ROSALIND FRANKLIN UNIVERSITY OF MEDICINE & SCIENCE COLLEGE OF PHARMACY STUDENT WRITING CLUB:

A Review of Overactive Bladder Treatment

by Sara Mehmood, 2023 PharmD Candidate, Victoria Ellaine Dizon, 2023 PharmD Candidate, Myrrh Elan Cagas, 2023 PharmD Candidate, Rucha Kulkarni, 2023 PharmD Candidate

Abstract

The sudden urge to urinate and the uncontrolled feeling of having to go frequently describes the life of an individual with an overactive bladder. As many as 30 percent of men and 40 percent of women in the United States live with an overactive bladder.[1] Many people feel embarrassed, don't ask for help, don't know how to talk with their health care provider about their symptoms, or think there are not treatments that can help. Symptoms can severely impact the physical and social life of an individual with an overactive bladder. In this article, we will explore the disease state and investigate the role of novel vibegron and of a combination of mirabegron/solifenacin in patients with overactive bladder.

Overactive bladder (OAB) is a syndrome classified by the compelling desire to pass urine, which presents with or without urinary incontinence and nocturia. OAB affects a significant proportion of the U.S. population, with an overall prevalence of 23.3%. Nearly twice as many women as men have OAB (30% of women and 16.4% of men).[2] Relative to race, 45.9% of Black, 43.4% of White, 42% of Hispanic, and 26.6% of Asian women have OAB, while for men the percentages are 33.3%, 28.0%, 27.0%, and 26.6%, respectively.

In healthy patients, normal bladder function is defined as a bladder free of bacterial infections or tremors and having the ability to store urine without discomfort.[3] Conversely, the pathophysiology of OAB has either neurogenic factors or non-neurogenic factors, which encompass myogenic and urotheliogenic factors.[4] Neurogenic factors include damage to the central inhibitory pathways of the brain or spinal cord, or sensitization of peripheral afferent terminals, leading to OAB. Non-neurogenic, myogenic factors involve unstable increases in the intravesical pressure leading to damage of the bladder wall, and secondary changes to the smooth wall muscles of the bladder. Meanwhile, urotheliogenic factors include damage to the urothelium that leads to an increase in urinary frequency and a decrease in storage of urine. The etiology of OAB consists of a multitude of factors, including weak pelvic muscles, nerve damage, urinary tract infection, excess weight, menopause, and intake of alcohol or caffeine.[5] The significant risk factors for OAB are increasing age, current smoking, hyperlipidemia, cardiovascular disease, and renal disease.[6]

Typical clinical presentations of OAB involve a sudden urge to urinate that is difficult to control, urinary urgency incontinence, urinating frequently (eight or more times in 24 hours), or waking up one to two times in the night due to urination.[6] Diagnosis of OAB includes an initial assessment of symptom history and fluid intake, and a urinalysis to rule out infection or hematuria. However, if a patient reports bothersome symptoms of urgency with or without urinary incontinence, and absence of a urinary tract infection, an OAB diagnosis may be made.[7] After a diagnosis is made, there are many healthcare professionals involved in the care of patients with OAB, including family practice physicians, urologists, nephrologists, gynecologists, and pharmacists, who optimize the care for these patients.

Treatment Modalities and Approach

The American Urological Association (AUA) and the Society of Urodynamic, Female Pelvic Medicine and Urogenital Reconstruction (SUFU) are the two organizations that co-publish the treatment guidelines for OAB.[8,9] The "Diagnosis and Treatment of Non-Neurogenic Overactive Bladder in Adults: an AUA/SUFU Guideline" outlines non-pharmacological and pharmacological treatment options for OAB.

