 3 months prior to the penile prosthesist or proceed directly with surgery. Primary outcomes include stretched penile length pre- and post-treatment and the size of prosthesis inserted between those using traction versus no traction. Secondary outcomes include subjective measures of satisfaction, compliance, and adverse events. Groupings will be matched on baseline penile length to limit confounders. RestoreX is currently used for the treatment of Peyronie’s disease.

Cell therapy yields significant improvement in erectile function

Phase I results from a trial of adipose-derived regenerative cells (ARDCs, Cytori Cell Therapy) in erectile dysfunction following radical prostatectomy were recently published in Urology (June 27, 2018 [Epub ahead of print]). In the trial, 21 patients with ED after radical prostatectomy, with no signs of recovery following conventional therapy, received a single intracavernous injection of autologous ARDCs. Six men were incontinent and 15 were continent at inclusion. At 12 months following treatment, erectile function assessed using the International Index of Erectile Function-5 showed a statistically significant improvement from a median baseline score of 6 to a median of 8; p=0.004. Although median Erection Hardness Score (EHS) was unchanged in the entire cohort, patients in the continent subset exhibited statistically significant improvement in EHS from a baseline median score of 1 to a median of 2 at 12 months; p=0.03.

Level 1 evidence of partial gland ablation for PCa published

The Journal of Urology has published 4-year follow-up data of the landmark phase III PCM301 trial of padeliporfin di-potassium (TOOKAD), a novel treatment for localized, low-risk prostate cancer (J Urol June 2, 2018 [Epub ahead of print]). Publication of this study provides the longest reported Level 1 evidence of safety and efficacy of partial gland ablation for early-stage prostate cancer to date, Steba Biotech said. Analysis of 4-year follow-up of PCM301 demonstrated that vascular targeted photodynamic therapy (VTP) mediated by padeliporfin di-potassium significantly reduced the subsequent finding of higher grade cancer on biopsy and, consequently, significantly fewer patients converted to radical therapy. The rate of conversion to radical therapy after padeliporfin di-potassium VTP compared with active surveillance at 2 years (7% vs. 32%) was maintained at 3 (15% vs. 44%) and 4 years (24% vs. 53%) (HR: 0.31, 95% CI: 0.21-0.46; p<0.001).
A
though loneliness is not a diagnosable illness, it is a common and misunderstood mental health problem for men and women of all ages. This is especially true for men over the age of 60 years who may view loneliness as a shameful secret. This applies to married as well as divorced or widowed men.

Our cultural stereotype of older men offers a sharp contrast to the emotional reality of loneliness. We focus on “socially desirable” messages such as retired men playing golf, fishing, or acting as the patriarch of family events. However, for many older men loneliness is a chronic problem, and for a large number it is a recent (since retirement) experience. Loneliness is multi-causal and multi-dimensional with large individual, relational, cultural, and value differences.

To provide perspective, it is important to note that the majority of men do thrive with aging and retirement. However, a significant number—as many as 30%—“crash and burn.” This involves high levels of anxiety and depression, alcohol or drug abuse, and greater risk of suicide attempts and completion (McCarthy B, McCarthy E. “Therapy with Men after Sixty.” New York: Routledge; 2014). One of the best predictors of major problems is when a man stops being sexual. This does not just mean stopping intercourse, but avoiding any type of sensual or sexual touch, including affectionate touch.

When a spouse dies, a majority of men eventually remarry and reestablish a new social support system with their new spouse and her family. In terms of quality friendships, men often report more acquaintances while women report more quality friendships and closer relationships with older and younger family members. For too many men, their only close relationship is with their spouse.

Health consequences of loneliness
There are a number of potential physical and mental health consequences of loneliness. The lonely man does not feel accountable to anyone so he may avoid making medical appointments and following through with recommended diagnostic tests (eg, colon cancer screening).

A particularly powerful example is the man who is told he needs a biopsy to rule out prostate cancer. He puts off scheduling the biopsy because he is afraid of the potential outcome. Embarrassed that he did not follow through on making an appointment, he cancels it altogether. Five years later, the man is admitted to the hospital with stage 4 prostate cancer with a poor prognosis.

