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THE USE OF α_1-ADRENOCEPTOR ANTAGONISTS IN LOWER URINARY TRACT SYMPTOMS: BEYOND BENIGN PROSTATIC HYPERPLASIA

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ABSTRACT

The first empirical use of α_1-adrenoceptor antagonists in urology occurred about 25 years ago in patients with lower urinary tract symptoms (LUTS) suggestive of benign prostatic hyperplasia (BPH), or LUTS/BPH. Today, many randomized, controlled trials have provided evidence for the efficacy and tolerability of α_1-adrenoceptor antagonists in LUTS/BPH, and they are the most frequently used initial treatment option for this cause of LUTS. For many years, α_1-adrenoceptor antagonists have also been used empirically in other types of lower urinary tract dysfunction (LUTD), such as chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) and neurogenic LUTD (NLUTD). Several investigators have shown that α_1-adrenoceptor antagonists may be useful in patients with CP/CPPS. This was recently confirmed by a 6-week, double-blind, placebo-controlled pilot study evaluating the efficacy and safety of tamsulosin in 58 CP/CPPS patients. Further well-designed and -powered research into the use of α_1-adrenoceptor antagonists in patients with CP/CPPS is currently ongoing. Several small-scale predominantly open-label studies have suggested that α_1-adrenoceptor antagonists may be of benefit in patients with NLUTD. Data from 2 recent large-scale studies with tamsulosin in patients with NLUTD caused by suprasacral spinal cord injury suggest that long-term tamsulosin treatment improves bladder storage and emptying and also reduces symptoms of autonomic dysreflexia. Tamsulosin has also shown promise in ameliorating (early) storage symptoms and urinary retention associated with transurethral microwave thermotherapy, external-beam radiotherapy, and brachytherapy. In BPH patients presenting with the ultimate form of LUTS—acute urinary retention—treatment with tamsulosin before catheter removal results in a higher success rate of catheter-free voiding. Finally, it seems that α_1-adrenoceptor antagonists may reduce the occurrence of urinary retention after (general) surgery. We can therefore conclude that α_1-adrenoceptor antagonists, such as tamsulosin, may be useful for treating men with LUTS beyond BPH. UROLOGY **62** (Suppl 3A): 34–41, 2003.

Although prevalence rates vary across countries, it appears that approximately 25% of older men (aged 40 to ≥50 years of age) have lower urinary tract symptoms (LUTS).[1–3] Benign prostatic hyperplasia (BPH) causing bladder outlet obstruction is the most common cause of LUTS in older men. However, LUTS may also be caused by other conditions. Storage (irritative) symptoms, such as increased daytime frequency, urgency, nocturia, and urge incontinence (recognized as being the most bothersome urinary symptoms),[4] are commonly seen in patients with LUTS suggestive of BPH (LUTS/BPH), but they may also occur in the absence of bladder outlet obstruction from BPH. For instance, many patients with chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) have storage symptoms. Voiding (obstructive) symptoms, such as hesitancy, slow stream, intermittency, and terminal dribble are caused by bladder outlet obstruction secondary to BPH, but it can also occur in patients with prostate cancer, a urethral stricture, chronic prostatitis, and other conditions. In addition, neurogenic factors, iatrogenic problems, and prostate-directed therapies, such as transurethral microwave therapy (TUMT) and

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brachytherapy, can result in storage and/or voiding symptoms.

It is important to determine the exact etiology in men presenting with LUTS in daily clinical practice because this has important consequences for the subsequent treatment of the patient. The standard diagnostic workup for men aged ≥50 years presenting with LUTS/BPH, as recommended by the International BPH Consultation Committee,[5] consists of (1) medical history, (2) physical examination including a focused neurologic examination, (3) urinalysis, (4) digital rectal examination, (5) standardized symptom questionnaire (International Prostate Symptom Score [I-PSS]), (6) assessment of quality of life (QOL), and, in selected patients, (7) measurement of prostate-specific antigen. This diagnostic strategy should rule out causes of LUTS other than BPH, such as prostate cancer, prostatitis, and potential neurogenic disorders.

