Drugs (2015) 75:1707–1713
DOI 10.1007/s40265-015-0456-0

CURRENT OPINION

Overactive Bladder and the β_3-Adrenoceptor Agonists: Current Strategy and Future Prospects

Ilias Giarenis[1] · Dudley Robinson[1] · Linda Cardozo[1]

Published online: 1 September 2015

Abstract Overactive bladder (OAB) is a clinical syndrome describing the symptom complex of urgency, with or without urgency incontinence, and is usually associated with frequency and nocturia. It is a common, under-diagnosed and therefore under-treated condition that can have a detrimental effect on physical functioning and psychological well-being. Initial treatment of OAB includes lifestyle advice, behavioural modifications, bladder retraining and pelvic floor muscle training, usually in combination with antimuscarinic agents. The β_3-adrenoceptor agonist mirabegron is the first of a new class of drugs that are now competing with the more established antimuscarinics for the treatment of OAB. Our review focuses on the mode of action, efficacy and tolerability of mirabegron. The place of β_3-adrenoceptor agonists in the treatment algorithm of OAB is discussed, considering the adverse events associated with antimuscarinics. Drug therapy tailored to different population groups appears a promising future prospect. Development of other β_3-adrenoceptor agonists is expected, and combination therapy regimens might revolutionise the treatment of OAB.

Key Points

The β_3-adrenoceptor agonist mirabegron is the first of a new class of drugs for the treatment of overactive bladder.

Available data do not allow us to identify the most appropriate role for the drug as either first- or second-line therapy after antimuscarinics.

1 Introduction

The overactive bladder (OAB) syndrome is defined by the International Continence Society (ICS) and International Urogynecological Association (IUGA) as "urinary urgency, usually accompanied by frequency and nocturia, with or without urgency urinary incontinence, in the absence of urinary tract infection or other obvious pathology" [1]. OAB is highly prevalent and is estimated to affect 10.7 % of the worldwide population (455 million individuals) [2]. Prevalence increases with age in both sexes, increasing to 41 % of men and 31 % of women over the age of 75 years [3]. While it is not life threatening, it can have a detrimental effect on the physical functioning, psychological well-being and health-related quality of life (HRQoL) of affected individuals [4]. It carries a significant economic impact, with an estimated total cost in Canada, Germany, Italy, Spain, Sweden and the UK of €9.7 billion per annum [5].

Initial treatment of OAB includes lifestyle advice, behavioural modifications, bladder retraining and pelvic floor muscle training [6]. However, most patients with troublesome OAB require pharmacological treatment, and

✉ Ilias Giarenis
ilias.giarenis@nhs.net

[1] Department of Urogynaecology, King's College Hospital NHS Foundation Trust, Denmark Hill, London SE5 9RS, UK

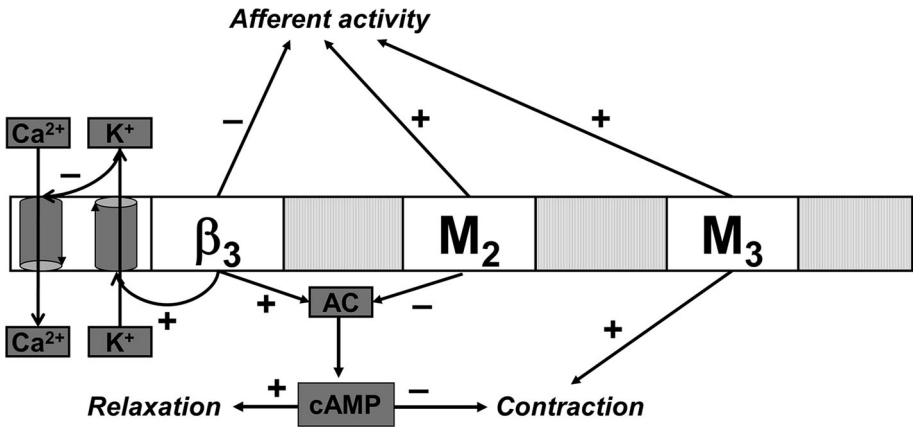

Fig. 1 Proposed mechanisms of action for antimuscarinic agents and β_3-adrenoceptor agonists. *AC* adenylyl cyclase, *Ca* calcium, *cAMP* cyclic adenosine monophosphate, *K* potassium, M_2 *and* M_3 muscarinic receptor subtypes