Lonely men usually do not engage in preventive health care. Seldom do they make yearly appointments with their primary care physician. In addition, poor behavioral health habits including poor sleep patterns, lack of exercise, poor eating habits, smoking, and...
alcohol or drug abuse are common and subvert health. Finally, the lonely man is unlikely to follow a disciplined regimen of taking prescribed medications.

This pattern of neglect and unhealthy behaviors increases the risk of mental health problems, while the lack of social support reduces the chance that the man will seek assistance. Over time the problems become chronic and severe. Health cannot be treated with “benign neglect.”

Role of the urologist

Should loneliness be a concern for the urologist? The traditional narrow approach to urology has been that of a specialist focused on assessing and treating a specific medical problem—a “plumber” who fixes a man’s broken parts. The biopsychosocial model for assessment and treatment of older men recommends that the urologist be an “askable” doctor who is available to discuss a range of biomedical, psychological, and relational/social concerns, including loneliness (table 1). Rather than asking “yes/no” questions, the urologist is encouraged to ask open-ended questions, giving the patient an opportunity to tell his story and disclose concerns (table 2).

It is difficult, though, for men to share their vulnerabilities as many try to emulate the “strong man” cultural stereotype. In reality, even the most psychologically and physically healthy men have vulnerabilities. Too often, a man has “contingent self-esteem,” believing that if others knew his problems they would not accept him or would feel sorry for him. The reality of men’s lives is that by age 60, everyone has had at least one experience (and usually many more) where they have felt guilt, regret, sadness, or loneliness. This is a normal part of the human condition, yet many men view it as a “shameful secret.”

Rather than assuming that loneliness is better treated by the primary care physician or a mental health professional, be an “askable” caring urologist. At minimum, this means listening and making specific suggestions. For example, you could suggest becoming involved as a volunteer in a community or religious organization, assisting with a Boy Scout group, teaching English as a second language, joining a gym or walking group, or volunteering for a social or political cause. This moves beyond simply telling a man to make new friends, which can be counter-therapeutic. Encouraging his involvement in new groups and activities is more likely to be helpful.

The lonely man does not feel accountable to anyone so he may avoid making medical appointments and following through with recommended diagnostic tests.

Specific suggestions can also be helpful for men dealing with marriage difficulties and alienation or contention in relationships, such as with a sibling or adult child. Just telling a man to restore these relationships will likely set him up for failure. A more helpful route is to bring up one specific activity that could facilitate re-engagement. It could be small, like going to a sporting event, or more significant like taking a weekend trip.

A urologist who engages with the patient demonstrates a personal interest in his quality of life and facilitates avenues for him to break the cycle of loneliness. In addition, ask the patient to report afterward whether the suggestion or referral was useful. Add this to your notes and check in with him at his next appointment.

Older men and sexuality

Most men learn to be sexual in an autonomous manner: they experience desire, erection, intercourse, and orgasm without needing anything from their partner. A core learning is that sexual function is predictable and in a man’s control, which does not serve him well as a 60-year-old. With aging, his vascular, neurologic, and hormonal systems are less efficient so that psychological, relational, and especially psychosexual skill factors become more important.

The good news is that there is solid scientific evidence that men can be sexual in their 60s, 70s, and 80s (N Engl J Med 2007; 357:762-74). The bad news is that when couples stop being sexual, it is usually the man’s choice because he has lost confidence with erections and intercourse. He falls into the cycle of anticipatory anxiety, intercourse as an individual pass-fail performance test, frustration, embarrassment, and eventually avoidance.

Both urologists and the public often believe that the answer to erectile dysfunction is oral medication as a stand-alone intervention, with penile injections as the back-up treatment. Sex therapists and sophisticated urologists use the biopsychosocial model of assessment and treatment, which includes the partner. The most important factor is to replace the individual intercoures pass-fail performance model with the Good Enough Sex (GES) couple approach of sharing pleasure (Metz M, McCarthy B. “Coping with Erectile Dysfunction.” Oakland, CA: New Harbinger; 2004). In addition, sexuality in this approach is viewed as a couple process, meaning that a man views his partner as his intimate and erotic friend. The key is acceptance that sexuality is more flexible with age; this is true whether he uses erectile dysfunction medications or not.