LUTS/BPH can be managed by watchful waiting, medical therapy (5α-reductase inhibitors and α_1-adrenoceptor antagonists), or surgery (minimally invasive or prostatectomy). α_1-Adrenoceptor antagonists are currently the most frequently used initial treatment option for this cause of LUTS.[6] The first empirical use of α_1-adrenoceptor antagonists in urology occurred approximately 25 years ago when Caine *et al*. applied these agents for treating patients with LUTS/BPH.[7] Today, many well-designed, adequately powered, randomized, placebo-controlled trials have provided evidence for the use of α_1-adrenoceptor antagonists in LUTS/BPH. It is currently believed that they improve urinary flow and voiding symptoms by blocking α_{1A}-adrenoceptors in the prostate, urethra, and bladder neck. Storage symptoms seem to be relieved by reducing bladder overactivity (caused by reversal of bladder changes after alleviation of obstruction and/or possibly because of direct blockade of [up-regulated] α_{1D}-adrenoceptors in the detrusor and/or spinal cord).[8]

For many years, α_1-adrenoceptor antagonists have also been used empirically in other types of lower urinary tract dysfunction (LUTD), such as prostatitis and neurogenic LUTD (NLUTD). They also treat storage symptoms induced by other prostate-directed therapies (eg, TUMT or brachytherapy) and increase the success rate of catheter withdrawal in patients with acute urinary retention (AUR). This article provides an update of the role of and available evidence for administering α_1-adrenoceptor antagonists in LUTS beyond BPH.

CHRONIC PROSTATITIS/CHRONIC PELVIC PAIN SYNDROME

CP/CPPS[9] (previously referred to as chronic nonbacterial prostatitis and prostatodynia) is the most common presentation of prostatitis (≈90% of all cases), with an estimated 2 million office visits per year in the United States (8% of urology outpatient visits).[10] A survey among Canadian urologists revealed that each urologist sees an average of 262 prostatitis patients per year (median, 132 patients), of whom 33% are newly diagnosed.[11] A previous diagnosis of CP/CPPS or the presence of symptoms resembling prostatitis are present in approximately 10% of men aged 20 to 74 years.[12,13] Although it is more common in younger men (11.5% of men <50 years), it also occurs frequently in older men (8.5% of men ≥50 years of age).[13] Pain, particularly after ejaculation, differentiates prostatitis from LUTS/BPH, with perineal and suprapubic pain being the major presenting complaints of CP/CPPS patients.[14]

Storage and voiding symptoms are, however, very bothersome. CP/CPPS can certainly coexist with BPH, but physicians are significantly more frustrated managing prostatitis than LUTS/BPH, and patients with prostatitis have a greater reduction in QOL.[11] This seems to be mainly because little is yet known about what causes prostatitis, how best to make the diagnosis, and what comprises optimum treatment. Although scientific evidence is largely lacking, an initial trial with antibiotics is often given to patients with CP/CPPS. If symptoms persist, α_1-adrenoceptor antagonists are frequently used as second-line therapy. It is not completely clear how α_1-adrenoceptor antagonists work in this condition. Many mechanisms have been suggested, including (1) reduction of increased intraurethral pressure, (2) blockade of α_1-adrenoceptors at the bladder neck and prostatic smooth muscle, (3) blockade of α_1-adrenoceptors in the bladder, and/or (4) central modulation of voiding and pain pathways. Several mainly small-scale studies have investigated the role of α_1-adrenoceptor antagonists in the treatment of CP/CPPS[15–20]; 4 of these were placebo-controlled trials.[15–17,20] Some of these studies indicated that these agents may be beneficial in this condition.[15,16,18–20] The evidence is, however, still weak.

