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# Mirabegron for intramural ureteral stones with vesical irritability: a prospective study

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**Objective:** To assess the efficacy of mirabegron in patients with intramural ureteral stones (6–10 mm).

**Methods:** We prospectively randomized 92 patients with intramural ureteral stones into two groups. Patients in the mirabegron group received 50 mg of mirabegron daily, while those in the tamsulosin group received 0.4 mg tamsulosin daily. All patients were required to use the Urinary Sensation Scale (USS) to assess the urinary urgency and the Visual Analog Scale (VAS) to assess pain. Patients were followed until stone expulsion or for up to 4 weeks.

**Results:** All of 80 patients were included in this study. 41 patients in mirabegron group and 39 patients in tamsulosin group as control. The average expulsion time was shorter in mirabegron group than in tamsulosin group ( $8.4 \pm 2.9$  vs.  $11.2 \pm 3.1$  days,  $P < 0.0001$ ). The stone expulsion rate (SER) was higher in mirabegron group than in tamsulosin group on 1 and 2 weeks (36.6% vs. 15.4%,  $P = 0.031$  and 75.6% vs. 43.6%,  $P = 0.004$ ). However, the SER on 4 weeks had no statistical difference between two groups ( $P > 0.05$ ). Post-treatment VAS and USS scores were lower in mirabegron group than tamsulosin group ( $P < 0.05$ ).

**Conclusion:** Mirabegron not only accelerates the expulsion of intramural ureteral stones but also relieves renal colic and vesical irritability.

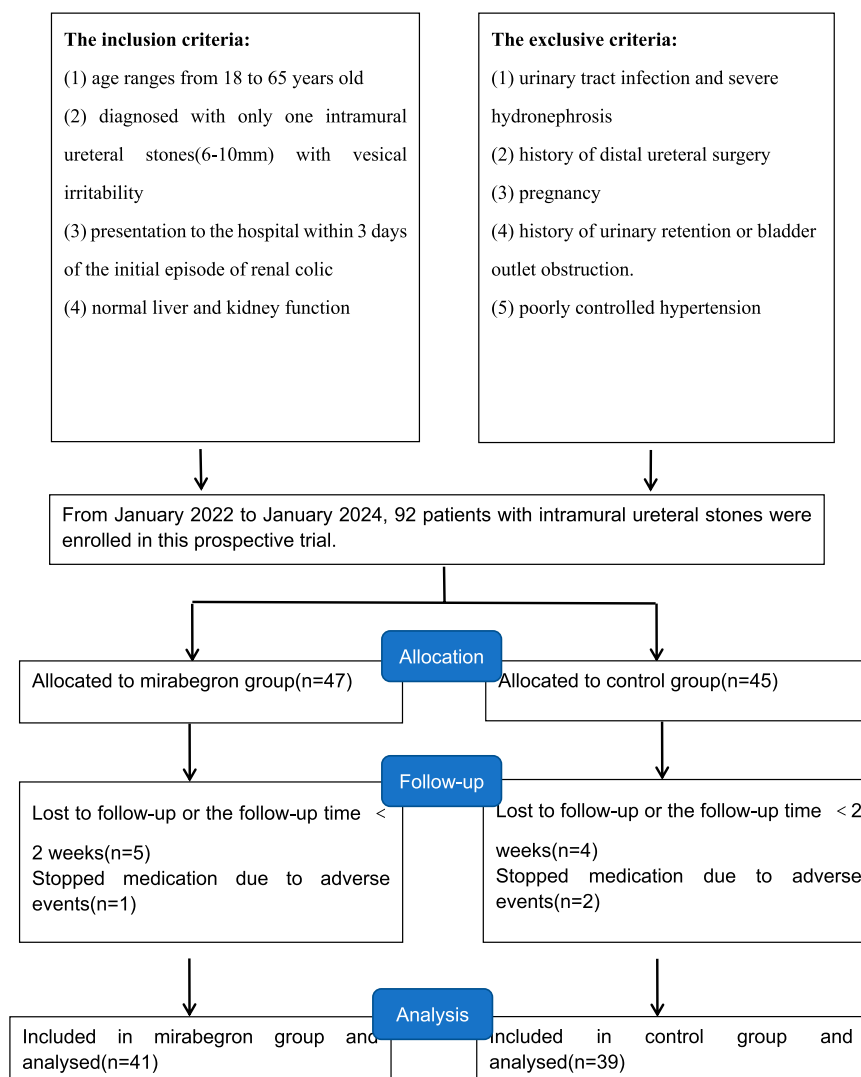
## KEYWORDS

adrenergic beta-3 receptor agonists, mirabegron, overactive bladder, ureteral calculi, urinary tract symptoms