TABLE 2. SUUGGESTED OPEN-ENDED QUESTIONS TO ASK MENS AGE 60+

<table>
<thead>
<tr>
<th>Question</th>
<th>Source: Barry McCarthy, PhD, and Tamara Oppliger, MA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Since turning 60, what is the best thing that has happened to you in terms of health, psychological factors, and relationships?</td>
<td></td>
</tr>
<tr>
<td>Since turning 60, what is the most difficult health, psychological, or relationship challenge you have faced?</td>
<td></td>
</tr>
<tr>
<td>Since retiring, are you satisfied with the social and family contacts in your life?</td>
<td></td>
</tr>
<tr>
<td>A problem that many men after 60 experience is loneliness. When in the last year have you felt lonely or isolated?</td>
<td></td>
</tr>
</tbody>
</table>

Let’s Talk Men’s Health

LONELINESS

continued from page 37

...
Let’s Talk Men’s Health

rebuilding erectile comfort and confidence, positive, realistic GES expectations are crucial. Perhaps 85% of sexual encounters will flow from comfort to pleasure, arousal, erotic flow, intercourse, and orgasm. When sex does not flow, rather than panic or apologize, the couple seamlessly transitions to either a sensual or erotic scenario. Although intercourse is highly valued, the couple does not need intercourse to enjoy desire, pleasure, eroticism, and satisfaction (Metz M, Epstein N, McCarthy B. “Cognitive-Behavioral Therapy for Sexual Dysfunction.” New York: Routledge; 2017).

This is a new way of thought for many men (and many urologists) but is key for them to continue to be sexual in them 60s, 70s, and 80s. Traditional men give up on sex because of performance fears. “Wise” men embrace GES and remain sexually active, which involves affectionate, sensual, playful, and erotic touch in addition to intercourse.

Rather than asking ‘yes/no’ questions, the urologist is encouraged to ask open-ended questions, giving the patient an opportunity to tell his story and disclose concerns.

The wise man turns toward his partner whether the sexual experience was wonderful, good, or dysfunctional. Lonely men avoid partner sex because they fear failure. The decision to stop being sexual is a self-defeating one. It reinforces isolation, alienation, and loneliness. The man feels he cannot perform like a “real man” and that he is alone in his failure even with using an erectile dysfunction medication. Based on the over-promising ads, almost all men fail.

The major mistake men make is rushing to intercourse as soon as they become erect for fear of losing their erection. A healthy strategy is not to transition to intercourse until both partners are in erotic flow (high levels of subjective and objective arousal). Sex with aging is an intimate sexual team experience. Healthy couple sexuality is an antidote to loneliness. As a doctor, you will have more success when you acknowledge the importance of the biopsychosocial model, rather than solely writing a prescription.

Acceptance and change
It is crucial that the urologist accept that loneliness is a common problem for men over 60 and accept its seriousness in impacting physical and mental health and making suggestions to break the cycle. Sexuality is an excellent example of using all of a man’s biopsychosocial resources, especially by enlisting a partner as his intimate and erotic ally. UT

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**BPH continued from page 1**

Mount Sinai’s Benign Urologic Diseases and Men’s Health Program.

Aquablation and prostate artery embolization (PAE) are newer, promising BPH treatments, but the guideline authors suggested there were not enough data at the time of publication to recommend them for clinical practice. Prostate artery embolization should be performed for the time being in a clinical trial rather than in practice, according to Dr. Kaplan.

“Most of the new technologies in BPH occupy a position between drugs and established surgery, such as transurethral resection of the prostate (TURP) and laser treatments,” said urologist Peter Gilling, MD, professor of surgery at the University of Auckland in New Zealand. “Durability is an important issue for each, but antegrade ejaculation is usually preserved.”

Urologists don’t remove as much tissue with the minimally invasive options as with TURP, so there’s a recurrence rate and urologists should discuss that with patients, according to Dr. Kaplan.

Recognizing minimally invasive options for BPH symptom improvement is a move in the right direction for patients because medical management might not be in patients’ best interest, according to Art R. Rastinehad, DO, associate professor of urology and radiology at the Icahn School of Medicine at Mount Sinai.

“Is giving BPH patients an alpha-blocker the right thing to do? These alpha-blockers can cause side effects: dementia, depression. And other treatments we use can alter men’s hormone levels and cause changes in mood and decreased libido,” Dr. Rastinehad said. “With minimally invasive treatments, men can be off their medications and get great results.”