A recently reported 6-week, double-blind, randomized, placebo-controlled pilot study evaluated the efficacy and safety of tamsulosin 0.4 mg once daily in 58 patients (21 to 56 years of age) with CP/CPPS after a 2-week, single-blind, washout period.[21] The recommended questionnaire for clinical trials in this condition, the 9-item National Institutes of Health (NIH)–Chronic Prostatitis Symptom Index (CPSI)[22,23]—which assesses the impact on pain, urinary symptoms, and QOL, and which has an overall score range from 0 to 43—was used to select appropriate patients. Subjects had to have an overall NIH-CPSI score ≥15 and a pain domain subscore ≥8. The data are promising be-

cause they show that the mean change from baseline to day 45 in overall NIH-CPSI score for tamsulosin was statistically significantly better than with placebo (difference, −3.6 points; $P = 0.04$; Figure 1). Especially among patients with severe prostatitis (overall NIH-CPSI score ≥30), the difference in response (−7.3 points, $P = 0.001$) was considered clinically significant. Further well-designed research into the use of α_1-adrenoceptor antagonists in patients with CP/CPPS seems to be appropriate. An example of such a trial was a placebo-controlled study with the α_1-adrenoceptor antagonist alfuzosin. Reported results indicate a significant benefit compared with placebo, but duration of treatment (>2 months) is necessary, and the beneficial effect slowly disappears when the drug is discontinued.[24]

Another trial currently being performed is under the auspices of the Chronic Prostatitis Collaborative Research Network sponsored by the NIH.[25] In this double-blind, randomized, placebo-controlled study, 195 patients with CP/CPPS (overall NIH-CPSI score ≥15) will be treated with placebo, the antibiotic ciprofloxacin, the subtype selective α_{1A}/α_{1D}-adrenoceptor antagonist tamsulosin, or the combination of ciprofloxacin and tamsulosin for 6 weeks and observed for an additional 6 weeks. The primary end point is the change in the overall NIH-CPSI score from baseline to 6 weeks. The last patient completed this trial in September 2002, and results will become available in 2003.

NEUROGENIC LOWER URINARY TRACT DYSFUNCTION

A variety of neurologic diseases, including multiple sclerosis, Parkinson disease, spinal cord injury, diabetes mellitus, and cerebrovascular accident, can cause NLUTD. The prevalence of spinal cord injury, multiple sclerosis, and Parkinson disease are all in the region of 0.1%; the prevalence of stroke is roughly 10 times higher.[26] NLUTD patients can be classified into 3 categories: (1) those who fail to empty their bladder successfully, (2) those who fail to store urine adequately, or (3) a combination of these.[27] Current treatment options for NLUTD are limited. Those for facilitating storage include surgical procedures and antimuscarinic drug treatment. For facilitating voiding, treatment options include catheterization or surgical procedures. α_1-Adrenoceptor antagonists have also been used empirically for many years. Studies with α-adrenoceptor antagonists in NLUTD show small but useful effects in facilitating both bladder storage and emptying and in reducing the symptoms of autonomic dysreflexia (eg, hypertension, headache, flushing, and sweating).[28–33] However, these were mainly small-scale, uncontrolled, nonrandomized trials of short duration. A recent large, randomized, placebo-controlled 4-week study evaluated the efficacy and safety of tamsulosin 0.4 and 0.8 mg once daily in 263 patients with NLUTD secondary to suprasacral spinal cord injury with neurogenic detrusor overactivity and possible symptoms of autonomic dysreflexia.[34] In all, 186 patients continued open-label tamsulosin treatment for 1 year. Figure 2 shows the mean reduction in maximal urethral pressure (MUP) between baseline and end point in both studies. Although the difference versus placebo was not statistically significant after 4 weeks, tamsulosin produced larger decreases in MUP. Long-term treatment with tamsulosin gave a further mean reduction in MUP and improved bladder storage and emptying. It also reduced symptoms of autonomic dysreflexia. Both tamsulosin doses were effective and well tolerated.