## Introduction

The incidence of urolithiasis has shown a continuous global increase and is one of the most common conditions encountered in urology. Ureteral stones account for approximately 20% of all urolithiasis cases, with the majority located in the distal ureter (Thongprayoon et al., 2020; Sakhaee et al., 2012; Shastri et al., 2023). If not removed in a timely manner, these stones may lead to complications such as renal colic, urinary tract infection, and progression to urosepsis (Miller and KANE, 1999; Reyner et al., 2016; Teichman, 2004; Wagenlehner et al., 2008). Patients who fail to spontaneously pass the stone often require additional interventions, depending on the stone's characteristics and clinical presentation (Kobayashi et al., 2003; Prina et al., 2002). Both the location and size of the stone significantly influence the likelihood of spontaneous expulsion (Skolarikos et al., 2010).

The intramural ureter, due to its unique anatomical structure, represents the narrowest portion of the ureter and serves as a major barrier to spontaneous stone passage. Medical expulsive therapy (MET) has been widely used in clinical practice for facilitating stone



**FIGURE 1**  
Flowchart of patient enrollment, randomization, follow-up, and analysis.

expulsion (De Coninck et al., 2019). Stones lodged in the intramural ureter not only cause symptoms and complications typical of ureteral stones but are also frequently associated with vesical irritability—manifested as pain, urinary urgency, and frequency—similar to overactive bladder (OAB). Although tolterodine has been shown to alleviate these irritative symptoms, it does not promote stone passage (Lv and Tang, 2013; Maghsoudi et al., 2018). Therefore, an ideal therapeutic approach for intramural ureteral stones should aim to both facilitate stone expulsion and relieve vesical irritability.

Mirabegron, a  $\beta_3$ -adrenergic receptor ( $\beta_3$ -AR) agonist, is primarily used to treat patients with OAB (Kennelly et al., 2021; Wada et al., 2024).  $\beta_3$ -ARs are expressed in both the urothelium and smooth muscle of the human ureter, and the inhibitory effect of  $\beta_3$ -AR agonists on ureteral contraction has been demonstrated in several *in vivo* animal pharmacology studies (Matsumoto et al., 2013).

This study aimed to investigate whether mirabegron, as a  $\beta_3$ -AR agonist, can effectively promote the expulsion of intramural ureteral stones while also alleviating vesical irritability.

## Methods and patients

From January 2022 to January 2024, patients presenting with vesical irritability caused by intramural ureteral stones (6–10 mm in diameter) were recruited at our hospital for this study (Figure 1). The inclusion criteria included: 1) age ranges from 18 to 65 years old; 2) diagnosed with single intramural ureteral stone (6–10 mm) with vesical irritability; 3) presentation to the hospital within 3 days of the initial episode of renal colic; 4) normal liver and kidney function. Exclusion criteria included: 1) urinary tract infection and severe hydronephrosis; 2) history of distal ureteral surgery; 3) pregnancy; 4) history of urinary retention or bladder outlet obstruction; 5) poorly controlled hypertension. This study complied with the 1964 Declaration of Helsinki and received approval from the Ethics Committee of the Affiliated Jiangning Hospital of Nanjing Medical University (202100529). Routine evaluations included medical history, physical examination, blood and urine routine tests, etc.

Abdominal ultrasound, kidney-ureter-bladder (KUB) radiography, or non-contrast computed tomography (CT) were used to diagnose the

TABLE 1 Baseline demographics and clinical characteristics of patients.