**UroLift System**

The prostatic urethral lift (UroLift System) essentially uses a staple that is inserted through a man’s urethra with a cystoscope. It opens the channel of the urethra, pushing the side lobes of the prostate laterally, according to Claus G. Roehrborn, MD, professor and chair of urology at the UT Southwestern Medical Center in Dallas, and an author of the revised AUA guideline.

“This is accomplished with a special delivery device by which the staple is basically applied through the wall of the urethra and the prostate to the capsule. It’s done with a certain pressure or compressive factor so that the side lobe of the prostate is compressed, as if you literally put a staple through it,” Dr. Roehrborn explained.

The number of staples needed depends on prostate size. For a man with a 40- to 50-gram prostate, UroLift treatment requires between two and six staples—usually three on each side, Dr. Roehrborn said.

“It is expensive as each staple is a separate device and sometimes many are placed,” Dr. Gilling said.

Researchers tested the UroLift device in a randomized trial against placebo, showing relative success in the short term, then followed the cohort of men 5 years. They found UroLift patients had symptom improvement of about 10 points and a flow rate improvement of 3 to 4 mL per second (Can J Urol 2017; 24:8802-13).

“Flow rates are modestly improved but noticeable immediately, and general anesthesia is usually employed,” Dr. Gilling said.

Dr. Roehrborn does the UroLift as an outpatient procedure and said patients usually can resume normal activities within 3 days.

“Eighty percent of patients don’t require a catheter for drainage, and they’re able to urinate fine right after the procedure,” Dr. Roehrborn said. “UroLift treatment with staples preserves ejaculation in about 98% to 100% of patients.”

**Rezum System**

Water vapor thermal therapy (Rezum System) is a type of steam therapy used to treat BPH.

“It injects steam in the prostate, also with the cystoscope through the urethra, through a needle,” Dr. Roehrborn said. Energy generated by the steam destroys prostate tissue.

“It’s pretty simple but it’s actually very effective, and since it’s water or steam there’s no real side effect other than just the injection with the needle,” Dr. Roehrborn said. “This treatment has 3-year data from a randomized controlled trial. It results in a 10-point improvement in the symptom score and in a 4- to 6- mL per second improvement in the urinary flow rate [Urology 2018; 111:1-9].”

Rezum treatment preserves ejaculation in 90% to 95% of patients.

The procedure can be done in the office in some cases but is painful and requires sedation, according to Dr. Gilling.

“Most of the new technologies in BPH occupy a position between drugs and established surgery, such as transurethral resection of the prostate (TURP) and laser treatments.”

PETER GILLING, MD

Dr. Roehrborn said he often performs Rezum treatment using a prostate block and lidocaine. It can be an insurance issue if patients need general anesthetic because the Rezum procedure is far more cost-effective to do in an office setting, he said.

“Significant improvements in symptoms can take 4 to 6 weeks to achieve. Improvements in urinary flow are modest at best,” Dr. Gilling said. Nearly all patients require a catheter in the days following the procedure because of edema, according to Dr. Roehrborn.

The FDA approved Rezum for prostates with side lobe enlargement up to 80 grams and middle lobe enlargement because the steam can also be injected into the middle lobe. The AUA guideline recommends it for treatment of middle and side lobes.

**Aquablation/AquaBeam System**

Aquablation using the AquaBeam System is a robot-assisted technique involving tissue ablation with a waterjet. Tissue removal occurs acutely and rapidly, according to Dr. Gilling.

Aquablation requires that patients be treated in the operating room with general anesthesia.

“The treatment is done through the urethra with a cystoscope that is then lined up with an ultrasound bulk in the rectum. After the treatment plan has been developed, the machine basically pushes water with very high pressure into the prostate, and that high pressure destroys the prostate tissue in the area that was planned under ultrasound guidance,” Dr. Roehrborn said.

“Aquablation was approved by the FDA on the strength of a study comparing it to

“Even this water ablation [Aquablation] treatment preserves ejaculation in a high percent of patients—far more than the TURP.”

CLAUS G. ROEHRBORN, MD

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**In patients who have bothersome symptoms and have prostates of 30 to 80 grams, the UroLift and Rezum are reasonable options.”

STEVEN A. KAPLAN, MD

The FDA approved UroLift for men with prostate enlargement with BPH, both with side lobe enlargement and middle point or intravesical lobe, for which there is a special technique to apply the staples.