antimuscarinic therapy is the mainstay of current medical treatment. The classical view of their mode of action (Fig. 1) is that antimuscarinic agents competitively bind to muscarinic acetylcholine receptors (MRs) in the bladder detrusor muscle that are stimulated by acetylcholine released from parasympathetic nerves, thereby inhibiting involuntary voiding contractions [7]. However, the mechanism of action has been revisited in the past few years and it is thought that therapeutic doses in humans have minimal effect on the detrusor muscle [8]. It is suggested that antimuscarinics decrease bladder afferent (sensory) activity by blocking MRs in the urothelium and suburothelial myofibroblasts, thereby improving OAB symptoms.

Seven different licensed antimuscarinic drugs are now available on the market (darifenacin, fesoterodine, oxybutynin, propiverine, solifenacin, tolterodine and trospium), which vary both in structure and in their functional profile. They are more effective than placebo and improve HRQoL [9]. However, side effects such as dry mouth, constipation and detrimental central nervous system effects, including cognitive impairment and sleep disturbances, particularly for oxybutynin, have limited their usefulness, with reported persistence rates of only 12.0–39.4 % at 12 months [10]. Most patients discontinue treatment primarily due to unmet treatment expectations and/or poor tolerability [11]. Despite the potential for better adherence with selective agents and different routes of administration, such benefits have not yet been realised in clinical practice, and many patients end up without effective pharmacotherapy [12].

2 β_3-Adrenoceptor Agonists: Mirabegron

Novel agents such as β_3-adrenoceptor (β_3-AR) agonists might offer an alternative option for women not responding to or experiencing serious side effects to antimuscarinics. Mirabegron (YM178) is the first β_3-AR agonist approved for use in OAB. Its chemical name is 2-(2-aminothiazol-4-yl)-*N*-[4-(2-{[(2R)-2-hydroxy-2-phenylethyl]amino}ethyl) phenyl]acetamide, having an empirical formula of $C_{21}H_{24}N_4O_2S$ and a molecular weight of 396.51. The recommended starting dose is 25 mg once daily (od) in the USA and Canada (Myrbetriq™, Astellas Pharma, Inc., Northbrook, IL, USA), with the possibility of increasing to 50 mg, while the recommended dose in Japan (Betanis®, Astellas Pharma, Inc. Chuo-ku, Tokyo, Japan) and Europe (Betmiga™, Astellas Pharma BV, Leiden, the Netherlands) is 50 mg od with the 25 mg dose reserved for special populations (i.e. patients with severe renal impairment or moderate hepatic impairment).

2.1 Mechanism of Action

Mirabegron is a selective β_3-AR agonist that exerts its activity in a different way from the antimuscarinics. The presence of all three β-AR subtypes (β_1, β_2 and β_3) has been demonstrated in the detrusor muscle and the urothelium [13]. There is a predominant expression of β_3-AR messenger RNA (mRNA) in human bladder tissue, with 97 % of total beta-AR mRNA being represented by the β_3-AR subtype and only 1.5 and 1.4 % by the β_1-AR and β_2-AR subtypes, respectively [14]. Bladder relaxation is obtained (Fig. 1) by the activation of β_3-AR and the subsequent activation of adenylyl cyclase, which catalyses the conversion of adenosine triphosphate (ATP) into cyclic adenosine monophosphate (cAMP) [15]. In addition to the cAMP-dependent pathway, potassium channels are involved in the β_3-AR agonist-induced detrusor muscle relaxation [16]. Mirabegron can also inhibit mechanosensitive bladder afferent activity, especially of Aδ-fibres, which may be related to suppression of bladder microcontractions [17].

2.2 Efficacy

Six large randomised phase III trials have evaluated mirabegron in comparison with a placebo group and/or an

active control group in a total of 9331 patients [18–23]. Of these patients, 5127 were in the mirabegron groups: 2943 receiving the 50-mg dose, 433 receiving the 25-mg dose and 1751 receiving the 100-mg dose. For the four studies that used an active control group [18, 20, 22, 23], the active control was tolterodine extended release (ER) 4 mg. Patients received treatment for 12 weeks in five of the trials and 12 months in the other [18].