Variable	Mirabegron (n = 41)	Control (n = 39)	p value
Sex, n			
Male	22	20	0.832
Female	19	19	
Age (years)	39.4 ± 5.1	40.3 ± 6.1	0.475
BMI(kg/m²)	24.1 ± 3.4	23.9 ± 3.6	0.799
stone size (mm)	7.9 ± 1.2	8.1 ± 1.4	0.494
Laterality, n			
Left	21	19	
Right	20	20	
Hypertension history, n			
No	26	27	0.582
Yes	15	12	
Smoker, n			
No	21	18	0.651
Yes	20	21	
Hydronephrosis, n			
Negative	17	20	0.100
Mild	15	12	
Moderate	9	7	

Abbreviations: BMI, body mass index.  
Note: \**P* < 0.05, \*\**P* < 0.01.

intramural ureteral stones based on clinical need. Stone size was measured as the maximal diameter via KUB, ultrasonography, or CT imaging. Upon providing informed consent, patients were randomized into two groups using sealed envelopes in a 1:1 allocation ratio. The mirabegron group received 50 mg once daily, while the control group was administered 0.4 mg of tamsulosin per day. If renal colic occurred, both groups received 100 mg oral ibuprofen. Participants were adviced to intake of at least 2 L water daily and filter their urine to determine whether the stone is expelled. Medication was discontinued upon stone expulsion. Patients were followed up for 4 weeks. Patients who had not expelled their stones after 4 weeks were referred to ureteroscopic lithotripsy. Urinary urgency was using the Urinary Sensation Scale (USS) to assess. Pain intensity during stone episodes was using the Visual Analog Scale (VAS) to evaluated.

Sample size calculation ensured 95% statistical power with a 5% type I error. Continuous variables with normal distribution are showed as mean ± standard deviation (SD) and analyzed using the Student's t-test. Categorical data are showed as counts and analyzed using the Chi-square test. Data was analyzed using SPSS v.22.0 (IBM Corp., United States). *P* < 0.05 was considered statistically significant.

## Results

92 patients were initially enrolled and randomly assigned to two groups. Nine patients lost follow-up and three patients withdrew

from the study due to adverse events, all of whom recovered with symptomatic management. Finally, 80 patients included in the study: 41 in the mirabegron group and 39 in the tamsulosin group (Figure 1). Patients demographic are summarized in Table 1. No statistically differences were showed between two groups in sex, age, BMI, stone size, stone laterality, history of hypertension, smoking, or hydronephrosis grade (*P* > 0.05).

The clinical outcomes for both groups are shown in Table 2. After 1 and 2 weeks of pharmacological treatment, more patients achieved stone-free status in the mirabegron group than tamsulosin group (36.6% vs. 15.4%, *P* = 0.031 and 75.6% vs. 43.6%, *P* = 0.004). However, by 4 weeks, there was no statistically difference in stone expulsion rate (SER) between the two groups (92.7% vs. 89.7%, *P* = 0.709). Patients in the mirabegron group reported fewer daily episodes of pain (1.4 ± 0.6 vs. 1.8 ± 0.8, *P* = 0.013) and shorter mean stone expulsion time than those in the tamsulosin group (8.4 ± 2.9 vs. 11.2 ± 3.1, *P* < 0.0001). There were no statistical differences in USS and VAS between two groups prior to treatment (*P* > 0.05). However, both in the mirabegron group were statistical lower than those in the tamsulosin group (3.4 ± 1.2 vs. 5.7 ± 1.4, *P* < 0.0001 and 2.1 ± 0.8 vs. 3.3 ± 1.1, *P* < 0.0001). There were no statistical differences in adverse events between two groups (*P* > 0.05). After 4 weeks, patients who had not passed their stones underwent ureteroscopic lithotripsy. Intraoperative findings revealed varying degrees of ureteral edema and stricture in these patients.

TABLE 2 Comparison of clinical outcomes between two groups.

Outcome	Mirabegron (n = 41)	Control (n = 39)	p value
Stone expulsion Rate (SER), n (%)			
1st-week follow-up	15/41 (36.6)	6/39 (15.4)	0.031*
2nd-week follow-up	31/41 (75.6)	17/39 (43.6)	0.004**
4th-week follow-up	38/41 (92.7)	35/39 (89.7)	0.709
Renal colic episodes (per day)	1.4 ± 0.6	1.8 ± 0.8	0.013*
Stone expulsion time (days)	8.4 ± 2.9	11.2 ± 3.1	<0.0001**
Visual Analog Scale (VAS)			
Before treatment	7.2 ± 1.4	6.9 ± 1.3	0.324
After treatment	3.4 ± 1.2	5.7 ± 1.4	<0.0001**
Urinary Sensation Scale (USS)			
Before treatment	3.5 ± 1.3	3.7 ± 1.2	0.477
After treatment	2.1 ± 0.8	3.3 ± 1.1	<0.0001**
Drug unwanted effects, n			0.521
Dry mouth	1	2	
Headache	1	2	
Dizziness	1	3	
Hypertension	3	2	
Constipation	2	1	
Ejaculation dysfunction	2	0	

Abbreviations: SER, stone expulsion rate; VAS, visual analogue scale; USS, urinary sensation scale.  
Note: \**P* < 0.05, \*\**P* < 0.01.