The positive effect of tamsulosin on bladder emptying can be attributed to blockade of α_{1A}-adrenoceptors in the bladder neck, urethra, and prostate. It is currently unknown where such drugs act, apart from the α_{1A}-adrenoceptors in the prostate, urethra, and/or bladder neck. Other potential sites of action that, at present, remain hypothetical include improvement of bladder storage from blockade of (upregulated) α_{1D}-adrenoceptors in the detrusor and/or spinal cord, thereby decreasing detrusor overactivity and improving the storage of urine in the bladder during the filling phase. Alternatively, tamsulosin may block prejunctional α_1-adrenoceptors on cholinergic nerve terminals in the bladder and/or at the peripheral ganglion level, thereby decreasing acetylcholine release and subsequent involuntary detrusor contractions.[8]

LOWER URINARY TRACT SYMPTOMS CAUSED BY PROSTATE-DIRECTED THERAPIES

Tamsulosin has also shown promise in ameliorating early (storage) symptoms and/or complications associated with prostate-directed therapies, such as TUMT,[35,36] radiotherapy,[37] and brachytherapy.[38]

In a trial by Djavan *et al.*,[35] 81 patients with LUTS/BPH were randomized to 12 weeks of treatment with high-energy TUMT alone (n = 40) or the combination of high-energy TUMT and tamsulosin 0.4 mg once daily, started 2 weeks before and stopped 6 weeks after the TUMT procedure (n = 41). TUMT patients receiving tamsulosin had statistically significantly faster symptom relief (Figure 3) and improvement in QOL than patients undergoing the TUMT procedure alone. The investigators also noted that tamsulosin also seemed to diminish the likelihood of developing

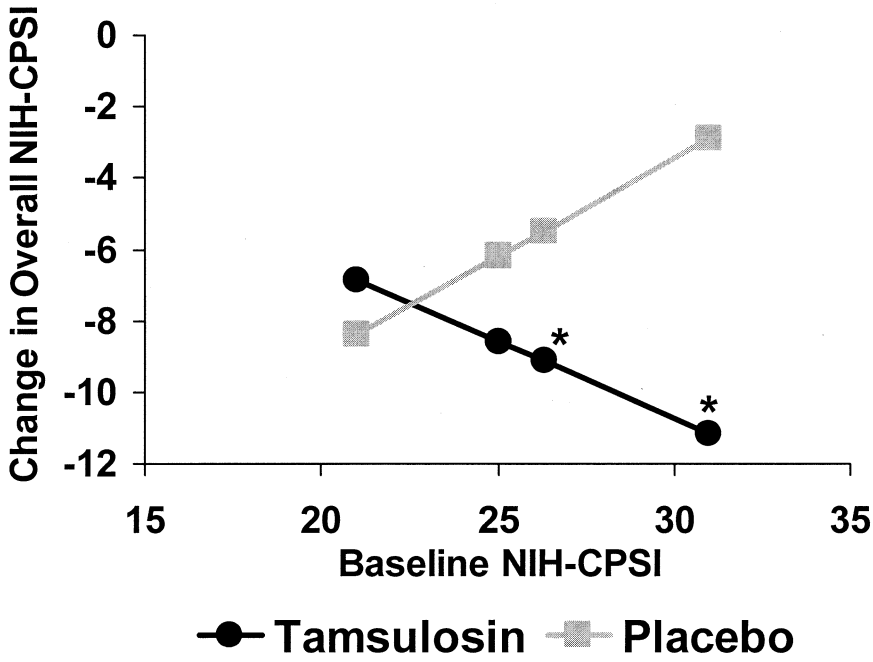

FIGURE 1. *Mean change in overall National Institutes of Health–Chronic Prostatitis Symptom Index (NIH-CPSI) scores with tamsulosin or placebo in relation to baseline score. Overall NIH-CPSI baseline scores ranged from 17 to 41. *P = <0.05 in favor of tamsulosin. (Adapted from* J Urol.[21]*)*