Statistically significant improvements in mean number of micturitions per 24 h, mean number of incontinence and urgency episodes per 24 h were noted for mirabegron compared with placebo. Groups treated with mirabegron demonstrated statistically significantly greater increases from baseline to final visit versus placebo in mean volume voided per micturition, significantly greater reductions in mean level of urgency and mean number of nocturia episodes per 24 h, as well as significantly greater improvements in HRQoL. The data demonstrated similar efficacy for the 50-mg and 100-mg doses [20], but a greater treatment effect for the 50-mg than the 25-mg dose, according to collective objective and subjective endpoints that comprise OAB [21]. Efficacy in patients who had used antimuscarinics was similar compared to that of treatment-naive patients [24]. Improvements of OAB symptoms with mirabegron were demonstrable from the first month and sustained throughout 12 months [18].

However, some limitations of published studies need to be highlighted. Mirabegron is another symptomatic drug able to improve symptoms of OAB, but not to 'cure' or modify the natural history of this bothersome condition [25]. Researchers have failed to consider urinary urgency (the defining and most bothersome symptom of OAB) as the primary endpoint in the published clinical trials. Furthermore, improvements in primary and secondary efficacy endpoints were not very impressive in terms of clinical relevance, although in line with those observed with well-established antimuscarinic treatments and statistically significant over placebo. There is also a lack of evidence on long-term efficacy (beyond 12 months).

The design of these phase III trials did not allow a head-to-head comparison of mirabegron and tolterodine, which was included simply as an active control [18, 20, 22, 23]. However, further analysis of these data by the National Institute for Health and Care Excellence (NICE) in the UK and the American Urological Association (AUA) demonstrated that the clinical effectiveness of mirabegron is similar to that of tolterodine ER 4 mg [26, 27].

2.3 Safety

The safety and tolerability of mirabegron have been also shown over 12 weeks and 12 months in the six phase III trials. The overall incidence of treatment-emergent adverse events (TEAEs) was similar for placebo, mirabegron and tolterodine ER 4 mg, with the majority being mild or moderate. The incidence of dry mouth in the mirabegron groups (0.5–2.8 %) was similar to that for placebo (1.5–2.9 %), while it was more than threefold higher in patients receiving tolterodine ER 4 mg (8.6–13.3 %). Regarding cardiovascular events, mirabegron did not exhibit any significant cardiac TEAEs. The overall incidence of hypertension was similar with mirabegron compared with placebo and tolterodine ER. More cardiac arrhythmia events were observed in tolterodine-treated patients than in mirabegron- and placebo-treated patients. A dose-dependent increase in pulse rate was observed with mirabegron 50 mg and 100 mg; these changes were small (less than 3 bpm), not clinically meaningful, and comparable with pulse rate changes with tolterodine.

3 Current Strategy and Future Concepts

3.1 First, Second, or Third Line?

While mirabegron is effective, safe and well tolerated, its place in the treatment algorithm of OAB remains debatable. As the majority of the relevant studies have been published recently, most of the national and international guidelines have not yet evaluated mirabegron for inclusion in the relevant treatment pathways. NICE in the UK concluded in 2013 that mirabegron is recommended as an option for treating the symptoms of OAB only for people in whom antimuscarinic drugs are contraindicated or clinically ineffective or have unacceptable side effects [26]. The NICE committee concluded that mirabegron offers an additional pharmacological treatment before invasive treatment options are considered. Contrary to this guidance, the AUA in 2014 recommended mirabegron as an alternative to antimuscarinics for first-line pharmacological treatment [27]. Table 1 presents the pros and cons of mirabegron or antimuscarinic agents for use as first choice.