Non-pharmacological treatments are considered first-line treatment options.[8,9] They include education and the implementation of behavioral therapies. Some key points to emphasize during patient education are: the benefits versus risks of treatment options; that multiple treatment options may be needed; and that not all symptoms may be resolved. Behavioral therapies include bladder training, pelvic floor training, and fluid management.[8] Bladder training allows patients to train their bladders to urinate on a fixed schedule in order to increase the amount of urine held in the bladder by urinating first thing in the morning, then urinating again after a set interval, such as 15 minutes. Over time, the patient should be able to increase their interval time in order to decrease urinary incontinence.[10] Pelvic floor muscle training, also known as Kegels, involves contracting and then relaxing the pelvic floor muscles, typically repeated in several sets throughout the day. This training provides patients with the ability to strengthen the muscles that control urination. Lastly, fluid management can be implemented as a behavioral therapy to manage urinary incontinence. Educating the patient on drinking smaller amounts of liquid throughout the day, drinking more fluids earlier in the day, or skipping the fluids that increase urine production, such as alcohol and caffeine, are methods that can help manage fluid for those with OAB.[11] The main goals of the education and behavioral therapies for OAB are to change voiding habits and improve the control of

TABLE 1. Clinical Trials of Blood Pressure Lowering Strategies in Patients with Diabetes

Generic/Brand	*Dosing & Modifications*	*Important Drug Interactions*	*Patient Education*
Antimuscarinic Antagonists[30-35] Mechanism of Action: competitively antagonizes the muscarinic receptor on urinary bladder smooth muscle, resulting in reduced contractions Class Adverse Drug Reactions: dry mouth, constipation, diarrhea, headache, somnolence, and dizziness Class Contraindications: urinary retention, gastric retention, uncontrolled narrow angle glaucoma			
Oxybutynin/Ditropan XL® [30]	Dosing: 5 mg, 10 mg or 15 mg extended-release tablets by mouth daily Modifications: • Adults: Start with 5 mg or 10 mg, once daily. Dose should not exceed 30 mg per day • Pediatric patients (6 years of age or older): Start with 5 mg, once daily. Dose should not exceed 20 mg per day	• Potent CYP3A4 inhibitors • Other anticholinergic drugs	• Take at approximately the same time each day. Should be swallowed whole with the aid of liquids. Patients should not chew, divide, or crush tablets. • May produce angioedema.
Tolterodine/Detrol® LA[31]	Dosing: 2 mg or 4 mg extended-release capsule by mouth daily Modifications: • Mild to moderate hepatic impairment, Creatinine Clearance 10-30 mL/min, and drugs that are potent CYP3A4 inhibitors: 2 mg by mouth daily • Severe renal and hepatic Impairment: Not recommended	• Potent CYP3A4 inhibitors • Other anticholinergic drugs	• Take with or without food and at the same time each day.
Trospium/Sanctura®[32]	Dosing: 20 mg tablets by mouth twice daily Modifications: • Creatinine clearance less than 30 mL/min): 20 mg once daily at bedtime • Geriatric patients greater than or equal to 75 years of age, dose may be titrated down to 20 mg once daily based upon tolerability	• Drugs elimination by active tubular secretion • Metformin immediate release tablets • Other anticholinergic drugs	• Should be taken with water on an empty stomach at least one hour before a meal.
Darifenacin/Enablex®[33]	Dosing: Extended-release tablets 7.5 mg or 15 mg by mouth daily Modifications: • Patients with moderate hepatic impairment and patients taking potent CYP3A4 inhibitors: daily dose should not exceed 7.5 mg daily • Severe hepatic impairment: Not recommended	• CYP3A4 inhibitors • CYP2D6 substrates • Other anticholinergic drugs	• May be taken with or without food. The tablet should be swallowed whole with water and not chewed, divided or crushed.
Solifenacin/Vesicare®[34]	Dosing: 5 mg or 10 mg tablets by mouth daily Modifications: • CrCl <30 ml/min, moderate hepatic impairment, concomitant use of potent CYP3A4 inhibitors: do not exceed 5 mg tablet once daily	• Inhibitors and inducers of CYP3A4 enzyme • Other anticholinergic drugs	• Take with water and swallow the tablet whole, can take with or without food.
Beta-3 Adrenoreceptor Agonist[35,36] Mechanism of Action: activates beta-3 receptors resulting in relaxation of the detrusor smooth muscle Class Adverse Drug Reaction: hypertension (Mirbegron only), nasopharyngitis, urinary tract infection and headache Class Contraindications: Hypersensitivity reaction			
Mirabegron/Myrbetriq®[35]	Dosing: 25 mg or 50 mg extended-release tablets by mouth daily Modifications: • Severe renal impairment or patients with moderate hepatic impairment: maximum dose of 25 mg once daily • End Stage Renal Disease and severe hepatic impairment: Not recommended	• Mirabegron is CYP2D6 inhibitor; appropriate monitoring and possible dose adjustment of those CYP2D6 substrate drugs may be necessary • Digoxin: prescribe the lowest dose of digoxin when concomitant use of mirabegron	Swallow whole with water, do not chew, divide or crush tablets
Virbegron/GEMTESA®[36]	Dosing: 75 mg tablet once daily Modifications: • End-stage Renal Disease with or without Hemodialysis: Not recommended. • Severe Hepatic Impairment: Not recommended	• Digoxin	• May be taken with out without food but must be swallow whole with water • May be crushed and mixed into applesauce