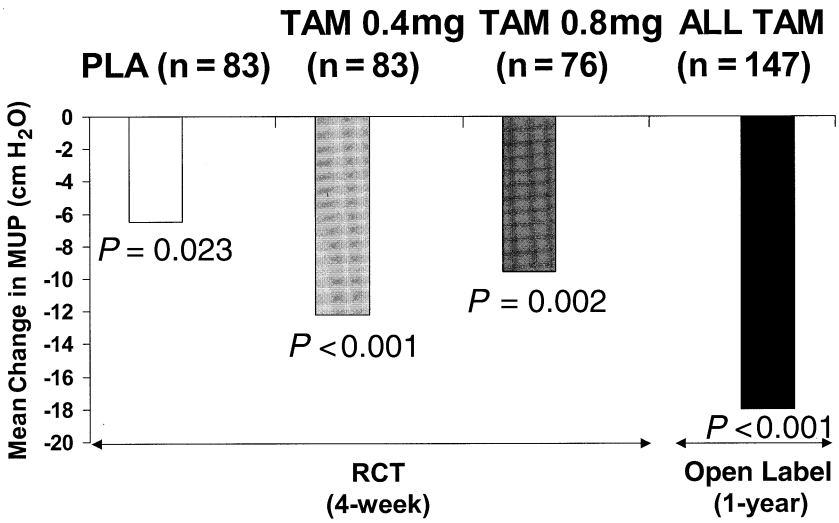

FIGURE 2. *Mean change in maximal urethral pressure (MUP) from baseline to end point in a randomized placebo (PLA)-controlled trial (RCT) and a 1-year, open-label follow-up with tamsulosin (TAM). (Adapted from* J Urol.[34]*)*

AUR (a major complication of TUMT that usually requires catheterization for up to ≥1 week). AUR developed in 5 patients (12%) receiving TUMT alone and in 1 patient (2%) receiving TUMT with tamsulosin. This was not statistically significant, but the study was not powered for this event.

Several therapies for the treatment of prostate cancer may also induce urinary symptoms for several weeks after the procedure, which considerably impair the patient's QOL. Radiotherapy can induce urethritis (nocturia, frequency, urgency, hesitancy, and weak stream). This occurs in approximately 50% of patients undergoing conformal external-beam radiotherapy and in nearly all patients (95%) treated with interstitial radiotherapy.[37] In 26 patients with prostate cancer who received radiotherapy and complained about troublesome urinary symptoms, tamsulosin (0.4 or 0.8 mg once daily) reduced these symptoms in 20 patients (77%) back to baseline (before radiotherapy) urinary function.[37] Almost all patients with prostate cancer treated with brachytherapy also develop early stor-

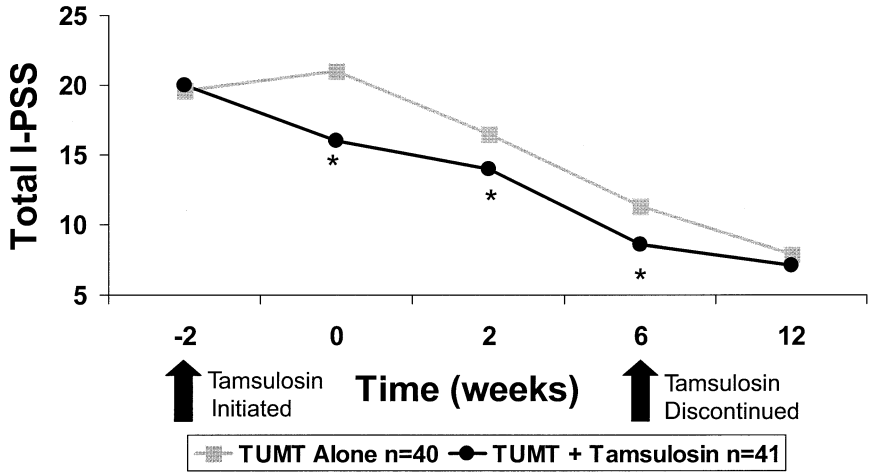

FIGURE 3. *Mean improvement in total International Prostate Symptom Score (I-PSS) in patients receiving transurethral microwave thermotherapy (TUMT) alone or the combination of TUMT and tamsulosin. * P <0.0005 vs TUMT alone. (Reprinted with permission from* Urology.[35]*)*