Table 1 First-line pharmacological treatment for overactive bladder syndrome. Mirabegron versus antimuscarinics: pros and cons

	Mirabegron	Antimuscarinics
Efficacy	Similar or lower[a]	Similar or higher[a]
Tolerability	Higher	Lower
Persistence	Higher	Lower
Cost[b]	Higher[c] or similar	Lower[c] or similar

[a] Compared with solifenacin 10 mg

[b] Prices vary in different countries

[c] Compared with generic antimuscarinic agents

In OAB management algorithms where mirabegron is not recommended as first line, the number of antimuscarinics that should be tried before considering it remains uncertain. In current clinical practice, a number of clinicians would suggest a selective or transdermal agent for patients not responding to or not tolerating the first prescribed antimuscarinic drug. Despite this commonly performed antimuscarinic cycling, there are no data to confirm its value and guide management [12]. Cost-effectiveness models might provide useful evidence for the sequential use of OAB drugs. The Markov model developed by Nazir et al. [28] considered the purchase cost of medication and secondary interventions for refractory cases but also efficacy, side effect management and medication adherence. In this model for the UK National Health Service, including a third-line oral medication, irrespective of the specific drug used, before considering more invasive treatments was cost effective. Low-cost generic treatments were not necessarily more cost effective than branded drugs, primarily because a better efficacy and tolerability balance improves both symptom control and persistence.

One of the limitations of the current literature about mirabegron is the lack of direct head-to-head comparison with other antimuscarinics except tolterodine ER. A large multicentre head-to-head comparison of mirabegron with solifenacin (BEYOND) has been completed but is not yet published [29]. To compensate for the lack of direct comparison evidence, advanced statistical methods such as network meta-analysis (NMA) are quickly gaining popularity among guideline developers, health technology agencies and clinicians [30]. A recent Bayesian mixed-treatment comparison NMA of medical treatments for OAB has shown that mirabegron 50 mg has similar efficacy to most of the antimuscarinics but is inferior to solifenacin 10 mg in improving frequency of micturition and urgency urinary incontinence episodes [31]. However, as these statistical methods have certain limitations, these conclusions should be interpreted with caution and, ideally, confirmed with direct comparison trials.

Additionally, there is a need for data from everyday clinical care to confirm the efficacy, safety profile, persistence and adherence with mirabegron. In a study presenting early experience in Canada, mirabegron was associated with higher levels of persistence and adherence than antimuscarinics [32]. At 6 months, persistence with mirabegron was 39.8 % for treatment-naïve patients and 51.4 % for treatment-experienced patients, while it was 22.9 and 39.3 % for solifenacin and 12.5 and 17.7 % for immediate release oxybutynin. In another study presenting the use of mirabegron in a clinical rather than a trial setting, palpitations in an unselected population had a similar incidence (2.9 %) to that demonstrated in the phase II and III trials [33].

3.2 Patient Selection

OAB is a symptom complex representing a spectrum of underlying pathophysiologic conditions. Very few studies are making an attempt to profile idiopathic OAB patients according to specific biomarkers, correlates or clinical risk factors for the underlying etiologic cause [34]. The most common method for phenotype profiling of patients is urodynamics, with detrusor overactivity (DO) being used as a screening test to detect myogenic OAB. Although DO has been shown to be associated with a greater degree of bladder dysfunction, no trials have demonstrated different treatment efficacy for patients with and without DO [35]. Therefore, with the current knowledge, tailored pharmacological treatment cannot be based on robust evidence. In order to choose optimal therapy based on pathophysiology, future studies should explore and validate standardised criteria for classification of idiopathic OAB sub-types. Clinicians may also wish to begin classifying patients empirically based on clinical profiles (demographics, symptoms and bladder diary variables).

A number of patient groups, such as the elderly and male patients with co-existing bladder outlet obstruction (BOO), might be better candidates for prescription of mirabegron as first-line therapy. A recent prospective population-based cohort study of 3434 participants aged 65 years or older showed that higher cumulative anticholinergic use is associated with an increased risk for dementia [36]. This study supports previously published evidence that the use of medications with anticholinergic activity increases the cumulative risk of cognitive impairment and mortality [37]. A sub-analysis of four phase III trials has demonstrated the efficacy of mirabegron over 12 weeks and tolerability over 12 weeks and 1 year in OAB patients aged $\geq$65 and $\geq$75 years, supporting its therapeutic value in older patients [38].