“The AUA guideline recognizes it for treatment of men’s prostates with side lobe enlargement but not for the middle lobe enlargement. The AUA guideline [authors] feel that there is not enough data yet for the indication for the middle lobe,” Dr. Roehrborn said.

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Water vapor thermal therapy (Rezum System) is a type of steam therapy used to treat BPH.

“It injects steam in the prostate, also with the cystoscope through the urethra, through a needle,” Dr. Roehrborn said. Energy generated by the steam destroys prostate tissue.

“It’s pretty simple but it’s actually very effective, and since it’s water or steam there’s no real side effect other than just the injection with the needle,” Dr. Roehrborn said. “This treatment has 3-year data from a randomized controlled trial. It results in a 10-point improvement in the symptom score and in a 4- to 6- mL per second improvement in the urinary flow rate [Urology 2018; 111:1-9].”

Rezum treatment preserves ejaculation in 90% to 95% of patients.

The procedure can be done in the office in some cases but is painful and requires sedation, according to Dr. Gilling.

“Most of the new technologies in BPH occupy a position between drugs and established surgery, such as transurethral resection of the prostate (TURP) and laser treatments.”

PETER GILLING, MD
TURP. And outcome by outcome it matched or excelled above and beyond the efficacy of TURP, which is after all our standby treatment,” he added.

Researchers compared Aquablation to TURP in patients with prostates between 30 and 80 grams, according to Dr. Roehrborn.

“And even this water ablation treatment preserves ejaculation in a high percent of patients—far more than the TURP,” Dr. Roehrborn said.

Patients require a catheter at least overnight, and hemostasis can be an issue, according to Dr. Gilling.

Aquablation’s recent data wasn’t ready for review when the AUA panel developed its guideline, so it is not yet recommended, Dr. Roehrborn said.

**Prostatic artery embolization**

Researchers have found that PAE has about the same efficacy at 9 months to 2 years post treatment as TURP, although it takes a while for embolization patients’ prostates to shrink. As a result, TURP patients will urinate better in the short term, according to Dr. Rastinehad.

“We get great results, similar to the Rezum treatment, in these patients. And we are treating a much broader population of men with 40-gram prostates to 750 grams, the largest we’ve ever done,” said Dr. Rastinehad, who is dual fellowship trained in interventional radiology and urologic oncology and has been doing PAE cases and research for almost 17 years.

“Prostate artery embolization hasn’t gotten the attention it deserves because urologists haven’t adopted it.”

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“Prostate artery embolization hasn’t gotten the attention it deserves because urologists haven’t adopted it,” Dr. Rastinehad said. “The guidelines call it investigational despite significant data on the approach and the FDA’s approval.”

Dr. Rastinehad performs PAE using a trans-radial approach. “So people can come into our angiography suite, we obtain radial access, and they can go home the same day with just a Band-Aid on their wrist,” he said.

“We do the entire procedure without a Foley catheter in place. Therefore, a lot of patients don’t have any burning or discomfort after the procedure.”

One catheter option for PAE, the Sniper Balloon Occlusion Microcatheter, is unique in that users can inflate it to occlude the artery and possibly change direction of the blood flow, redirecting it toward the prostate, according to Dr. Rastinehad.

Dr. Rastinehad performs PAE with sedation but said it can also be done using a local anesthetic.

“It’s a useful technique for patients who are not great candidates for anesthesia,” he said. “And it’s especially good for patients that are out of the normal size limits with respect to UroLift and Rezum—for patients with a prostate that’s bigger than 100 grams. We’re able to do large prostates with ease, without the complications or risks associated with major surgery.”

**Additional guideline updates**

Among other updates to the AUA guideline: The panel no longer recommends transurethral needle ablation because of concerns about long-term data. But it gave a higher recommendation to prostate ultrasound prior to treatment with newer minimally invasive therapies to determine prostate size and configuration.

Other devices for BPH symptom treatment are in the pipeline, including stents and radiofrequency options, according to Dr. Gilling.

In the meantime, Dr. Kaplan said he’s confident enough in the newer therapies to have one, himself, if needed.

“If I were a person who needed such a therapy, I would not even use medical therapy anymore. If I had an enlarged middle lobe, I would have the Rezum. If not, I would have the UroLift,” Dr. Kaplan said.