urge suppressions.

Per the AUA/SUFU guidelines, pharmacological treatments options are considered as second-line therapies, which are to be added if behavior therapies alone are not sufficient to treat the symptoms.[8] Antimuscarinics such as oxybutynin, tolterodine, trospium, darifenacin, and solifenacin are commonly used drug agents to treat OAB. Guidelines suggest that the extended-release form of the antimuscarinics should be used due to fewer side effects, specifically dry mouth.[8,12,13] In addition to antimuscarinics, beta-3 adrenoreceptor agonists, such as mirabegron, are commonly used for overactive bladders, with vibegron being the most recently approved drug agent in this class.[13] Table 1 describes available agents in detail. These medications can be used as monotherapy, or in a combination of the two different drug classes if the disease state becomes refractory, in order to achieve better clinical outcomes.[8]

Third- and fourth-line OAB therapies include the use of surgical and non-surgical procedures.[8] Intradetrusor onabotulinumtoxinA (100U) can be administered in order to cause bladder muscle contraction.[14] Peripheral tibial nerve stimulation is a non-surgical procedure in which a needle is placed near the tibial nerve. When stimulated, electrical impulses block the nerve signals that cause unwanted muscle spasms.[15] Sacral neuromodulation simulation is a surgical procedure that sends electrical impulses directly to the sacral nerve to alter the bladder function.[16] In rare cases, patients may undergo bladder augmentation cystoplasty, in order to enlarge the bladder, or may undergo urinary diversion, in order to create a new pathway for voiding.[17] These procedures are reserved for patients categorized with OAB refractory to previous therapies, patients not candidates for second-line therapies, and those who are willing to undergo surgery.

Novel Pharmacologic Approaches

Gemtesa® - vibegron

In December of 2020, a new beta-3 adrenergic agonist, Gemtases®, emerged to treat overactive bladder with symptoms of urinary incontinence, urgency, and urinary frequency in adults. Gemtases® is also known by its generic name, vibegron, and was approved by the Food and Drug Administration (FDA). The drug comes in a 75 mg tablet and is generally administered once daily. Vibegron's common adverse reactions include headache, urinary tract infection, nausea and diarrhea; and it is contraindicated for those who have hypersensitivity to the drug. Also, vibegron has a potential to interact with digoxin by increasing the blood levels of digoxin. The approval was based on a randomized, double-blind, placebo and active controlled phase III trial called the EMPOWUR trial.[18] This trial assessed the efficacy and safety of vibegron in OAB "wet" (urinary urgency with urge incontinence) and "dry" patients (urinary urgency without urge incontinence). It followed 1,518 eligible participants who were randomized to receive 75 mg vibegron or matching placebo or tolterodine for 12 weeks.