## Discussion

The intramural ureter, located within the muscular wall of the bladder, extends from its lateral entrance to the trigonal orifice. As the most constricted segment of the ureter, it is the primary site of stone impaction during urinary passage (Bensalah et al., 2008). Obstruction at this site often induces vesical irritability, manifesting as bladder discomfort, urinary urgency, and increased frequency of micturition (Lv and Tang, 2013).

The therapeutic principle of MET involves relaxation of ureteral smooth muscle to promote stone clearance. Pharmacological agents employed in MET include α-adrenergic receptor antagonists, calcium channel blockers, phosphodiesterase inhibitors, and antispasmodics (Türk et al., 2017). Among them, the α1-adrenergic receptor antagonist tamsulosin has demonstrated superior clinical efficacy, supported by multiple randomized clinical trials (Ye et al., 2011; Ye et al., 2018). Its mechanism involves inhibition of α1-ARs, reducing ureteral contractility and promoting luminal dilation (Kwon et al., 2015). Additionally, β2- and β3-adrenergic receptors expressed in ureteral smooth muscle and urothelium also contribute to smooth muscle relaxation.

Notably, mirabegron—a selective β3-AR agonist originally approved for the treatment of OAB—may exert off-target effects beneficial for stone expulsion (Dehvari et al., 2018). In a prospective trial, tamsulosin and mirabegron used preoperatively for semi-rigid

ureterolithotripsy improved stone-free rates (SFR) and facilitated stone access, without increasing complication rates (Bayar et al., 2019). Solakhan et al. (Solakhan et al., 2019) reported that mirabegron improved the SER for intramural stones smaller than 5 mm, though not for larger stones, and noted a limited sample size. Another study by Bayar et al. (Bayar et al., 2020) suggested mirabegron had no significant effect on stone passage; however, it included only 22 cases of stones <6 mm, and did not specify their locations. Previous studies have shown that mirabegron can significantly reduce renal colic episodes (Faridi and Deshpande, 2024). Our findings are consistent with this, revealing a significant reduction in renal colic frequency among patients treated with mirabegron compared to those receiving tamsulosin. Since β3 receptors are primarily distributed in the distal ureter, persistent obstruction and smooth muscle contraction may lead to receptor downregulation, potentially compromising drug efficacy. To mitigate this, we included only patients who sought medical attention within 3 days of their initial renal colic episode, reducing the likelihood of β3-AR downregulation interfering with stone expulsion. Unlike previous studies, our investigation focused specifically on intramural ureteral stones and included a larger sample size. We found that the SER in the mirabegron group was higher than that of the tamsulosin group at 1 and 2 weeks post-treatment, although no significant difference was observed at 4 weeks. Additionally, patients in the mirabegron group had a shorter mean stone expulsion time and fewer daily renal colic episodes. These findings suggest that mirabegron, through β3-AR-

mediated ureteral smooth muscle relaxation, effectively facilitates stone passage and reduces spasms. No serious complications were observed in either group, and there was no statistically significant difference in adverse events between them ( $P > 0.05$ ), supporting the safety profile of mirabegron. While previous studies have explored the role of mirabegron in MET, limited research has addressed its efficacy in relieving vesical irritability associated with intramural ureteral stones. In our study, pre-treatment USS and VAS scores were comparable between groups. Post-treatment, both scores significantly reduced in both groups, with the mirabegron group showing greater reductions. This indicates that mirabegron may provide superior symptom relief for stone-related pain and irritative voiding symptoms, possibly through its relaxant effect on ureteral smooth muscle. Lu et al. (Lv and Tang, 2013) demonstrated that a combination of tamsulosin and tolterodine effectively managed intramural calculi with vesical irritability. However, combination therapy may reduce patient compliance due to pill burden. Mirabegron, as a monotherapy, may offer a more convenient alternative.