Regarding male patients with storage symptoms and co-existing BOO, mirabegron might also be a valuable option in combination or sequential treatments with α-blockers, considering the lack of effects on voiding urodynamics (maximum urinary flow and detrusor pressure at maximum urinary flow) [39]. To our knowledge, no robust data exist for mirabegron use in neurogenic bladder dysfunction, but a placebo-controlled multicentre trial is currently recruiting patients with multiple sclerosis or suprasacral spinal cord injury to determine its effectiveness in this challenging population [40].

3.3 Combination Treatment

As mirabegron has a different mechanism of action, combining it with other available drugs may improve efficacy in OAB treatment; combinations with reduced doses may

deliver an improved tolerability profile compared with monotherapy without compromising efficacy. A phase II trial has explored the potential synergistic effect of mirabegron with solifenacin in the treatment of OAB [41]. Combination therapy with solifenacin/mirabegron was well tolerated and significantly improved OAB symptoms compared with solifenacin 5 mg monotherapy. Another recent study examined the safety and efficacy of mirabegron as 'add-on' therapy in patients treated with solifenacin 2.5 or 5 mg in Japan [42]. 'Add-on' therapy with mirabegron 25 mg once daily for 16 weeks, with an optional dose increase to 50 mg at week 8, was well tolerated and significantly improved OAB symptoms from baseline. In those groups in which the mirabegron dose was escalated from 25 to 50 mg, a further improvement was found after the increase. The potential of combination treatment with mirabegron and solifenacin is being further explored by a phase III trial currently recruiting (SYNERGY) [43].

Mirabegron has also been evaluated as 'add-on' therapy in men with benign prostatic obstruction and remaining OAB symptoms after α_1-blocker (tamsulosin) treatment [44]. In this randomised controlled trial, the 50-mg add-on mirabegron treatment was more effective for ameliorating storage symptoms and improving HRQoL than tamsulosin monotherapy. Mirabegron might also be combined with other second-line medical treatments for OAB, such as local oestrogens or desmopressin [45]. Therapeutic strategies combining mirabegron with local oestrogens in postmenopausal women or desmopressin in patients with coexisting nocturia or nocturnal polyuria could be explored in the future.

3.4 Other β_3-Adrenoceptor Agonists

There are other β_3-AR agonists in the pipeline, but none has yet been licensed for the management of OAB. A highly selective β_3-AR agonist (solabegron) has been studied in a clinical proof-of-concept multicentre randomised, double blind, placebo-controlled trial. It significantly reduced the symptoms of OAB in women with moderate to severe OAB. Solabegron was safe, well tolerated, and did not demonstrate significant differences in adverse events as compared with placebo [46]. Solabegron is about to enter phase III clinical studies in the EU and the USA.

Ritobegron is another agent with promising in vitro and in vivo animal data [47]. A phase III randomised, double blind, placebo controlled study of ritobegron in patients with OAB has been initiated and completed [48]. This 12-week study recruited 750 patients to assess change from baseline in the mean number of micturitions per 24 h as the primary outcome measure. Change from baseline in the mean number of urgency episodes per 24 h and change from baseline in the mean number of incontinence episodes per 24 h were secondary outcome measures. The results of this study have not been published, but a press release by the pharmaceutical company stated that preliminary analysis indicated that the study's primary efficacy endpoint was not met [49]. MK-4618 and MK-0634 (by Merck Sharp & Dohme) are potent and selective β_3-AR agonists under development in phase I–II proof-of-concept trials (11/LO/0679, NCT01500382, NCT01314872, NCT00231790), while TRK-380 and AJ-9677 are currently under preclinical evaluation [50].

4 Conclusions

OAB is a common and distressing condition that is known to have a significant effect on quality of life. Muscarinic receptor antagonists have been the standard first-line drug therapy for OAB. Overall, mirabegron is an efficacious, safe and well tolerated new treatment. It may represent a revolution in the treatment of OAB due to its different mechanism of action and favourable tolerability profile compared with the antimuscarinic agents. Comparative trials of mirabegron versus antimuscarinics that are in current use for the treatment of OAB would be of considerable interest. However, the available data do not allow us to identify the most appropriate role for the drug as either first- or second-line therapy after antimuscarinics, and randomised controlled trials aiming at identifying the best sequences of treatments in different populations are eagerly awaited. The availability for the first time of a second class of oral drug may open the door to the combination of mirabegron and an antimuscarinic, α-blocker or other established treatments for OAB. These strategies may provide an attractive therapeutic approach to maximise efficacy and minimise the side effect burden. Development of other β_3-AR agonists is expected, but currently there no other agents with license for treatment of OAB.