The trial primarily investigated the change in the average number of daily urge urinary incontinence (UUI) episodes in patients with one or more episodes per day, and the change in daily urinary micturitions.[18] The average change of UUI episodes was statistically significant in the vibegron group by -2.0 episodes per day vs. -1.4 episodes for placebo ($p < 0.0001$) and -1.8 episodes for tolterodine with a p-value of 0.0123. The mean change of urinary micturitions at week 12 was statistically significant by -1.8 episodes per day for vibegron vs. -1.3 for placebo ($p < 0.001$) and -1.6 for tolterodine with a p-value of 0.0020. Vibegron exhibited a statistically significant improvement in the key secondary outcome measures, such as number of urgency episodes, volume per micturition, and proportion of incontinent patients with a ≥75% reduction in urge incontinence episodes ($p < 0.01$).

In the vibegron group, the incidence of adverse events that were observed 2% or more than in the placebo group were headache (4%), nasopharyngitis (2.8%), and diarrhea and nausea (2.2%).[18] Furthermore, other adverse events were consistent with cystitis and urinary tract infection. Safety measures also included vital signs assessments. The proportion of patients at week 12 that had an increase in blood pressure was 0.7% for vibegron, 0.9% for placebo, and 1.9% for tolterodine. The proportion of patients who experienced tachycardia in both the placebo and tolterodine groups was 0.2% while there was no tachycardia reported in the vibegron group.These results were not statistically significant. Furthermore, based on the adverse effects observed during the study, vibegron was less associated with adverse events such as dry mouth and cognitive decline, which are commonly observed with anticholinergics agents used in the treatment of OAB. In conclusion, vibegron provided a significant improvement in OAB symptoms with a better safety profile.

Similar to the antimuscarinics, all beta-3 adrenergic agonists are second-line agents after trialing first-line therapy of behavioral therapies.[19] Vibegron's place in therapy falls as second-line among the other beta-3 adrenergic agonists.[20] Further, as vibegron is a relatively newer agent, it is unavailable in the generic formulation. This is the reason behind its limited insurance coverage and high cost.[21]

Combined Use of Mirabegron and Solifenacin

Mirabegron, a beta-3 adrenergic agonist, and solifenacin succinate, a muscarinic receptor antagonist, are two drugs approved by the FDA in 2012 and 2004 respectively as monotherapies for treatment of OAB.[22,23] More recently in 2018, the FDA approved the use of mirabegron in combination with solifenacin for treatment of OAB with evidence of increased efficacy over use as monotherapy.[23]

Mirabegron (Myrbetriq®) eases symptoms of OAB such as urinary urgency, urinary frequency, and urinary incontinence. It is a beta-3 adrenergic agonist that works by relaxing the bladder muscles to prevent symptoms of OAB. Mirabegron comes as an extended-release tablet with an initial dosage of 25 mg orally once daily and may be titrated up to 50 mg once daily after 4 to 8 weeks as necessary.[23] Mirabegron for OAB is recommended to be taken with food in children ages 8-18, and can be taken with or without food in adults. A max dose of 25 mg daily is recommended in patients with renal or hepatic impairment. This medication is also indicated in children ages 3 and older as a suspension in treatment for neurogenic detrusor overactivity (NDO), a bladder control condition caused by brain, spinal cord, or nerve problems. Mirabegron is a moderate CYP2D6 inhibitor and should be monitored in patients also taking medications such as digoxin and warfarin. Patients initiating treatment with digoxin and mirabegron should consider the lowest

digoxin dose initially and monitor serum digoxin concentrations when titrating up. While effects of mirabegron on multiple doses of warfarin have not fully been investigated and no effect was seen in the pharmacodynamic endpoints of a single dose of warfarin, prothrombin time should be monitored with concurrent use of both agents. The most common adverse effects reported with monotherapy include hypertension, nasopharyngitis, urinary tract infection, angioedema, and headache. Blood pressure should be monitored periodically, especially in patients with hypertension. Worsening of pre-existing hypertension has been reported infrequently with mirabegron in clinical trials and is not recommended for use in patients with severe uncontrolled hypertension (>180/110 mmHg). Mirabegron reportedly has lower incidences of dry mouth and constipation compared to antimuscarinic counterparts.[29]