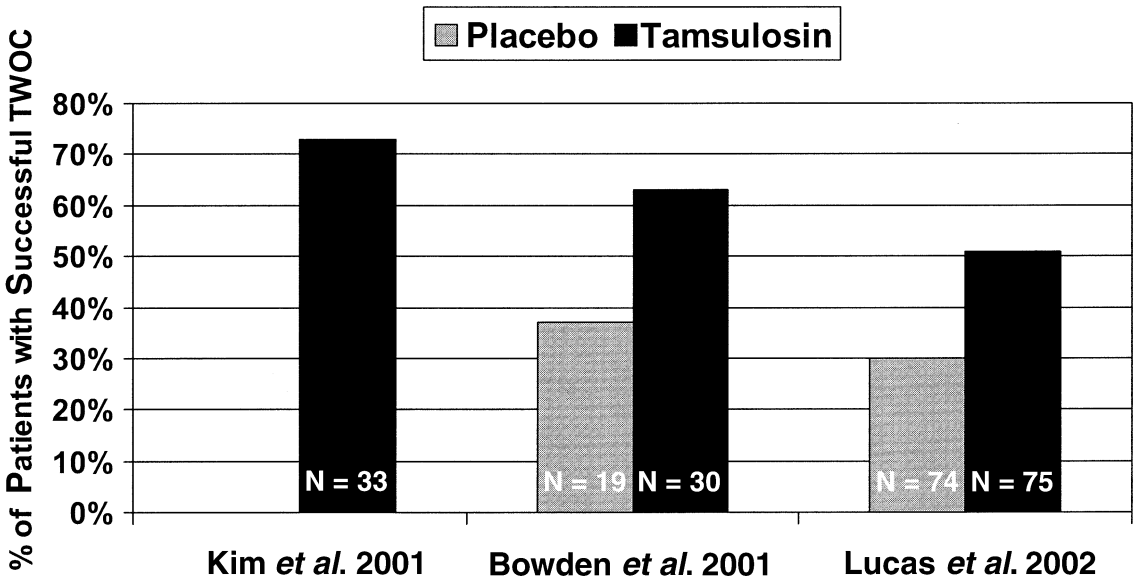

FIGURE 4. *Percentage of patients who void successfully after a trial without catheter (TWOC). (Adapted from* Tech Urol,[45] BJU Int,[46] *and* J Urol.[47]*)*

age and voiding symptoms, and 3% to 22% develop AUR as a complication; the risk of AUR is related to the severity of baseline symptoms (total I-PSS).[38]

A study involving 170 patients with prostate cancer receiving brachytherapy evaluated whether α_1-adrenoceptor antagonists (tamsulosin in 92% of patients) were able to diminish the development of urinary symptoms and improve the success rate of early catheter removal or the development of AUR.[38] α_1-Adrenoceptor antagonist treatment started 2 to 3 weeks before the implantation of the seeds and continued until symptoms (total I-PSS) had returned to baseline. The catheter could be successfully removed on the day of brachytherapy in 150 patients (88%). In addition, the total I-PSS returned to baseline (ie, before implant) levels within a median of 6 weeks and a mean of 13.3 weeks. Within 8 weeks, 50% of patients had returned to baseline values. These data suggest that prophylactic and long-term use of α_1-adrenoceptor antagonists can reduce the urinary morbidity associated with brachytherapy.

ACUTE URINARY RETENTION CAUSED BY BENIGN PROSTATIC HYPERPLASIA

Acute urinary retention is the ultimate form of LUTS/BPH. The incidence of AUR in patients on watchful waiting or placebo is 1% to 1.5% per year, ranging from 0.3% to 3.5% depending on symptom severity at baseline and whether the study was based in the community (0.7% per year)[39] or in the

urologist's office (1% to 2.5% per year).[40,41] Moreover, the Olmsted County study has demonstrated that the risk of AUR increases with age (10-fold increased risk for men aged 70 to 79 years vs men aged 40 to 49 years), in patients with a total I-PSS >7, a maximum flow rate <12 mL/sec, or a prostate size >30 g.[39] Immediate catheterization is the usual initial treatment for patients developing AUR caused by LUTS/BPH, which is followed by prostatic surgery (transurethral resection of the prostate) several weeks later. Only 20% to 30% of men void spontaneously after a trial without catheter (TWOC).[42,43]