Dr. Roehrborn receives research support from and is a consultant for NeoTract (now Teleflex), NxThera (now Boston Scientific), and PROCEPT BioRobotics. Dr. Gilling is a study investigator for PROCEPT BioRobotics.
Upon passage of the Medicare law in 1965, several decades of growing concern by American urologists soon culminated with the founding of the American Association of Clinical Urologists. The organization dedicated to influencing socioeconomic and political affairs via direct communication between urologist and legislator recently celebrated its 50th anniversary with a high-profile annual meeting in Washington, D.C.

In addition to reuniting with past presidents dating back more than 30 years, the leaders of tomorrow came together at this event to address issues that affect all urologists and the patients they serve.

Fifty years ago, AUA President Charles A. Hoffman, MD, convened a couple dozen colleagues on the sidelines of the AUA annual meeting over which he presided. Wary of the government’s widening role in the practice of medicine, the group resolved to establish an organization to which urologists could turn that would shape public policy and influence legislative affairs. Within months, leaders of the nascent group were called to testify before a congressional committee on competing national health insurance proposals written by Sen. Edward Kennedy and President Richard Nixon.

Fast forward 40 years and the AUC faced a watered-down version of the same concept—the Affordable Care Act.

The adage, “The more things change, the more things stay the same” doesn’t necessarily apply across the board, however. Indeed, as evidenced by the AUC’s conference, the profession has undergone significant and important changes that have transformed the urologic work force.

One revolutionary trend was identified by Association of American Medical Colleges Chief Health Care Officer Janis Orlowski, MD, MACP, who noted that while females currently comprise just 8% of all urologists, the population of female residents and fellows is three times that total. Health care industry consolidation and increasingly expensive overhead costs have likewise contributed to a radical change in the nature of urologic practice.

Newly elected UROPAC Treasurer Amanda North, MD, led an informative panel discussing how practice type affects work-life integration, while North Central Section Representative Peter Knapp, MD, called on colleagues to build a Unique Ability Team comprised of physicians, non-physician providers, and administrative staff to reduce burnout.

Scope of practice an emerging issue

Non-physician providers’ scope of practice was identified by Gene Ransom, CEO of Maryland’s state medical association, as an emerging legislative issue impacting urology. Ransom reported that his organization is currently investigating non-physicians operating erectile dysfunction clinics. Maryland is also a laboratory for an innovative program that furthers the shift to population- and value-driven payment design.

That ‘Maryland Waiver’ was the subject of Carson Lecture honoree Nelson Sabatini, the state’s former Secretary of Health who currently chairs the Maryland Health Services Cost Review Commission (HSCRC). The HSCRC is an independent state agency that oversees a hospital payment system in which all payers—public and private—pay the same rates. In addition to Sabatini, the AUC honored U.S. Rep. Andy Harris, MD, an emergency room physician on the eastern shore of Maryland who serves as co-chair of the GOP Doctors Caucus. Rep. Harris supplied an inside perspective on the prospect of prior authorization requirements for Medicare Advantage plans and provided graphic representation of how insurance profits soar and hospitals prosper while Medicare physician payments are legally bound to a 0% increase from 2019 to 2025.

Another elected official was recognized by the AACU as its Distinguished Leadership Award honoree. Arizona state Rep. Heather Carter, PhD, addressed a packed room on her efforts to secure support for a new law that authorizes reimbursement for urologic telemedicine services.

The integration of telemedicine in the health care delivery system was also covered by AACU Health Policy Chair Jonathan Henderson, MD, who explained how proposed changes to Medicare payments for 2019 would increase coverage and reimbursement for telehealth services.

Dr. Henderson also highlighted the role of UROPAC in representing urologists’ political interests. He reported that UROPAC members attended more than two dozen in-district events in the last year-and-a-half, thereby establishing personal relationships between urologists and legislators.

Throughout the AACU’s 50th Anniversary Annual Meeting, it was made clear that it’s those personal relationships that truly affect change in Washington. Professional organizations like the AACU have long existed to initiate and facilitate urologists’ interactions with policymakers. Supporting these efforts via membership, first and foremost, and then engagement as your professional and personal lives allow, ensure that urologists’ patients, practices, and profession are well represented in national and state capitals.

ROSS E. WEBER
Mr. Weber is state affairs manager, policy and engagement, for the American Association of Clinical Urologists.