Solifenacin succinate (Vesicare®) is a muscarinic receptor antagonist, selective for the M3 receptor to relax and reduce spasms of bladder muscles.[22] Solifenacin, similar to mirabegron, is indicated for OAB and NDO in children ages 2 and older. The oral tablet is initially dosed at 5 mg daily and can be titrated up to 10 mg daily. A max dose of 5 mg is recommended in patients with severe renal impairment or moderate hepatic impairment. It is not recommended for use in patients with severe hepatic impairment. Solifenacin is metabolized by CYP3A4 and should be used with caution in concurrent administration of CYP3A4 inhibitors. Grapefruit juice and St. John's Wort should be avoided, and a maximum dose of 5 mg should be used with concomitant use of ketoconazole, an azole antifungal. Solifenacin should not be used in pregnant or breastfeeding women. It is contraindicated in patients with narrow-angle glaucoma, gastric retention, and urinary retention. Furthermore, anticholinergic CNS effects have been reported with monotherapy, including headache, confusion, somnolence, and hallucinations. Patients should be monitored for anticholinergic CNS effects, especially at initiation or dose titration, and be advised not to operate heavy machinery until they know how solifenacin affects them. Solifenacin should be discontinued or reduced in dose for patients who experience such CNS effects.

Combination therapy with these two agents have been shown to improve OAB symptoms compared to monotherapy with either agent. Most effects of combination therapy were seen by week 4 in clinical trials with effect sizes consistent with an additive effect and without any significant effect in the safety profile.[24] Dual therapy improved number of incontinence episodes, number of micturition, and volume voided per micturition.[24-26,28] Long-term data shows these results were maintained over the course of one year. The most current 2019 AUA/SUFU guidelines for diagnosis and treatment of OAB suggest combination therapy as a second-line treatment, refractory to monotherapy.[8] Guidelines were based on four major trials that compared combination mirabegron (25 to 50 mg) plus solifenacin (5 mg) with monotherapies and placebos over a period either 12 or 52 weeks.[24-26,28] While these trials showed overall significant increased efficacy with combination therapy, there were increased reports of adverse effects.[29] Patient-assessed symptoms were measured in all four trials using the Patient Perception of Bladder Condition questionnaire (PPBC) and the OAB-q Symptom Bother score. Based on the SYNERGY and SYMPHONY trials showing significant reduction in OAB symptoms including urinary urgency, urinary frequency, and urinary incontinence, the combination therapy doses are mirabegron 50 mg and solifenacin 5 mg daily.[24,28] Adverse effects seen in clinical trials were additive for dual therapy with increased rates of dry mouth, constipation, and dyspepsia compared to monotherapy. Additionally, more incidents of urinary retention were reported with the combination of mirabegron and solifenacin.[24,25] Combination therapy is still a new concept with lack of robust data, and is currently considered secondary to monotherapy.

Conclusion

OAB is a chronic condition with varying symptoms among patients that requires a treatment plan tailored to each patient's needs. While a cure for this condition is rare, management of OAB through non-pharmacologic and pharmacologic options greatly improves symptoms and increases patient satisfaction. Non-pharmacologic treatments are first-line, and are intended to help develop strategies to manage urge and urge incontinence. These options include bladder training, pelvic floor training, and fluid intake management. Patients should be educated on OAB and the consistency needed for non-pharmacologic options to see long-term improvements. Pharmacologic treatments are intended to be used as additional management if non-pharmacologic options are not enough.

Sara Mehmood, Victoria Ellaine Dizon, Myrrh Elan Cogas and Rucha Kulkarni are 2023 Doctor of Pharmacy Candidates at Rosalind Franklin University of Medicine & Science College of Pharmacy in North Chicago, IL.

PR *This article has been peer-reviewed. The contribution in reviewing is greatly appreciated!*

Acknowledgments: We thank internal reviewer Khyati Patel, PharmD, BCACP, for her guidance and support in completing this manuscript. We also want to thank Jessica Schwartzwald, PharmD candidate, for organizing this opportunity.

Disclosure: The authors declare no real or potential conflicts or financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employment, gifts, and honoraria. The content of this publication does not necessarily reflect the views or policies of the Rosalind Franklin University of Medicine and Science.