Compliance with Ethical Standards

Funding No funding was received for the conduct of this review manuscript.

Conflict of interest Dr Giarenis has received speaker honoraria and travel expenses from Astellas. Mr Robinson has been a consultant to Allergan, Astellas, Ferring, and Pfizer and has received speaker honoraria from Allergan, Astellas, Ferring and Pfizer. Professor Cardozo has been a consultant to Allergan and Astellas and has received speaker honoraria from Astellas and Allergan. Their institution (King's College Hospital) has received trial funding from Allergan, Astellas and Pfizer.

References

1. Haylen BT, de Ridder D, Freeman RM, Swift SE, Berghmans B, Lee J, et al. An International Urogynecological Association (IUGA)/International Continence Society (ICS) joint report on the terminology for female pelvic floor dysfunction. Neurourol Urodyn. 2010;29:4–20.
2. Irwin DE, Kopp ZS, Agatep B, Milsom I, Abrams P. Worldwide prevalence estimates of lower urinary tract symptoms, overactive bladder, urinary incontinence and bladder outlet obstruction. BJU Int. 2011;103:1132–9.
3. Milsom I, Abrams P, Cardozo L, Roberts RG, Thüroff J, Wein AJ. How widespread are the symptoms of an overactive bladder and how are they managed? A population-based prevalence study. BJU Int. 2001;87(9):760–6.
4. Kelleher CJ, Cardozo LD, Khullar V, Salvatore S. A new questionnaire to assess the quality of life of urinary incontinent women. BJOG. 1997;104:1374–9.
5. Irwin DE, Mungapen L, Milsom I, Kopp Z, Reeves P, Kelleher C. The economic impact of overactive bladder syndrome in six Western countries. BJU Int. 2009;103:202–9.
6. Moore K, Dumoulin C, Bradley C, Burgio K, Chambers T, Hagen S, et al. Adult Conservative Management. In: Abrams P, Cardozo L, Khoury S, Wein A, editors. Incontinence. 5th ed. Paris: Health Publication Ltd; 2013. p. 1101–228.
7. Andersson KE. Antimuscarinics for treatment of overactive bladder. Lancet Neurol. 2004;3:46–53.
8. Andersson KE. Antimuscarinic mechanisms and the overactive detrusor: an update. Eur Urol. 2011;59(3):377–86.
9. Chapple CR, Khullar V, Gabriel Z, Muston D, Bitoun CE, Weinstein D, et al. The effects of antimuscarinic treatments in overactive bladder: an update of a systematic review and meta-analysis. Eur Urol. 2008;54:543–62.
10. Veenboer PW, Bosch JL. Long-term adherence to antimuscarinic therapy in everyday practice: a systematic review. J Urol. 2014;191(4):1003–8.
11. Benner JS, Nichol MB, Rovner ES, et al. Patient-reported reasons for discontinuing overactive bladder medication. BJU Int. 2010;105:1276–82.
12. Chancellor MB, Migliaccio-Walle K, Bramley TJ, Chaudhari SL, Corbell C, Globe D. Long-term patterns of use and treatment failure with anticholinergic agents for overactive bladder. Clin Ther. 2013;35(11):1744–51.
13. Tyagi P, Thomas CA, Yoshimura N, Chancellor MB. Investigations into the presence of functional Beta1, Beta2 and Beta3-adrenoceptors in urothelium and detrusor of human bladder. Int Braz J Urol. 2009;35:76–83.
14. Yamaguchi O. Beta3-adrenoreceptors in human detrusor muscle. Urology. 2002;59(5 Suppl 1):25–9.
15. Andersson KE, Arner A. Urinary bladder contraction and relaxation: physiology and pathophysiology. Physiol Rev. 2004;84:935–86.
16. Uchida H, Shishido K, Nomiya M, Yamaguchi O. Involvement of cyclic AMP-dependent and -independent mechanisms in the relaxation of rat detrusor muscle via betaadrenoceptors. Eur J Pharmacol. 2005;518:195–202.
17. Aizawa N, Homma Y, Igawa Y. Effects of mirabegron, a novel beta3-adrenoceptor agonist, on primary bladder afferent activity and bladder microcontractions in rats compared with the effects of oxybutynin. Eur Urol. 2012;62:1165–73.