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LUGPA urges Congress to update Stark law

Existing legislation blocks value-based pay models

The federal Stark physician self-referral law and federal Anti-Kickback Statute threaten to derail the federal government’s value-based care initiative unless changes are enacted so alternative payment models can be developed without participating physicians risking violating these laws. That’s the view of LUGPA and Gary M. Kirsh, MD, past president of that organization and chair of LUGPA’s Alternative Payment Model Task Force. Dr. Kirsh testified before the House Ways and Means Subcommittee on Health in July as Congress is currently considering legislation to update Stark.

“The concept of value-based care was set forth in the Medicare Access and CHIP Reauthorization Act (MACRA) of 2015, which repealed the sustainable growth rate formula for Medicare payments to physicians, changed the way Medicare rewards clinicians for value over volume, streamlined multiple quality programs under a new Merit-based Incentive Payment System, and provided for bonus payment for participation in eligible alternative payment models (APMs).”

Only 5% participate in an APM

“Unfortunately, the vision of MACRA and value-based delivery is in jeopardy,” Dr. Kirsh told lawmakers at the hearing, noting that only 5% of U.S. physicians participate in an APM and there are almost no APMs in the pipeline for approval.

Last year, LUGPA developed a urology-specific APM that would give physicians incentives to pursue active surveillance rather than active intervention in patients with localized prostate cancer. It is predicated on the belief that many patients who receive active intervention could benefit from having that deferred, thus avoiding overutilization of services while reducing morbidity and cost.

“Existing Stark and associated fraud and abuse laws are one of the principal barriers to the development of APMs and the advancement of value-based care.”

GARY M. KIRSH, MD

Like all proposed APMs, LUGPA’s proposal must be approved by the Department of Health and Human Services (HHS) Physician-Focused Payment Model Technical Advisory Committee, and if approved there, by HHS.

But the Stark law gets in the way, said Dr. Kirsh. “Existing Stark and associated fraud and abuse laws are one of the principal barriers to the development of APMs and the advancement of value-based care,” he said, noting that it was written 30 years ago and has not been modified since 1993.

“Congress recognized long ago that the Stark law was an obstacle to care coordination and value-based delivery when it authorized the Secretary of Health and Human Services to waive the self-referral and anti-kickback prohibitions for accountable care organizations,” he said. “Yet independent physician practices were left behind. Congress should level the playing field to provide same protections for independent physicians to test and participate in APMs.”

For now, unless waivers are approved on a case-by-case basis, organizations wishing to develop APMs “find themselves in a catch-22,” said Dr. Kirsh. “They cannot test an APM in the real world without financial waivers to Stark and anti-kickback laws, yet these waivers cannot be granted unless there is an approved APM.”

Dr. Kirsh noted that organizations such as LUGPA may spend years of work, resources, and substantial investments designing an APM, “but it remains a theoretical, mathematical model whose actual impact on patient care and health care financing is unknown without testing in the clinical environment.”

Essentially, that is why LUGPA and 24 other physician groups have endorsed the Medicare Care Coordination Improvement Act (H.R. 4206), “which provides a means for the [HHS Office of Inspector General] to grant waivers to test a proposed APM when it is submitted in writing and approved by the [HHS] Secretary,” Dr. Kirsh said.

The waivers would have to be recertified every 6 months until the APM is approved or denied.

Dr. Kirsh explained to Health Subcommittee members that the Stark law also represents a barrier to the development and adoption of APMs because it explicitly prohibits remuneration of physicians who receive revenue from designated health services based on the “volume or value” of their referrals to these services.

“While this may be crucial in fee-for-service models, this hampers practices from incentivizing physicians to adhere to treatment pathways and agreed-upon clinical guidelines that improve patient outcomes and promote efficient use of health care resources in the context of an APM,” said Dr. Kirsh. “Current Stark law prevents practices from utilizing revenue from designated health services to financially reward or penalize physicians for adherence or deviation from clinical best practice standards or appropriate increases or decreases in utilization of services.”

What is needed, said Dr. Kirsh, is elimination of “volume or value” from Stark prohibitions for the testing and operation of APMs, which would “result in a clean, targeted, modernized version of the Stark and anti-kickback statutes.”