References

1. Reynolds WS, Fowke J, Dmochowski R. The burden of overactive bladder on US public health. *Curr Bladder Dysfunct Rep*. 2016;11(1):8-13. doi:10.1007/s11884-016-0344-9
2. Clinic C. Overactive bladder: causes, symptoms, treatment & prevention. Cleveland Clinic. Accessed December 9, 2021. https://my.clevelandclinic.org/health/diseases/14248--overactive-bladder
3. Lukacz ES, Sampselle C, Gray M, et al. A healthy bladder: a consensus statement. *Int J Clin Pract.* 2011;65(10):1026-1036. doi:10.1111/j.1742-1241.2011.02763.x
4. Meng E, Lin W-Y, Lee W-C, Chuang Y-C. Pathophysiology of overactive bladder. *Low Urin Tract Symptoms.* 2012;4(suppl 1):48-55. doi:10.1111/j.1757-5672.2011.00122.x
5. Chae J, Yoo EH, Jeong Y, Pyeon S, Kim D. Risk factors and factors affecting the severity of overactive bladder symptoms in Korean women who use public health centers. *Obstet Gynecol Sci.* 2018;61(3):404-412. doi:10.5468/ogs.2018.61.3.404
6. Clinic M. Overactive bladder. Mayo Clinic. Published March 20, 2020. Accessed December 9, 2021. https://www.mayoclinic.org/diseases-conditions/overactive-bladder/symptoms-causes/syc-20355715
7. Nitti VW, Patel A, Karram M. Diagnosis and management of overactive bladder: a review. *J Obstet Gynaecol Res.* 2021;47(5):1654-1665. doi:10.1111/jog.14708