This study has several limitations. First, the follow-up duration was limited to 4 weeks, potentially overlooking long-term adverse effects. Second, the USS and VAS scores are subjective measures and may be influenced by individual perception, lacking objective validation. Third, this was a single-center study. Future multi-center studies are warranted to further evaluate the efficacy and safety of mirabegron in managing intramural ureteral stones.

## Conclusion

Mirabegron is a safe and effective option for accelerating the expulsion of intramural ureteral stones, while also alleviating pain and vesical irritability. These advantages highlight its potential for broader clinical application.

## Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

## Ethics statement

The studies involving humans were approved by the Affiliated Jiangning Hospital of Nanjing Medical University. The studies were

conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

## Author contributions

MD: Writing – original draft. YS: Writing – original draft. HW: Writing – original draft, Writing – review and editing.

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## Conflict of interest

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## References

- Bayar, G., Kilinc, M. F., Yavuz, A., and Aydin, M. (2019). Adjunction of tamsulosin or mirabegron before semi-rigid ureterolithotripsy improves outcomes: prospective, randomized single-blind study. *Int. urology Nephrol.* 51 (6), 931–936. doi:10.1007/s11255-019-02142-0
- Bayar, G., Yavuz, A., Cakmak, S., Ofluoglu, Y., Kilinc, M. F., Kucuk, E., et al. (2020). Efficacy of silodosin or mirabegron in medical expulsive therapy for ureteral stones: a prospective, randomized-controlled study. *Int. urology Nephrol.* 52 (5), 835–840. doi:10.1007/s11255-019-02368-y
- Bensalah, K., Pearle, M., and Lotan, Y. (2008). Cost-effectiveness of medical expulsive therapy using alpha-blockers for the treatment of distal ureteral stones. *Eur. Urol.* 53 (2), 411–418. doi:10.1016/j.eururo.2007.09.012
- De Coninck, V., Antonelli, J., Chew, B., Patterson, J. M., Skolarikos, A., and Bultitude, M. (2019). Medical expulsive therapy for urinary stones: future trends and knowledge gaps. *Eur. Urol.* 76 (5), 658–666. doi:10.1016/j.eururo.2019.07.053
- Dehvari, N., da Silva Junior, E. D., Bengtsson, T., and Hutchinson, D. S. (2018). Mirabegron: potential off target effects and uses beyond the bladder. *Br. J. Pharmacol.* 175 (21), 4072–4082. doi:10.1111/bph.14121
- Faridi, M. S., and Deshpande, S. (2024). Comparing silodosin and mirabegron as medical expulsive therapy for distal ureteral calculus: a prospective, randomised study. *Central Eur. J. urology* 77 (2), 286–290.