This, he said, is needed for clinicians to be willing to enter into APMs, which by definition limit financial exposure to the Medicare program. According to Deepak Kapoor, MD, chairman of LUGPA’s Health Policy Committee, holding clinicians harmless for APM participation is simply a matter of common sense.

“How can you have value-based care if you are not allowed to compensate physicians based on value?” Dr. Kapoor asked in an interview with Urology Times. “I think this is something that everybody acknowledges has got to get done.”

Certainly, physicians will not knowingly risk violating Stark, which could subject them to treble damages regardless of their intent, he said.

“Congress needs to enact these reforms if we are to move forward with value-based care.”
AMA discharges: What you may not know

What to do when a patient disregards medical advice

Y

ou are called to the emergency room to consult on a 57-year-old woman who, as a pedestrian, was struck by a car in a crosswalk. She has polytrauma, the most serious of which is a stage IV right renal laceration. She is admitted to urology for conservative management, serial hemoglobin and hematocrit, and repeat CT scan. Bedrest is ordered and the patient is compliant and hemodynamically stable for the first 48 hours.

At the close of hospital day two, she is feeling well and wants to go home. As the attending urologist, you advise against this as she is still having some hematuria, her hemoglobin and hematocrit have not fully rebounded, and you are planning to get a repeat CT scan at 72 hours. The patient is adamant about leaving the hospital, and does so against medical advice (AMA).

The patient is found down at home by her daughter later that evening and brought back to the emergency room by ambulance. She is found to have a delayed renal hemorrhage requiring activation of the hospital’s massive transfusion protocol, and is admitted to the intensive care unit. She is discharged 9 days later and subsequently sues you for medical malpractice under a claim of medical malpractice for the patient who left AMA and was subsequently harmed will hinge on the clinical assessment and associated documentation.

Successfully defending a claim of medical malpractice for the patient who left AMA and was subsequently harmed will hinge on the clinical assessment and associated documentation.

Informed consent and leaving AMA

In dealing with patients who want to be discharged AMA, informed consent is at the crux of any potential future legal issues. In deciding to leave AMA, the patient is effectively revoking his consent to a voluntary hospital admission. Informed consent in deciding to leave AMA means that the patient has come to the decision after consultation with his or her physician, without coercion, and with a full understanding of the risks, benefits, and alternatives of the decision. Assessment of a patient’s ability to make decisions is essential, and a conflict can arise when a patient’s right to self-determination and autonomy comes into direct opposition with what is best for the patient.

Informed consent is documented in the medical record. Having a patient sign an “AMA form” in and of itself, is not enough, as it does not prove an absence of negligence. Specifics to address in the medical records might include:

• an assessment of the patient’s understanding of his or her illness and prognosis
• the risks, benefits, and alternatives to leaving the hospital AMA
• the patient’s level of health literacy
• whether an attempt was made, if permission given, to engage the patient’s family or friends in the decision-making process
• the patient’s ability to make and communicate a choice clearly
• if and how the patient’s choice aligns with his or her values
• whether the patient’s decision was communicated to the patient’s primary care physician, to ensure close outpatient follow-up
• what information the patient was given at discharge about how and where to follow up, reasons to return to the emergency department, and instructions on medications.

In an attempt to balance patient autonomy and patient safety, some institutions follow a “sliding scale” for capacity assessments that require the physician to have a higher certainty of the patient’s decisional capacity for higher risk AMA discharges (Mayo Clin Proc 2009; 84:255-60). If there is incongruence in the level of risk the patient is willing to accept and the physician’s certainty of decision-making capacity, it is prudent to invoke whatever additional resources are available to aid in this, such as additional mental status screening exams, a psychiatry consult, or involvement of an ethics committee.

Patients’ decisions to leave AMA are multifactorial, ranging from dissatisfaction with care, to extended wait times for interventions, to financial or insurance fears. Proactive development of strategies to reduce the number of AMA discharges is a first step organizations can take to lower their rate. When these strategies do not work, and an AMA discharge is inevitable, a thorough assessment and documentation of that assessment is a physician’s best tool should any litigation arise out of injuries a patient sustains connected with that discharge.
Most common adverse events reported include hematuria, dysuria, micturition urgency, pelvic pain, and urge incontinence. Most symptoms were mild to moderate in severity and resolved within two to four weeks after the procedure.

1. No instances of new, sustained erectile or ejaculatory dysfunction McVary, J Sex Med 2014

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