Several trials have shown that administering α_1-adrenoceptor antagonists (alfuzosin, terazosin, or tamsulosin) several days before catheter removal results in a higher success rate of catheter-free voiding.[43–47] Figure 4 summarizes the results of the 3 studies performed with tamsulosin. Kim *et al*.[45] treated 33 consecutive men with AUR with tamsulosin 0.4 mg once daily for ≥4 days before a trial of voiding. Initially, 88% of these men were able to void after catheter removal. After a median follow-up duration of 6.5 months, 73% were still able to void without additional treatment. The patients who failed medical therapy did so within the first 3 months. They were treated by transurethral resection of the prostate or clean intermittent catheterization. The success rate was highest in patients with a precipitating factor for AUR (nonurologic surgery). A second study by Bowden *et al*.[46] was randomized and placebo controlled. They treated 49 patients with LUTS/BPH with placebo (n = 19) or tamsulosin 0.4 mg once daily (n = 30) for 2 weeks. A first TWOC was performed after 2 days of therapy; those unable to void were recatheterized and received a second TWOC after 2 weeks. After 2 days, 37% of placebo- and 63% of tamsulosin-treated patients voided successfully. The difference was not statistically significant, probably because of the small sample size. None of the patients who failed the first TWOC voided successfully after the second TWOC at 2 weeks. The patients who voided successfully were slightly younger (mean age, 69.0 vs 73.3 years) and had a lower postvoid residual (760 mL vs 955 mL). A third larger double-blind, randomized, placebo-controlled study was recently reported.[47] A total of 141 patients with LUTS/BPH received placebo (n = 70) or tamsulosin 0.4 mg once daily (n = 71) for 3 to 7 days when a TWOC was performed. Statistically significantly more patients on tamsulosin (51%) than on placebo (30%) remained catheter free ($P = 0.011$).

POSTOPERATIVE URINARY RETENTION

Several studies have shown that an α_1-adrenoceptor antagonist can also reduce the development of postoperative urinary retention (PUR) and/or the subsequent need for catheterization in patients after general surgery.[48–52] They also increase the percentage of patients who void successfully after removal of the catheter because of PUR.[50,51,53]

However, it should be mentioned that negative results have also been reported.[54,55] A recent study by Avdoshin *et al*.[56] demonstrated a reduced occurrence of PUR in LUTS/BPH patients who received tamsulosin 0.4 mg once daily 5 days before and 10 days after an operation for rectal cancer, sigmoid cancer, or a hemorrhoid or anal fissure. In the group of patients on tamsulosin, there were no episodes of PUR, compared with 13% of the patients in the control group who needed catheterization. The positive effect of α_1-adrenoceptor antagonists on preventing PUR has been attributed to the pain and stress during the operation, which may cause sympathetic stimulation causing bladder outlet obstruction. This, in combination with an inhibited micturition reflex after spinal anesthesia and an inhibition of parasympathetic-mediated contraction of the bladder, may induce urinary retention. α_1-Adrenoceptor antagonists can block the sympathetic nervous system–induced bladder outlet obstruction and may therefore prevent PUR.

CONCLUSIONS

α_1-Adrenoceptor antagonists are the major initial treatment for patients with LUTS suggestive of BPH. They have also been used empirically for many years in other urologic conditions. There is now increasing evidence that they may be beneficial in patients with CP/CPPS and NLUTD and may prevent or reduce the development of urinary symptoms or complications (eg, AUR) caused by prostate-directed therapies. Furthermore, they may increase the success rate of a TWOC in patients who develop (acute) urinary retention from BPH or after nonurologic surgery (eg, general surgery or hysterectomy, or total hip or knee arthroplasty). Using a subtype selective α_{1A}/α_{1D} -adrenoceptor antagonist, such as tamsulosin, has the advantage in that it is not only effective, but it is also well tolerated and has a very fast onset of action because it can be administered at its therapeutic dose from the start of treatment. Therefore, it can be concluded that α_1-adrenoceptor antagonists, such as tamsulosin, may be useful for treating men with LUTS beyond BPH.

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