18. Chapple CR, Kaplan SA, Mitcheson D, Klecka J, Cummings J, Drogendijk T, et al. Randomized double-blind, active-controlled phase 3 study to assess 12-month safety and efficacy of mirabegron, a β(3)-adrenoceptor agonist, in overactive bladder. Eur Urol. 2013;63:296–305.
19. Nitti VW, Auerbach S, Martin N, Calhoun A, Lee M, Herschorn S. Results of a randomized phase III trial of mirabegron in patients with overactive bladder. J Urol. 2013;189:1388–95.
20. Khullar V, Amarenco G, Angulo JC, Cambronero J, Høye K, Milsom I, et al. Efficacy and tolerability of mirabegron, a β(3)-adrenoceptor agonist, in patients with overactive bladder: results from a randomised European-Australian phase 3 trial. Eur Urol. 2013;63:283–95.
21. Herschorn S, Barkin J, Castro-Diaz D, Frankel JM, Espuna-Pons M, Gousse AE, Stölzel M, Martin N, Gunther A, Van Kerrebroeck P. A phase III, randomized, double-blind, parallel-group, placebo-controlled, multicentre study to assess the efficacy and safety of the β_3 adrenoceptor agonist, mirabegron, in patients with symptoms of overactive bladder. Urology. 2013;82(2):313–20.
22. Yamaguchi O, Marui E, Kakizaki H, Homma Y, Igawa Y, Takeda M, Nishizawa O, Gotoh M, Yoshida M, Yokoyama O, Seki N, Ikeda Y, Ohkawa S. Phase III, randomised, double-blind, placebo-controlled study of the β3-adrenoceptor agonist mirabegron, 50 mg once daily, in Japanese patients with overactive bladder. BJU Int. 2014;113(6):951–60.
23. Kuo HC, Lee KS, Na Y, Sood R, Nakaji S, Kubota Y, Kuroishi K. Results of a randomized, double-blind, parallel-group, placebo- and active-controlled, multicenter study of mirabegron, a β3-adrenoceptor agonist, in patients with overactive bladder in Asia. Neurourol Urodyn. 2015;34(7):685–92.
24. Khullar V, Cambronero J, Angulo JC, et al. Efficacy of mirabegron in patients with and without prior antimuscarinic therapy for overactive bladder: a post hoc analysis of a randomized European-Australian Phase 3 trial. BMC Urol. 2013;13:45.
25. Sacco E, Bientinesi R, Tienforti D, Racioppi M, Gulino G, D'Agostino D, Vittori M, Bassi P. Discovery history and clinical development of mirabegron for the treatment of overactive bladder and urinary incontinence. Expert Opin Drug Discov. 2014;9(4):433–48.
26. National Institute for Health and Care Excellence. Mirabegron for treatment of overactive bladder. Technology appraisal guidance 290. 2013. http://www.nice.org.uk/guidance/ta290. Accessed 10 May 2015.
27. Gormley EA, Lightner DJ, Faraday M, Vasavada SP. Diagnosis and treatment of overactive bladder (non-neurogenic) in adults: AUA/SUFU guideline amendment. J Urol. 2015;193(5):1572–80.
28. Nazir J, Posnett J, Walker A, Odeyemi IA, Hakimi Z, Garnham A. Economic evaluation of pharmacological treatments for overactive bladder from the perspective of the UK National Health Service. J Med Econ. 2015;18(5):390–7.
29. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT01638000. Accessed 15 May 2015.
30. Mills EJ, Thorlund K, Ioannidis JP. Demystifying trial networks and network meta-analysis. BMJ. 2013;346:f2914.
31. Maman K, Aballea S, Nazir J, Desroziers K, Neine ME, Siddiqui E, Odeyemi I, Hakimi Z. 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):755–65.
32. Wagg A, Franks B, Ramos B, Berner T. Persistence and adherence with mirabegron, a new beta-3 receptor agonist versus antimuscarinics in overactive bladder: early experience in Canada. Value in Health. 2014;17(7):A471.
33. Balachandran AA, Duckett JR. The risk and severity of developing symptomatic palpitations when prescribed mirabegron for overactive bladder. Eur J Obstet Gynecol Reprod Biol. 2015;187:60–3.
34. Hanna-Mitchell AT, Kashyap M, Chan WV, Andersson KE, Tannenbaum C. Pathophysiology of idiopathic overactive bladder