- Kennelly, M. J., Rhodes, T., Girman, C. J., Thomas, E., Shortino, D., and Mudd Jr, P. N. (2021). Efficacy of vibegron and mirabegron for overactive bladder: a systematic literature review and indirect treatment comparison. *Adv. Ther.* 38 (11), 5452–5464. doi:10.1007/s12325-021-01902-8
- Kobayashi, T., Nishizawa, K., Watanabe, J., and Ogura, K. (2003). Clinical characteristics of ureteral calculi detected by nonenhanced computerized tomography after unclear results of plain radiography and ultrasonography. *J. urology* 170 (3), 799–802. doi:10.1097/01.ju.0000081424.44254.45
- Kwon, J. K., Cho, K. S., Oh, C. K., Kang, D. H., Lee, H., Ham, W. S., et al. (2015). The beneficial effect of alpha-blockers for ureteral stent-related discomfort: systematic review and network meta-analysis for alfuzosin versus tamsulosin versus placebo. *BMC Urol.* 15 (1), 55. doi:10.1186/s12894-015-0050-5
- Lv, J. L., and Tang, Q. L. (2013). Tamsulosin and tolterodine in the medical expulsive therapy for intramural ureteral stones with vesical irritability: a prospective randomized study. *Urolithiasis* 41 (5), 417–421. doi:10.1007/s00240-013-0599-y
- Maghsoudi, R., Farhadi-Niaki, S., Etemadian, M., Kashi, A. H., Shadpour, P., Shirani, A., et al. (2018). Comparing the efficacy of tolterodine and gabapentin versus placebo in catheter-related bladder discomfort after percutaneous nephrolithotomy: a randomized clinical trial. *J. Endourol.* 32 (2), 168–174. doi:10.1089/end.2017.0563
- Matsumoto, R., Otsuka, A., Suzuki, T., Shinbo, H., Mizuno, T., Kurita, Y., et al. (2013). Expression and functional role of  $\beta_3$ -adrenoceptors in the human ureter. *Int. J. Urology* 20 (10), 1007–1014. doi:10.1111/iju.12093
- Miller, O. F., and Kane, C. J. (1999). Time to stone passage for observed ureteral calculi: a guide for patient education. *J. urology* 162 (3 Part 1), 688–690. doi:10.1097/00005392-199909010-00014
- Prina, L. D., Rancatore, E., Secic, M., and Weber, R. E. (2002). Comparison of stone size and response to analgesic treatment in predicting outcome of patients with renal colic. *Eur. J. Emerg. Med.* 9 (2), 135–139. doi:10.1097/00063110-200206000-00007
- Reyner, K., Heffner, A. C., and Karvetski, C. H. (2016). Urinary obstruction is an important complicating factor in patients with septic shock due to urinary infection. *Am. J. Emerg. Med.* 34 (4), 694–696. doi:10.1016/j.ajem.2015.12.068
- Sakhaee, K., Maalouf, N. M., and Sinnott, B. (2012). Clinical review. Kidney stones 2012: pathogenesis, diagnosis, and management. *J. Clin. Endocrinol. and Metabolism* 97 (6), 1847–1860. doi:10.1210/jc.2011-3492
- Shastri, S., Patel, J., Sambandam, K. K., and Lederer, E. D. (2023). Kidney stone pathophysiology, evaluation and management: core curriculum 2023. *Am. J. kidney Dis.* 82 (5), 617–634.
- Skolarikos, A., Laguna, M. P., Alivizatos, G. E., Kural, A. R., and De La Rosette, J. J. M. C. H. (2010). The role for active monitoring in urinary stones: a systematic review. *J. endourology* 24 (6), 923–930. doi:10.1089/end.2009.0670
- Solakhan, M., Bayrak, O., and Bulut, E. (2019). Efficacy of mirabegron in medical expulsive therapy. *Urolithiasis* 47 (3), 303–307. doi:10.1007/s00240-018-1075-5
- Teichman, J. M. (2004). Clinical practice. Acute renal colic from ureteral calculus. *N. Engl. J. Med.* 350 (7), 684–693. doi:10.1056/NEJMc030813
- Thongprayoon, C., Krambeck, A. E., and Rule, A. D. (2020). Determining the true burden of kidney stone disease. *Nat. Rev. Nephrol.* 16 (12), 736–746. doi:10.1038/s41581-020-0320-7
- Türk, C., Knoll, T., Seitz, C., Skolarikos, A., Chapple, C., and McClinton, S. (2017). Medical expulsive therapy for ureterolithiasis: the EAU recommendations in 2016. *Eur. Urol.* 71 (4), 504–507.
- Wada, N., Mizunaga, M., Abe, N., Miyauchi, K., Kobayashi, S., Ohtani, M., et al. (2024). Comparison of mirabegron and vibegron for clinical efficacy and safety in female patients with overactive bladder: a multicenter prospective randomized crossover trial. *World J. Urol.* 42 (1), 113. doi:10.1007/s00345-024-04799-4
- Wagenlehner, F. M. E., Pilatz, A., Naber, K. G., and Weidner, W. (2008). Therapeutic challenges of urosepsis. *Eur. J. Clin. Investigation* 38, 45–49. doi:10.1111/j.1365-2362.2008.02008.x
- Ye, Z., Yang, H., Li, H., Zhang, X., Deng, Y., Zeng, G., et al. (2011). A multicentre, prospective, randomized trial: comparative efficacy of tamsulosin and nifedipine in medical expulsive therapy for distal ureteric stones with renal colic. *BJU Int.* 108 (2), 276–279. doi:10.1111/j.1464-410X.2010.09801.x
- Ye, Z., Zeng, G., Yang, H., Tang, K., Zhang, X., Li, H., et al. (2018). Efficacy and safety of tamsulosin in medical expulsive therapy for distal ureteral stones with renal colic: a multicenter, randomized, double-blind, placebo-controlled trial. *Eur. Urol.* 73 (3), 385–391.