8. Lightner DJ, Gomelsky A, Souter L, et al. Diagnosis and treatment of overactive bladder (non-neurogenic) in adults: AUA/SUFU guideline amendment 2019. *J Urol.* 2019;202:558. doi: 10.1097/JU.0000000000000309
9. Gormley EA, Lightner DJ, Burgio KL, et al. Diagnosis and treatment of overactive bladder (non-neurogenic) in adults: AUA/SUFU guideline. *J Urol.* 2012;188(suppl 6):2455-2463. doi: 10.1016/j.juro.2012.09.079
10. Harvard Health Publishing. Training your bladder - Harvard Health. Harvard Health. Published 2019. https://www.health.harvard.edu/healthbeat/training-your-bladder
11. Bladder control: lifestyle strategies ease problems. Mayo Clinic. Published 2017. https://www.mayoclinic.org/diseases-conditions/urinary-incontinence/in-depth/bladder-control-problem/art-20046597
12. Abrams P, Andersson K-E. Muscarinic receptor antagonists for overactive bladder. *BJU Int.* 2007;100(5):987-1006. doi:10.1111/j.1464-410x.2007.07205.x
13. Overactive bladder: best medications to treat it. Healthline. Published July 19, 2016. Accessed December 9, 2021. https://www.healthline.com/health/overactive-bladder/medications-for-overactive-bladder#anticholinergic-drugs
14. Urineincontinence. Botulinum toxin treatment for overactive bladder (OAB). Dr Karen McKertich. Published April 1, 2016. Accessed December 9, 2021. https://www.urineincontinence.com.au/overactive-bladder/botulinum-toxin-treatment-overactive-bladder-oab
15. Percutaneous tibial nerve stimulation (PTNS). University of Colorado Urogynecology. Accessed December 9, 2021. https://urogyn.coloradowomenshealth.com/treatments/ptns.html
16. What is sacral nerve stimulation? Continence Foundation of Australia. Accessed December 9, 2021. https://www.continence.org.au/news/what-sacral-nerve-stimulation
17. Urine Incontinence. Other surgery for overactive bladder (OAB). Dr Karen McKertich. Published April 1, 2016. Accessed December 9, 2021. https://www.urineincontinence.com.au/overactive-bladder/other-surgery-overactive-bladder-oab
18. Staskin D, Frankel J, Varano S, Shortino D, Jankowich R, Mudd P. International phase iii, randomized, double-blind, placebo and active controlled study to evaluate the safety and efficacy of vibegron in patients with symptoms of overactive bladder: EMPOWUR. *J Urol.* 2020;204(2):316-324. doi: 10.1097/JU.0000000000000807
19. Nambiar A, Lucas M. Chapter 4: guidelines for the diagnosis and treatment of overactive bladder (OAB) and neurogenic detrusor overactivity (NDO). *Neurourol Urodyn.* 2014;33(suppl 3):S21-5. doi: 10.1002/nau.22631
20. Gemtesa prices, coupons and patient assistance programs. Drugs.com. 2021. Accessed December 13, 2021.. https://www.drugs.com/price-guide/gemtesa
21. Wagg AS, Foley S, Peters J, Nazir J, Kool-Houweling L, Scrine L. Persistence and adherence with mirabegron vs antimuscarinics in overactive bladder: retrospective analysis of a UK General Practice prescription database. *Int J Clin Pract.* 2017;71(10):e12996. doi: 10.1111/ijcp.12996
22. VESIcare(R) tablets, solifenacin succinate tablets. GlaxoSmithKline, Research Triangle Park, NC, 2004.
23. MYRBETRIQ(R) oral extended-release tablets, mirabegron oral extended-release tablets. Astellas Pharma US, Inc. (per manufacturer), Northbrook, IL, 2021.
24. Herschorn S, Chapple CR, Abrams P, et al. Efficacy and safety of combinations of mirabegron and solifenacin compared with monotherapy and placebo in patients with overactive bladder (SYNERGY study). *BJU Int.* 2017;120(4):562-575. doi: 10.1111/bju.13882
25. Gratzke C, van Maanen R, Chapple C, et al. Long-term safety and efficacy of mirabegron and solifenacin in combination compared with monotherapy in patients with overactive bladder: a randomised, multicentre phase 3 study(Synergy ii). *European Urology.* 2018;74(4):501-509. doi: 10.1016/j.eururo.2018.05.005
26. Drake MJ, Chapple C, Esen AA, et al. Efficacy and safety of mirabegron add-on therapy to solifenacin in incontinent overactive bladder patients with an inadequate response to initial 4-week solifenacin monotherapy: a randomised double-blind multicentre phase 3B study (BESIDE). *Eur Urol.* 2016;70(1):136-145. doi:10.1016/j.eururo.2016.02.030
27. Cornu J-N. Combination of solifenacin and mirabegron for overactive bladder management. BJU Int. 2015;116(4):498-499. doi:10.1111/bju.13142
28. Abrams P, Kelleher C, Staskin D, et al. Combination treatment with mirabegron and solifenacin in patients with overactive bladder: efficacy and safety results from a randomised, double-blind, dose-ranging, phase 2 study (SYMPHONY). *Eur Urol.* 2015;67(3):577-588. 10.1016/j.eururo.2014.02.012
29. Maman K, Aballea S, Nazir J, et al. Comparative efficacy and safety of medical treatments for the management of overactive bladder: a systematic literature review and mixed treatment comparison. *Eur Urol.* 2014;65(4):755-765. doi: 10.1016/j.eururo.2013.11.010
30. DITROPAN XL (oxybutynin chloride) label - Food and Drug Administration. Accessed April 19, 2022. https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/020897s035lbl.pdf
31. Detrol LA (tolterodine tartrate extended release capsules) label - Food and Drug Administration. Accessed April 19, 2022. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/021228s023lbl.pdf
32. SANCTURA (trospium chloride) label - Food and Drug Administration. Accessed April 19, 2022. https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/021595s009lbl.pdf
33. ENABLEX (darifenacin) label - Food and Drug Administration. Accessed April 19, 2022. https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/021513s010lbl.pdf
34. VESIcare (solifenacin succinate) label - Food and Drug Administration. Accessed April 19, 2022. https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/021518s012lbl.pdf
35. MYRBETRIQ (mirabegron) label - Food and Drug Administration. Accessed April 19, 2022. https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/202611s006lbl.pdf
36. GEMTESA (vibegron) label - Food and Drug Administration. Accessed June 2, 2022. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/213006s000lbl.pdf