and the success of treatment: a systematic review from ICI-RS 2013. Neurourol Urodyn. 2014;33(5):611–7.
35. Giarenis I, Mastoroudes H, Srikrishna S, Robinson D, Cardozo L. Is there a difference between women with or without detrusor overactivity complaining of symptoms of overactive bladder? BJU Int. 2013;112:501–7.
36. Gray SL, Anderson ML, Dublin S, Hanlon JT, Hubbard R, Walker R, Yu O, Crane PK, Larson EB. Cumulative use of strong anticholinergics and incident dementia: a prospective cohort study. JAMA Intern Med. 2015;175(3):401–7.
37. Fox C, Richardson K, Maidment ID, Savva GM, Matthews FE, Smithard D, Coulton S, Katona C, Boustani MA, Brayne C. Anticholinergic medication use and cognitive impairment in the older population: the medical research council cognitive function and ageing study. J Am Geriatr Soc. 2011;59(8):1477–83.
38. Wagg A, Cardozo L, Nitti VW, Castro-Diaz D, Auerbach S, Blauwet MB, Siddiqui E. The efficacy and tolerability of the β3-adrenoceptor agonist mirabegron for the treatment of symptoms of overactive bladder in older patients. Age Ageing. 2014;43(5):666–75.
39. Nitti VW, Rosenberg S, Mitcheson DH, He W, Fakhoury A, Martin NE. Urodynamics and safety of the β_3-adrenoceptor agonist mirabegron in males with lower urinary tract symptoms and bladder outlet obstruction. J Urol. 2013;190(4):1320–7.
40. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT02044510. Accessed 17 May 2015.
41. Abrams P, Kelleher C, Staskin D, Rechberger T, Kay R, Martina R 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):577–88.
42. Yamaguchi O, Kakizaki H, Homma Y, Igawa Y, Takeda M, Nishizawa O, Gotoh M, Yoshida M, Yokoyama O, Seki N, Okitsu A, Hamada T, Kobayashi A, Kuroishi K. Safety and efficacy of mirabegron as 'add-on' therapy in patients with overactive bladder treated with solifenacin: a post-marketing, open-label study in Japan (MILAI study). BJU Int. 2015. doi:10.1111/bju.13068 **(Epub ahead of print)**.
43. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT01745094. Accessed 19 May 2015.
44. Ichihara K, Masumori N, Fukuta F, Tsukamoto T, Iwasawa A, Tanaka Y. A randomized controlled study of the efficacy of tamsulosin monotherapy and its combination with mirabegron for overactive bladder induced by benign prostatic obstruction. J Urol. 2015;193(3):921–6.
45. Robinson D, Giarenis I, Cardozo L. The medical management of refractory overactive bladder. Maturitas. 2013;74(4):386–90.
46. Ohlstein EH, von Keitz A, Michel MC. A multicenter, double-blind, randomized, placebo-controlled trial of the β3-adrenoceptor agonist solabegron for overactive bladder. Eur Urol. 2012;62(5):834–40.
47. Maruyama I, Goi Y, Tatemichi S, Maruyama K, Hoyano Y, Yamazaki Y, Kusama H. Bladder selectivity of the novel β_3-agonist ritobegron (KUC-7483) explored by in vitro and in vivo studies in the rat. Naunyn Schmiedebergs Arch Pharmacol. 2012;385(8):845–52.
48. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT01004315. Accessed 18 May 2015.
49. http://www.kissei.co.jp/e_contents/relation/2010/20100702.html. Accessed 18 May 2015.
50. Sacco E, Bientinesi R. Innovative pharmacotherapies for women with overactive bladder: where are we now and what is in the pipeline? Int Urogynecol J. 2015;26(5):629–40.